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Protocol for a randomised controlled trial of Body Brain Life – GP and a Lifestyle Modification Program to decrease dementia risk exposure in a primary care setting

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Abstract

Introduction: It has been estimated that a 10% to 25% reduction in seven key risk factors could potentially prevent 1.1 to 3.0 million Alzheimer's disease cases globally per annum. In addition, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impact, effective preventative interventions would likely have more extensive benefits. The current study evaluates in primary care a multi-domain risk reduction intervention targeting adults with high risk of developing dementia.

Methods and analysis: A randomised controlled trial (RCT) is being conducted to evaluate three intervention programs: 1) A 12-week online and face-to-face dementia risk reduction intervention (BBL-GP); 2) A 6-week face-to-face group intervention (LMP); and 3) A 12-week email-only program (active control). We aim to recruit 240 participants to undergo a comprehensive cognitive and physical assessment at baseline and follow ups (post intervention, 18, 36 and 62 weeks). The primary outcome is dementia risk measured with the modified version of the ANU-ADRI-Short Form. Secondary outcomes are cognitive function measured with Trail A and B, and the Digit Symbol Modalities Test; physical activity with Moderate-Vigorous Physical Activity and the International Physical Activity Questionnaire; depression with the Centre for Epidemiological Studies Depression Scale; cost evaluation with the SF-12 health survey, Framingham coronary heart disease risk score, and Australian type 2 diabetes risk assessment tool; diet quality with the Australian Recommended Food Score; and sleep quality with the Pittsburgh Sleep Quality Index.

Ethics and dissemination: This RCT is a novel intervention applied in a primary care setting to reduce the dementia risk exposure in adults at high risk. If successful, BBL-GP and LMP will provide a versatile, evidence-based package that can be easily and quickly rolled-out to other primary care settings and which can be scaled up at relatively low cost compared to other strategies involving intensive interventions.

Trial registration: Reg. no. ACTRN12616000868482

Keywords: RCT, dementia, lifestyle change, online, physical activity, diet, cardiovascular risk factors, Australia, general practice, primary care.

Strengths and limitations of this study

- This study has been built on our dementia prevention research programs which has been shown to reduce cognitive decline in older adults at-risk of dementia.
- This trial evaluates a multi-domain risk reduction intervention targeting adults with high risk of developing dementia in primary care.
- A naturalistic approach is used in this trial to ensure the program can be adapted efficiently in primary care settings if proven effective.
- We are aware that most of our outcomes are self-reported and therefore can be subjective. Accordingly, we will interpret data conservatively.

Introduction

No cure is available for Alzheimer's disease and other types of dementia. However, it is estimated that an achievable 10% to 25% reduction in seven key risk factors could prevent 1.1 to 3.0 million Alzheimer's disease (AD) cases internationally per annum (Barnes & Yaffe, 2011). It is also estimated that if each of seven risk factors was to be reduced by 5%, 10%, 15% and 20% per decade, dementia prevalence would be reduced by between 1.6 and 7.2% in 2020, 3.3-14.9% in 2030, 4-9 – 22.8% in 2040 and 6.6-30.7% in 2050 (Ashby-Mitchell, Burns, Shaw, & Anstey, 2017). Furthermore, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impacts, effective preventative interventions would likely have additional benefits.

Increasingly and to afford a greater chance of producing detectable changes during study timeframes, the dementia research community has focused on multi-domain interventions that address multiple risk factors simultaneously (Ngandu et al., 2015). Among individuals with high risk factor burden, cognitive decline can be reduced (and possibly reversed) as a result of cardiovascular risk reduction and increase in activities that stimulate and protect the brain including cognitive, social and physical activity and an appropriate diet (Prince, Albanese, Guerchet, & Prina, 2014). Alzheimer's disease and cardiovascular disease share cardiometabolic and lifestyle risk factors and cardiovascular risk reduction can be achieved by smoking cessation, increasing physical activities, adopting a healthy diet, reducing abnormally high blood pressure and cholesterol, and managing major depression, overweight/obesity and diabetes if present (Santos et al., 2017). Altogether, the literature supports the view that multi-domain interventions aimed at reducing cardiometabolic risk and promoting behaviours shown to protect against dementia will contribute to preventing cognitive decline, reduce overall risk of AD, and lower depressive symptoms.

Insufficient physical activity is the risk factor with the most evidence to support its

role as a treatment for Mild Cognitive Impairment (MCI; Blondell, Hammersley-Mather, & Veerman, 2014) and more generally cognitive decline (Northey, Cherbuin, Pumpa, Smee, & Rattray, 2017). Physical activity has also been shown in RCTs to benefit several other risk factors for dementia including depression (Mammen & Faulkner, 2013), and cardiovascular risk factors (Brouwer, van der Graaf, Soedamah-Muthu, Wassink, & Visseren, 2010). Physical activity not only modifies multiple risk factors but it has direct benefits for brain health and cognition.

To bring about risk reduction, there needs to be long-lasting behavioural change in multiple areas. Achieving this requires using techniques such as goal setting, decreasing barriers to change, improving self-monitoring, having access to information, and maintaining motivation (Locke, 1996; Middleton, Anton, & Perri, 2013). Therefore, this RCT investigates whether lifestyle management programs that offer not only health promoting information, but also practical behaviour change techniques which can be implemented in daily life can reduce dementia risk.

Recruitment in general practice setting

Primary care is an ideal setting for the implementation of the current program because it is where adults with high risk of developing dementia are identified and early intervention and treatment are provided (The Department of Health, 2013). Assessment of cardiovascular risk factors is common in primary care, as is advice about physical activity and diet. General practitioners (GP) commonly screen for diabetes and increasingly identify depression. GPs are often the first point of contact for patients who are worried that they may have dementia (Robinson, Tang, & Taylor, 2015).

Although there has been one study conducted in primary care setting with elderly participants (70-78 years old; Richard et al., 2009), the current program is the first of its kind to provide interventions to adults (18 years and above) at the primary care setting, addressing

both cardiovascular and lifestyle risk factors of dementia.

Methods and analysis

Study setting and design

This project is a 6-12 week, single-blind randomised controlled trial that is designed to assist participants develop and maintain a healthy lifestyle, as well as manage chronic diseases. The study evaluates the implementation of an evidence-based dementia risk reduction program that we developed and have evaluated previously on volunteers and which has now been adapted for primary care (BBL-GP). The primary care setting in which the study is held already conducted a lifestyle management program (LMP) aimed to reduce vascular risk factors. The LMP program was initially developed to consist of 12 sessions over 12 weeks. However, its format was changed prior to this trial to have 12 sessions over 6 weeks. This decision was made by the clinic which provides this program in order for the program to be offered 4 times a year. The current LMP program was chosen as a comparison condition for feasibility and to enable evaluation of an existing program for dementia and cardiovascular risk reduction. The efficacy of the existing program had not previously been evaluated.

The existing LMP program included 6 weeks of face-to-face group education sessions. The BBL-GP program included 12 weeks of individually tailored online education sessions with one hour face-to-face individual sessions with a dietitian and an exercise physiologist. The BBL-GP and LMP are being compared to an active control group receiving weekly email with links to health information. The study is being conducted in Canberra, Australian Capital Territory, Australia. The trial has been designed and is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Participants

Participants are being recruited from the National Health Co-op (NHC), the largest bulk billing general practice organisation in Canberra comprising of eight clinics. Bulk Billing is a payment option where the doctor bills directly the universal health insurance system (Medicare) in Australia for a medical service that the patients receive. Invitation emails have been sent to all members excluding members who are inactive (those who did not renew their memberships), those aged less than 18 years, or without email addresses. Posters at the clinics are also being used for the recruitment. Potential participants who express their interest by contacting the LMP coordinator at the NHC or registering on the NHC's website are assessed against the inclusion and exclusion criteria. These are the types of adults who a GP would refer to a dementia risk reduction trial in 'real life' and on whom we are aiming to evaluate our intervention in a naturalistic context. If criteria are met, information sheets and consent forms are sent to potential participants. Upon return of consent forms, each participant is officially registered to the study and allocated a unique identity numbers and as well as an online account.

Inclusion criteria

A naturalistic approach is used in recruitment and the study inclusion criteria being used for this study are those already used by the NHC to refer patients to the LMP program (prior to this research project). We aimed to optimize the seamlessness of the intervention in primary care and utilize existing referral pathways to increase the probability that the intervention is conducted in a manner that could lead to implementation in real life. Participants must be aged 18 years and over, reside in the Australian Capital Territory, be current financial members of the NHC, have access to a computer and internet connection at home, be fluent in English, Australian permanent residents or citizens (to be able to bulk billed), and must be

the only person in their household who is taking part in this study. To be eligible for the study, participants are also required to have a chronic health condition (high blood pressure, heart disease, type 2 diabetes or 'pre-diabetes', osteoporosis, osteoarthritis, polycystic ovary syndrome (PCOS), kidney or liver disease, and depression/anxiety) or be overweight or obese (BMI>25). They are also required to agree to commit 1-2 hours a week to complete the program and be interested in obtaining advice on improving their lifestyle to reduce the risk of or better manage chronic disease. Participants are required to complete online assessments and attend NHC at baseline and 18, 36, and 62 weeks after commencement of the intervention for medical and cognitive assessments.

Exclusion criteria

Participants are not eligible to enrol in the trial if they have significant and unstable medical and psychiatric conditions that would prevent participation in the trial. They are also ineligible if they have sensory deficits or mobility limitations that would prevent or substantially restrict the delivery of the assessment or intervention, have cognitive impairment, or are pregnant.

Sample size calculations

Sample size calculations were estimated using G*Power (version 3.1.9.2; http://www.gpower.hhu.de/en.html) and have been based on medium effect size as observed in the previous Body Brain Life project. To detect a medium effect in a 3-group design (1:1:1), 4 measurements with a 5% risk of type 1 error (α) and 80% power, a total sample size of 159 persons is required. To account for a 33% attrition (based on previous lifestyle modification program by NHC), a baseline sample of 240 is being recruited (80 in BBL-GP group, 80 in LMP group and 80 in control group).

Assessments

Participants who meet all inclusion and no exclusion criteria are invited to complete online surveys and visit NHC for the baseline evaluation, and for week 18, 36, and 62 follow ups. Immediate follow up is also conducted online at week 7 for LMP, and week 13 for BBL-GP and control groups. Table 1 summarizes the assessment measures and schedule.

Screening measures and covariate

In addition to the above inclusion and exclusion criteria, further screening measures are conducted to ensure that participants are capable of taking part in the study. The Adult Pre-exercise Screening System (APSS; Exercise & Sports Science Australia, 2011) is used at the baseline assessment to identify individuals with acute/high risk conditions, or who may be at higher risk of an adverse event during exercise. To screen for any cognitive impairment (<25), the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) is administered to participants aged 60 and older.

Health efficacy and motivation for healthiness subscales from the Multidimensional Health Questionnaire (MHQ; Snell & Johnson, 1997) is used to measure the extent to which people believe they have the ability, capability, skills and talents to take care of their own physical health, and to measure people's motivation to keep in good physical health.

Primary outcome

The primary outcome is one's exposure profile to demonstrated risk factors for Alzheimer's disease. It is measured with a modified version of the Australian National University Alzheimer's Disease Risk Index – Short form (ANU-ADRI – SF; Kim, Cherbuin, & Anstey, 2016). The ANU-ADRI-SF is comprised of validated scales assessing 15 individual risk and protective factors for Alzheimer's disease and dementia. However, for the assessment of engagement in cognitive activities levels only, items from the original ANU-ADRI (Anstey,

Cherbuin, & Herath, 2013; Anstey et al., 2014) are used in place of those from the ANU-ADRI-SF due to limitations of the latter.

Secondary outcomes

Secondary outcomes include cognitive function, physical activity level, depressive symptoms, cost of interventions, diet and sleep quality. They are measured as follows: cognitive function is assessed with processing speed and task switching using Trails A and B, and the Digit Symbol Modalities Test. Moderate-vigorous Physical Activity (MVPA) is a continuous measure of activity that registers three or more Metabolic Equivalents (METs) for 10 minutes or longer on an ActiGraph Link activity monitor (http://actigraphcorp.com/products/actigraph-link/), which is worn for 7 days. Self-reported physical activity is also being recorded using the short form of IPAQ (Craig et al., 2003), which is part of the ANU-ADRI-SF. Depression is being assessed with the Centre for Epidemiological Studies Depression Scale (Radloff, 1977), which is also part of the ANU-ADRI.

Health outcomes are assessed with the SF-12 health survey (Ware, Kosinski, & Keller, 1996), Framingham coronary heart disease risk score (Wilson et al., 1998), and Australian type 2 diabetes risk assessment tool (AUSDRISK; Chen et al., 2010) to enable cost effectiveness evaluation of the two health promotion interventions.

Dietary quality is assessed with a food-based diet quality index, the Australian Recommended Food Score (ARFS; Collins et al., 2015). The ARFS is aligned with Australian Dietary Guidelines (National Health and Medical Research Council, 2013) and the Australian Guide to Healthy Eating (National Health and Medical Research Council, 2003) recommendations. The ARFS total ranges from 0 to 73 and includes eight subscales: vegetables (0 to 21), fruit (0 to 12), protein (0 to 7), vegetarian alternatives (0 to 6), grains (0

to 13), dairy (0 to 11), water (0 to 1), sauces and condiments (0 to 2). Higher scores indicate greater compliance with the Australian Dietary Guidelines and therefore better diet quality. The ARFS has demonstrated good validity and reproducibility (Collins et al., 2015).

Lastly, the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

Randomization

Upon completion of the baseline assessment, participants are randomly allocated into one of the three groups. The allocation sequence is generated by an independent researcher and is not known to the study team at the time of enrolment and baseline assessment. A permuted block randomization sequence comprising block sizes of 6 stratified by gender and age group (18-49 vs 50+) is used.

Interventions

Group 1: Body Brain Life – General Practice (BBL-GP)

BBL-GP is an intervention package that builds on our dementia prevention research programs. This includes an online dementia risk reduction program called the Body Brain Life (BBL; Trial ID: ACTRN12612000147886) (Anstey et al., 2015; Anstey, Bahar-Fuchs, Herath, Rebok, & Cherbuin, 2013) and the Fitness for the Ageing Brain Study (FABS; Trial ID: ACTRN 12609000755235) (Cyarto et al., 2010; Lautenschlager et al., 2008). Contents for the BBL-GP online modules have been revised after extensive consumer evaluation by members of the Alzheimer's Australia Consumer Dementia Research Network as well as members of the public and from participant feedback after the previous trial. The physical activity

program has also been modified for a younger age-group to 18 years and older. The Actigraph device was introduced to measure the objective amount and intensity of physical activity. This revised program (Body Brain Life – Fit) was piloted with the general public (Trial ID: ACTRN12615000822583).

Participants in the BBL-GP group are required to complete 8 modules (dementia literacy, risk factors, physical activity, nutrition, health, cognitive activity, social activity and mood) delivered online. Prior to commencing online modules, participants in the BBL-GP group also receive an individually tailored plan/program for both dietary and physical activity interventions developed and delivered by a dietitian and an exercise physiologist, respectively during a face-to-face assessment. This is to ensure the dietary prescription and level of physical activity are suitable and tailored to individual participants.

Physical activity session

The session duration and frequency of the physical activity (PA) program varies between participants based on baseline physical activity levels and individual tailoring. An exercise physiologist designs an individual program for the participant, delivers this in a face-to-face workshop and monitors the physical activity program via the returned diaries and telephone monitoring. For those not doing any regular PA at baseline, the target is 150 minutes/week moderate intensity PA, with moderate intensity defined as a score of 10-12 on the Borg Rating of Perceived Exertion scale (RPE; Borg, 1982). For those who are doing regular PA but for less than 100 minutes/week, an additional 100 minutes/week is prescribed, and for those meeting the target, an additional 50 minutes/week is prescribed. Printed material guiding participants to increase their activity level with worksheets are also provided. A diary in the format of a calendar returned monthly for 24 weeks is used to record PA and RPE to assess PA and intensity adherence.

Dietary session

Participants at baseline who had unintentional weight loss of 5 kg or weight gain of 5 kg over the previous six months were seen by the dietitian. Furthermore, participants whose diets at baseline scored low on one or more of the subscales of the (ARFS) (vegetables <14, fruit <8, protein <4, grains <9, dairy <8, water <1) (Collins et al., 2015), were also seen by the dietitian. Dietary counselling was provided by a trained dietitian and overseen by the coordinating dietitian. During the one hour face-to-face counselling session, participants received individually tailored dietary advice and printed material explaining the diet in detail.

Follow ups

Participants in the BBL-GP group are monitored through phone calls at week 4, 12 (14 for PA) and week 20 by the dietitian and exercise physiologist to monitor the progress and for reassurance. In addition, they receive a general booster session at 12 months with a phone call and a mailed out booklet summarising materials from the online modules. They are being asked to continue being active and follow a healthy eating plan after completion of the intervention.

Online modules

Once participants in the BBL-GP group have received face-to-face PA and dietary counselling sessions, they are asked to log on to the trial website and complete one module per week, each taking approximately 30-40 minutes. The 12-week program is detailed in Table 2. The first 8 weeks include the completion of 8 educational and individually tailored behaviour change modules. In the remaining 4 weeks, participants undertake online activities focused on goal monitoring and revision of the modules materials. Tailoring of the six behaviour change modules (weeks 3-8) is conducted using an automated algorithm that presents content on the basis of whether or not the participant has a relevant risk factor, as well as on the basis of their responses to several questions measuring psychological determinants of behaviour. These questions are presented at the beginning of each of the

behaviour change modules. For instance, a person who is classified as having a poor diet (e.g. lack of fish intake) on the basis of their responses on the ANU-ADRI, and who does not regard himself/herself as a role model to others with respect to their diet habits will not be presented with information focusing on becoming a role model to others.

The program is built in such a way that participants are only able to access the relevant component of the intervention at a given time. The modules become active, 1 per week, on the same day for the first 8 weeks. Participants are unable to access a newly activated module before completing the previously scheduled module. Each week, participants receive a notification email on the same day of the week alerting them when a new module has become active and a list of already activated modules that they have either not started or completed. Participants who are late completing modules will be followed up with an email from the project manager to identify if there is a reason (e.g. holidays, illness, work commitments) preventing their participation, and encouraging them to continue with the study. Compliance is recorded for each module if they are completed on time, delayed or not completed.

Group 2: Lifestyle Modification Program (LMP)

The lifestyle modification program (LMP), developed by NHC, is designed to enhance general wellbeing and improve lifestyle to reduce the risk of chronic disease. LMP is a six-week group program provided by various health professionals (dietitian, exercise physiologist, nurse practitioner, psychologist, pharmacist and sleep physician) providing information on basic nutrition, meal planning, physical activity, health conditions, motivation and goals, medications, and sleep. Every week, 2 sessions are provided on the same day with each session lasting an hour. The course is currently run by the NHC for their patients to assist them in improving their lifestyle and management of chronic disease so it is a real-life comparison condition. Attendance is recorded for compliance and motivation checking.

Although the LMP is a free nationally recognized program that is designed to provide individuals with tools to help manage chronic disease and maintain a healthy lifestyle, evaluation of the program has not been carried out as yet.

Group 3: Active control/Email only

The active control group or email only group proceed with their normal activities and access health services as required over the trial period. Participants in this group also receive weekly emails containing links to various websites providing information on lifestyle risk factors and disease management for a duration of 12 weeks. The weekly emails contain several links, and participants are encouraged to spend approximately an hour each week browsing through the material. The material is generally organized around the same themes as the ones included in the BBL-GP program. An effort has been made to include links to relevant information and educational material, but that otherwise does not include the use of identifiable behaviour-change techniques which are the 'active ingredient' of the BBL-GP program. In addition, other than providing participants with the weekly emails, no further contact is made with the participants in this group, such as reminders and prompts that are provided to the BBL-GP group.

Masking

To prevent performance bias, research staff conducting the assessments remain masked to participants' group allocation. The contact person for participants' website queries, access issues, and technical difficulties is independent of all baseline assessment data. All participants are informed that they are being randomly allocated to one of three study groups and that one group may be more effective than others. They are also notified at the start of the study that one of these groups involves face-to-face group sessions which require them to travel to NHC head office. Hence, the research team members who recruit participants, conduct individual diet and physical activity sessions, and professionals who are involved in

the LMP are naturally able to tell which group they have been allocated to. Nurses who conduct baseline and follow-up assessments are however masked to group allocation.

Data management and monitoring

Data management is handled independently from the researchers who interpret the data. All data are stored electronically and in an independent spreadsheet and SPSS data file, which is only accessible by the researchers involved in this study.

Statistical analyses

Statistical analyses will be based on an intention-to-treat approach. As applied in the previous BBL project (Anstey et al., 2015), multiple imputation and mixed models will be applied to analyse data. We hypothesise that the effectiveness of the intervention programs will be in the following order: BBL-GP> LMP > active control. The hypothesis that BBL-GP will be more effective than LMP is based on research showing that a tailored program is better than a one size fits all group program in most cases (Kreuter, Oswald, Bull, & Clark, 2000). This is also based on the previous BBL project where those in BBL groups improved more than those in the control group. We will also adjust for compliance in completing the online modules and following recommendations provided by the dietitian and exercise physiologist (for BBL-GP group), or for attendance to weekly group sessions (for LMP group).

Ethics and trial registration

The Human Research Ethics Committee at the Australian National University has approved the study protocols and procedures (protocol #2016/157). This project has also been registered at the Australian New Zealand Clinical Trials Registry (ACTRN: 12616000868482).

Adverse events

This study evaluates lifestyle intervention programs to reduce risk factors for AD. The target population is adults in a primary care setting who have some of the known risk factors for

dementia, but are at the time of the intervention, healthy and free of any dementia-related symptoms. We do not anticipate that participants will be placed at a greater risk than that associated with self-driven educational activities over the Internet. Medical assessments are done by the participants' usual nurses and doctors and if any abnormality is detected in their results, they are required to discuss these abnormalities with participants as usual. To address issues of potential fatigue, the assessments have been kept to a minimum length. In addition, all online and face-to-face sessions are designed in an interactive way and are limited to 1-hour sessions (LMP has 2 themed sessions per week and has a break between sessions). As mentioned above, all online modules are delivered in an individually tailored fashion to maximize relevance for each individual.

Dissemination plan

Positive, neutral and negative results of the trial will be submitted to international peer-reviewed journals. In addition, results will be presented at national and international conferences relevant to the subject matters. Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors and depends on personal involvement.

Discussion

The project is currently under way as an evaluation of the efficacy of health promotion interventions in adults with risk factors for dementia. The program aims to reduce cardiometabolic risk and promote behaviours shown to protect against dementia. The trial, recruiting from a primary care setting has generated considerable interest, and to date, approximately half of the total target sample has been assessed and randomised into the intervention groups. We anticipate that all data collection will be completed by December 2018. The results of the study are likely to form an evidence base for the feasibility of dementia risk reduction campaigns to lead to lifestyle changes and the reduction of dementia

risk factors at the population level. This trial will also support the feasibility of such interventions being applied in primary care settings. Successful outcomes of the current trial may lead to significant public health impact and benefits once the intervention is made available at the population level pending positive results.

Conclusion

Interventions to reduce risk of developing dementia are needed as a cure is not available. This project compares three different approaches to promote healthy lifestyles and to reduce risk of developing dementia applied in a primary care setting. This unique trial demonstrates real life application of dementia risk reduction intervention rather than more controlled but less ecologically valid interventions typically tested in a research setting.

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Authors' contributions

KJA conceived the study and built relationship with NHC. KJA, NC, SK developed the overall design of the intervention. NL and KC designed the implementation of the physical activity related intervention. CD and KJA designed the statistical analysis plan for the protocol. DP and GR contributed knowledge of primary care setting and advised on implementing the intervention in a GP clinic. ST designed the implementation of the dietary intervention. NC and SK managed the implementation of the online component in the dedicated web portal. All authors wrote the study protocol and critically reviewed the manuscript.

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Competing interests

None declared.

Table 1. Assessment measures at the baseline and follow up evaluations

Assessment measure	Baseline	Immediate follow up (Week 7 for LMP and week 13 for BBL-GP and active control group)	Week 18	Week 36	Week 62
Screening					
APSS	√				
MMSE (if 60+)	√				
Questionnaires					
ANU-ADRI	√	√	√	√	√
Sleep Quality Assessment	√	√	√	√	√
Diet questionnaire	√	√	√	√	√
SF-12	√	√	√	√	√
MHQ	√				

Cognitive measures					
Trails A + B	√		√	√	√
Digit symbol matching	√		√	√	√
Physical and medical evaluation (by doctors and nurses)					
MVPA	√		√	√	√
Blood pressure	√		√	√	√
Height, cm	√				
Weight, kg	√		√	√	√
Waist and hip, cm	√		√	√	√
Body Composition	√		√	√	√
Framingham coronary heart	√		√	√	√
AUSDRISK	√		√	√	√

Note: ANU-ADRI: Australian National University – Alzheimer's Disease Risk Index; SF-12: SF-12 Health Survey; APSS: Adults Pre-exercise Screening System; MHQ: Multidimensional Health Questionnaire; MMSE: Mini-Mental State Examination; MVPA: Moderate-vigorous Physical Activity; AUSDRISK: Australian type 2 diabetes risk assessment tool.

Table 2: Description of the 12-week online program delivered through the Body Brain Life – GP (BBL-GP) website

Week	Activity	Description
1	Module 1: Dementia literacy	The first module focuses on providing participants with general information about dementia including types, causes, prevalence, social and economic impact, symptoms, brain function, treatment, risk factors (modifiable and non-modifiable), and prevention. This module serves as an introduction to the subsequent modules.
2	Module 2: Dementia risk factors	This module is aimed at building awareness and knowledge of the various health conditions associated with an increased risk of Alzheimer's dementia (AD). Specifically, this module provides details regarding the association between AD and several medical conditions (abnormal weight, high cholesterol, diabetes, hypertension, and depression), as well as lifestyle factors (alcohol use and smoking, physical activity, nutrition, stroke and head injury, mental health, social and cognitive engagement). The module also briefly covers non-modifiable risk factors that contribute to AD, including age and genetics.
3	Module 3: BBL FIT - physical activity	This is a theory-driven, individually-tailored module that aims to help participants incorporate regular physical activity into their daily routine and reduce sedentary behaviour by focusing on increasing endurance, strength, balance, and flexibility. This module targets several barriers to engaging in physical activity, such as increasing motivation, creating opportunities to exercise, and developing a social network that supports physical activity goals.
4	Module 4: BBL nutrition	This is a theory-driven, individually-tailored module aimed at helping people develop healthy dietary habits. This module targets the risk associated with abnormal weight, and the protective effects associated with fish intake and other dietary components.
5	Module 5: BBL health self-management	This is a theory-driven, individually-tailored module aimed at increasing participants' health monitoring and management of chronic health conditions. Because several chronic health conditions are associated with increased risk for dementia, prevention and appropriate management of such conditions is also likely to be protective against dementia.
6	Module 6: BBL Think – cognitive engagement	This is a theory-driven, individually-tailored module aimed at increasing participants' levels of engagement with mentally stimulating activities, which is a protective factor against dementia.

7	Module 7: BBL connect – social engagement	This is a theory-driven, individually-tailored module aimed at increasing participants' levels of social engagement. The module targets the risk factor for dementia associated with loneliness and depression, and the protective effects of regular social engagement.
8	Module 8: BBL mood	This is a theory-driven, individually-tailored module that aims to help participants monitor and maintain good mental health. The module targets risk factors for dementia associated with mental health and mood, focusing on depression and anxiety. Information is provided on symptoms, types, treatment, and tips for managing mood.
9	9 to 12 Self-guided online activities	During these sessions, participants are encouraged to engage in a range of online activities for 1 h, including accessing the many tools they have accumulated during the first 7 weeks. Examples include the goal-setting tool, behaviour-monitoring tool, unhelpful thoughts monitoring tool, videos, and so on.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____4, 18_____
	2b	All items from the World Health Organization Trial Registration Data Set	____N/A_____
Protocol version	3	Date and version identifier	____N/A_____
Funding	4	Sources and types of financial, material, and other support	____26_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1, 26____
	5b	Name and contact information for the trial sponsor	____ N/A _____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____N/A_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____N/A____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____5-8_____
	6b	Explanation for choice of comparators	____7-8_____
Objectives	7	Specific objectives or hypotheses	____7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____7_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____9-11____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____13-17____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____N/A_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____14-16____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___14-17_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___11-13_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____11, 27-29__

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____13_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____13_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____13_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____17-18_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____17_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ 16-17_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle Modification Program to decrease dementia risk exposure in a primary care setting

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Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle Modification Program to decrease dementia risk exposure in a primary care setting

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Abstract

Introduction: It has been estimated that a 10% to 25% reduction in seven key risk factors could potentially prevent 1.1 to 3.0 million Alzheimer's disease cases globally. In addition, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impact, effective preventative interventions would likely have more extensive benefits. The current study evaluates in primary care a multi-domain risk reduction intervention targeting adults with high risk of developing dementia.

Methods and analysis: A randomised controlled trial (RCT) is being conducted to evaluate three intervention programs using a pragmatic approach suitable to the clinic: 1) A 12-week online and face-to-face dementia risk reduction intervention (BBL-GP); 2) A 6-week face-to-face group lifestyle modification program (LMP); and 3) A 12-week email-only program providing general health information (active control). We aim to recruit 240 participants, aged 18 and over, to undergo a comprehensive cognitive and physical assessment at baseline and follow ups (post intervention, 18, 36 and 62 weeks). The primary outcome is dementia risk measured with the modified version of the ANU-ADRI-Short Form. Secondary outcomes are cognitive function measured with Trail A and B, and the Digit Symbol Modalities Test; physical activity with Moderate-Vigorous Physical Activity and the International Physical Activity Questionnaire; depression with the Centre for Epidemiological Studies Depression Scale; cost evaluation with the SF-12 health survey, Framingham coronary heart disease risk score, and Australian type 2 diabetes risk assessment tool; diet quality with the Australian Recommended Food Score; and sleep quality with the Pittsburgh Sleep Quality Index.

Ethics and dissemination: This RCT is a novel pragmatic intervention applied in a primary care setting to reduce the dementia risk exposure in adults at high risk. If successful, BBL-GP and LMP will provide a versatile, evidence-based package that can be easily and quickly

rolled-out to other primary care settings and which can be scaled up at relatively low cost compared to other strategies involving intensive interventions.

Trial registration: Reg. no. ACTRN12616000868482

Keywords: RCT, dementia, lifestyle change, online, physical activity, diet, cardiovascular risk factors, Australia, general practice, primary care.

Strengths and limitations of this study

- BBL-GP program has been built on our dementia prevention research programs which has been shown to reduce cognitive decline in older adults at-risk of dementia.
- This pragmatic trial evaluates a multi-domain risk reduction intervention targeting adults with high risk of developing dementia in primary care.
- A naturalistic approach is used in this trial to ensure the program can be adapted efficiently in primary care settings if proven effective.
- We are aware that most of our outcomes are self-reported and therefore can be subjective. Accordingly, we will interpret data conservatively.

Introduction

No cure is available for Alzheimer's disease and other types of dementia. However, it is estimated that an achievable 10% to 25% reduction in seven key risk factors could prevent 1.1 to 3.0 million Alzheimer's disease (AD) cases internationally (1). It is also estimated that if each of seven risk factors was to be reduced by 5%, 10%, 15% and 20% per decade, dementia prevalence would be reduced by between 1.6 and 7.2% in 2020, 3.3-14.9% in 2030, 4-9 – 22.8% in 2040 and 6.6-30.7% in 2050 (2). Furthermore, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impacts, effective preventative interventions would likely have additional benefits.

Increasingly and to afford a greater chance of producing detectable changes during study timeframes, the dementia research community has focused on multi-domain interventions that address multiple risk factors simultaneously (3). Among individuals with high risk factor burden, cognitive decline can be reduced (and possibly reversed) as a result of cardiovascular risk reduction and increase in activities that stimulate and protect the brain including cognitive, social and physical activity and an appropriate diet (4). Alzheimer's disease and cardiovascular disease share cardiometabolic and lifestyle risk factors and cardiovascular risk reduction can be achieved by smoking cessation, increasing physical activities, adopting a healthy diet, reducing abnormally high blood pressure and cholesterol in mid-life, and managing major depression, overweight/obesity in mid-life and diabetes if present (5). Altogether, the literature supports the view that multi-domain interventions aimed at reducing cardiometabolic risk and promoting behaviours shown to protect against dementia will contribute to preventing cognitive decline, reduce overall risk of AD, and lower depressive symptoms.

Insufficient physical activity is the risk factor with the most evidence to support its role as a treatment for Mild Cognitive Impairment (MCI) (6) and more generally cognitive

decline (7). Physical activity has also been shown in RCTs to benefit several other risk factors for dementia including depression (8), and cardiovascular risk factors (9). Physical activity not only modifies multiple risk factors but it has direct benefits for brain health and cognition.

To bring about risk reduction, there needs to be long-lasting behavioural change in multiple areas. Achieving this requires using techniques such as goal setting, decreasing barriers to change, improving self-monitoring, having access to information, and maintaining motivation (10, 11). Therefore, this RCT investigates whether lifestyle management programs that offer not only health promoting information, but also practical behaviour change techniques which can be implemented in daily life can reduce dementia risk.

Recruitment in general practice setting

Primary care is an ideal setting for the implementation of the current program because it is where adults with high risk of developing dementia are identified and early intervention and treatment are provided (12). Assessment of cardiovascular risk factors is common in primary care, as is advice about physical activity and diet. General practitioners (GP) commonly screen for diabetes and increasingly identify depression. GPs are often the first point of contact for patients who are worried that they may have dementia (13).

Although there has been one study conducted in primary care setting with elderly participants (70-78 years old) addressing cardiovascular risk factors (14), the current program is the first of its kind to provide interventions to adults (18 years and above) at the primary care setting, addressing both cardiovascular and lifestyle risk factors of dementia.

Methods and analysis

Study setting and design

This project is a 6-12 week, pragmatic single-blind randomised controlled trial that is designed to assist participants develop and maintain a healthy lifestyle, as well as manage

chronic diseases. The study evaluates the implementation of an evidence-based dementia risk reduction program that we developed and have evaluated previously on volunteers (15) and which has now been adapted for primary care (BBL-GP). The primary care setting in which the study is held already conducted a lifestyle management program (LMP) aimed at helping to manage chronic disease and maintaining a healthy lifestyle. The LMP program was initially developed to consist of 12 sessions over 12 weeks. However, its format was changed prior to this trial to have 12 sessions over 6 weeks. This decision was made by the clinic which provides this program in order for the program to be offered 4 times a year. The current LMP program was chosen as a comparison condition for feasibility and to enable evaluation of an existing program for dementia and cardiovascular risk reduction. The efficacy of the existing program had not previously been evaluated.

The existing LMP program included 6 weeks of face-to-face group education sessions. The BBL-GP program included 12 weeks of individually tailored online education sessions with one hour face-to-face individual sessions with a dietitian and an exercise physiologist. The BBL-GP and LMP are being compared to an active control group receiving weekly email with links to health information. The study is being conducted in Canberra, Australian Capital Territory, Australia. The trial has been designed and is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) statements for non-pharmaceutical (16) and pragmatic (17) trials and will be reported according to the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines (18).

Participants

Participants are being recruited from the National Health Co-op (NHC), the largest bulk billing general practice organisation in Canberra comprising of eight clinics. Bulk Billing is a payment option where the doctor bills directly the universal health insurance system (Medicare) in Australia for a medical service that the patients receive. Invitation emails have

been sent to all members excluding members who are inactive (those who did not renew their memberships), those aged less than 18 years, or without email addresses. Posters at the clinics are also being used for the recruitment. Potential participants who express their interest by contacting the LMP coordinator at the NHC or registering on the NHC's website are assessed against the inclusion and exclusion criteria. These are the types of adults who a GP would refer to a dementia risk reduction trial in 'real life' and on whom we are aiming to evaluate our intervention in a naturalistic context. In addition, risk factors for dementia exert their influence over decades and thus the earlier one decreases their risk exposure, the more impact it is likely to have over their lifespan. Therefore, this intervention program is open to anyone aged 18 and older. If criteria are met, information sheets and consent forms are sent to potential participants. Upon return of consent forms via email, each participant is officially registered to the study and allocated a unique identity numbers as well as an online account.

Inclusion criteria

A naturalistic approach is used in recruitment and the study inclusion criteria being used for this study are those already used by the NHC to refer patients to the LMP program (prior to this research project). The inclusion criteria is pragmatic as the practice already had criteria for referral to their LMP and in developing the protocol, it became clear that introducing a second set of inclusion criteria would make implementation difficult and reduce participant numbers. We therefore decided to use the principle that if a GP would refer the patient to the LMP then they would be eligible for the trial. This is a pragmatic feature of the current trial that significantly differs from our original BBL trial. We aimed to optimize the seamlessness of the intervention in primary care and utilize existing referral pathways to increase the probability that the intervention is conducted in a manner that could lead to implementation in real life. Participants must be aged 18 years and over, reside in the Australian Capital Territory, be current financial members of the NHC, have access to a computer and internet

connection at home, be fluent in English, Australian permanent residents or citizens (for bulk billing eligibility), and must be the only person in their household who is taking part in this study to prevent being randomly assigned to different groups and sharing information about their interventions with each other received. To be eligible for the study, participants are also required to have a chronic health condition (high blood pressure, heart disease, type 2 diabetes or 'pre-diabetes', osteoporosis, osteoarthritis, polycystic ovary syndrome (PCOS), kidney or liver disease, and depression/anxiety) or be overweight or obese (BMI>25). They are also required to agree to commit 1-2 hours a week to complete the program and be interested in obtaining advice on improving their lifestyle to reduce the risk of or better manage chronic disease. Participants are required to complete online assessments and attend NHC at baseline and 18, 36, and 62 weeks after commencement of the intervention for medical and cognitive assessments.

Exclusion criteria

Participants are not eligible to enrol in the trial if they have significant and unstable medical and psychiatric conditions that would prevent participation in the trial. They are also ineligible if they have sensory deficits or mobility limitations that would prevent or substantially restrict the delivery of the assessment or intervention, have cognitive impairment, or are pregnant.

Sample size calculations

Sample size calculations were estimated using G*Power (version 3.1.9.2; http://www.gpower.hhu.de/en.html) and have been based on medium effect size as observed in the previous Body Brain Life project with same primary outcome (19). To detect a medium effect (0.5 standard deviation (SD)) in a 3-group design (1:1:1), 4 measurements with a 5% risk of type 1 error (α) and 80% power, a total sample size of

159 persons is required. To account for a 33% attrition (based on previous lifestyle modification program by NHC using the same inclusion and exclusion criteria and targeting same age group), a baseline sample of 240 is being recruited (80 in BBL-GP group, 80 in LMP group and 80 in control group).

Assessments

Participants who meet all inclusion and no exclusion criteria are invited to complete online surveys and visit NHC for the baseline evaluation, and for week 18, 36, and 62 follow ups. Immediate follow up is also conducted online at week 7 for LMP, and week 13 for BBL-GP and control groups. Table 1 summarizes the assessment measures and schedule.

Screening measures and covariate

In addition to the above inclusion and exclusion criteria, further screening measures are conducted to ensure that participants are capable of taking part in the study. The Adult Pre-exercise Screening System (APSS) (20) is used at the baseline assessment to identify individuals with acute/high risk conditions, or who may be at higher risk of an adverse event during exercise. To screen for any cognitive impairment (<25), the Mini-Mental State Examination (MMSE) (21) is administered to participants aged 60 and older.

Health efficacy and motivation for healthiness subscales from the Multidimensional Health Questionnaire (MHQ) (22) is used to measure the extent to which people believe they have the ability, capability, skills and talents to take care of their own physical health, and to measure people's motivation to keep in good physical health.

Primary outcome

The primary outcome is one's exposure profile to demonstrated risk factors for Alzheimer's disease. It is measured with a modified version of the Australian National University

Alzheimer's Disease Risk Index – Short form (ANU-ADRI – SF) (23). The ANU-ADRI-SF is comprised of validated scales assessing 15 individual risk and protective factors for Alzheimer's disease and dementia. Intra class correlation coefficients suggested that the reliability of the ANU-ADRI-SF compared to the original ANU-ADRI were moderate to strong (0.77 to 0.99) and statistically significant ($p<.001$) except for cognitive activity. Therefore, for the assessment of engagement in cognitive activities levels only, items from the original ANU-ADRI (19, 24) are used in place of those from the ANU-ADRI-SF due to limitations of the latter.

Secondary outcomes

Secondary outcomes include cognitive function, physical activity level, depressive symptoms, cost of interventions, diet and sleep quality. They are measured as follows: cognitive function is assessed with processing speed, task switching and executive function using Trails A and B, and the Digit Symbol Modalities Test (DSMT). These tests were chosen because the executive function is the most sensitive cognitive domain to physical activity interventions (25) and a decline in processing speed is associated with cardiovascular risk factors (26). Both Trails and DSMT have been used widely and have been reported to have good reliability and validity (27-30). Moderate-vigorous Physical Activity (MVPA) is a continuous measure of activity that registers three or more Metabolic Equivalents (METs) for 10 minutes or longer on an ActiGraph Link activity monitor (http://actigraphcorp.com/products/actigraph-link/), which is worn for 7 days. Self-reported physical activity is also being recorded using the short form of IPAQ (31), which is part of the ANU-ADRI-SF. Reliability and validity of IPAQ has been tested and confirmed across 12 countries (31). Depression is being assessed with the Centre for Epidemiological Studies Depression (CES-D) Scale (32), which is also part of the ANU-ADRI. CES-D scale has a very high internal consistency and validity (33).

Health outcomes are assessed with the SF-12 health survey (34), Framingham coronary heart disease (CHD) risk score (35), and Australian type 2 diabetes risk assessment tool (AUSDRISK) (36) to enable cost effectiveness evaluation of the two health promotion interventions. SF-12 measures both physical and mental health status and has acceptable validity and reliability (37, 38). Framingham CHD is a validated tool to assess cardiovascular diseases (39) and AUSDRISK is a diabetes risk assessment tool based on demographic, lifestyle and simple anthropometric measures (36).

Dietary quality is assessed with a food-based diet quality index, the Australian Recommended Food Score (ARFS) (40). The ARFS is aligned with Australian Dietary Guidelines (41) and the Australian Guide to Healthy Eating (42) recommendations. The ARFS total ranges from 0 to 73 and includes eight subscales: vegetables (0 to 21), fruit (0 to 12), protein (0 to 7), vegetarian alternatives (0 to 6), grains (0 to 13), dairy (0 to 11), water (0 to 1), sauces and condiments (0 to 2). Higher scores indicate greater compliance with the Australian Dietary Guidelines and therefore better diet quality. The ARFS has demonstrated good validity and reproducibility (40).

Lastly, the Pittsburgh Sleep Quality Index (PSQI) (43) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. PSQI reports great test-retest reliability (0.87) and high correlations with sleep log data (44).

Randomization

Upon completion of the baseline assessment, participants are randomly allocated into one of the three groups (see Table 2 and Figure 1). The allocation sequence is computer generated

by an independent researcher and is not known to the study team at the time of enrolment and baseline assessment. A permuted block randomization sequence comprising block sizes of 6 stratified by gender and age group (18-49 vs 50+) is used. The project manager who is not involved with conducting assessments assigns the participants into groups according to the generated sequence and notifies participants of their group allocation via email.

Interventions

Group 1: Body Brain Life – General Practice (BBL-GP)

BBL-GP is an intervention package that builds on our dementia prevention research programs. This includes an online dementia risk reduction program called the Body Brain Life (BBL; Trial ID: ACTRN12612000147886) (15, 45) and the Fitness for the Ageing Brain Study (FABS; Trial ID: ACTRN 12609000755235) (46, 47). Contents for the BBL-GP online modules have been revised after extensive consumer evaluation by members of the Alzheimer's Australia Consumer Dementia Research Network as well as members of the public and from participant feedback after the previous trial. The physical activity program has also been modified for a younger age-group to 18 years and older as previous programs targeted middle aged and older adults. The Actigraph device was introduced to measure the objective amount and intensity of physical activity. This revised program (Body Brain Life – Fit) was piloted with the general public (Trial ID: ACTRN12615000822583).

Participants in the BBL-GP group are required to complete 8 modules (dementia literacy, risk factors, physical activity, nutrition, health, cognitive activity, social activity and mood) delivered online. Prior to commencing online modules, participants in the BBL-GP group also receive an individually tailored plan/program for both dietary and physical activity interventions developed and delivered by a dietitian and an exercise physiologist, respectively during a face-to-face assessment. This is to ensure the dietary prescription and level of

physical activity are suitable and tailored to individual participants.

Physical activity session

The session duration and frequency of the physical activity (PA) program varies between participants based on baseline physical activity levels and individual tailoring. An exercise physiologist designs an individual program for the participant, delivers this in a face-to-face workshop and monitors the physical activity program via the returned diaries and telephone monitoring. For those not doing any regular PA at baseline, the target is 150 minutes/week moderate intensity PA, with moderate intensity defined as a score of 10-12 on the Borg Rating of Perceived Exertion scale (RPE) (48). For those who are doing regular PA but for less than 100 minutes/week, an additional 100 minutes/week is prescribed, and for those meeting the target, an additional 50 minutes/week is prescribed. Printed material guiding participants to increase their activity level with worksheets are also provided. A diary in the format of a calendar returned monthly for 24 weeks is used to record PA and RPE to assess PA and intensity adherence. Participants may develop a medical problem or undergo treatment that can make exercising difficult or impossible. If this happens, prescribed amount of exercise is reviewed and re-prescribed, or stopped.

Dietary session

Participants at baseline who had unintentional weight loss of 5 kg or weight gain of 5 kg over the previous six months were seen by the dietitian. Furthermore, participants whose diets at baseline scored low on one or more of the subscales of the (ARFS) (vegetables <14, fruit <8, protein <4, grains <9, dairy <8, water <1) (40), were also seen by the dietitian. Dietary counselling was provided by a trained dietitian and overseen by the coordinating dietitian. During the one hour face-to-face counselling session, participants received individually tailored dietary advice and printed material explaining the diet in detail.

Follow ups

Participants in the BBL-GP group are monitored through phone calls at week 4, 12 (14 for PA) and week 20 by the dietitian and exercise physiologist to monitor the progress and for reassurance. In addition, they receive a general booster session at 12 months with a phone call and a mailed-out booklet summarising materials from the online modules. They are being asked to continue being active and follow a healthy eating plan after completion of the intervention.

Online modules

Once participants in the BBL-GP group have received face-to-face PA and dietary counselling sessions, they are asked to log on to the trial website and complete one module per week, each taking approximately 30-40 minutes. The 12-week program is detailed in Table 3. The first 8 weeks include the completion of 8 educational and individually tailored behaviour change modules. In the remaining 4 weeks, participants undertake online activities focused on goal monitoring and revision of the modules materials. Tailoring of the six behaviour change modules (weeks 3-8) is conducted using an automated algorithm that presents content on the basis of whether or not the participant has a relevant risk factor, as well as on the basis of their responses to several questions measuring psychological determinants of behaviour. These questions are presented at the beginning of each of the behaviour change modules. For instance, a person who is classified as having a poor diet (e.g. lack of fish intake) on the basis of their responses on the ANU-ADRI, and who does not regard himself/herself as a role model to others with respect to their diet habits will not be presented with information focusing on becoming a role model to others.

The program is built in such a way that participants are only able to access the relevant component of the intervention at a given time. The modules become active, 1 per week, on the same day for the first 8 weeks. Participants are unable to access a newly activated module before completing the previously scheduled module. Each week,

participants receive a notification email on the same day of the week alerting them when a new module has become active and a list of already activated modules that they have either not started or completed. Participants who are late completing modules will be followed up with an email from the project manager to identify if there is a reason (e.g. holidays, illness, work commitments) preventing their participation, and encouraging them to continue with the study. Compliance is recorded for each module if they are completed on time, delayed or not completed.

Group 2: Lifestyle Modification Program (LMP)

The lifestyle modification program (LMP), developed by NHC, is designed to provide individuals with tools to help manage chronic disease and maintain a healthy lifestyle. LMP is a six- week group program provided by various health professionals (dietitian, exercise physiologist, nurse practitioner, psychologist, pharmacist and sleep physician) providing information on basic nutrition, meal planning, physical activity, health conditions, motivation and goals, medications, and sleep. Every week, 2 sessions are provided on the same day with each session lasting an hour. The course is currently run by the NHC for their patients to assist them in improving their lifestyle and management of chronic disease so it is a pragmatic real-life comparison condition. Attendance is recorded for compliance and motivation checking. Although the LMP is a free nationally recognized program that is designed to provide individuals with tools to help manage chronic disease and maintain a healthy lifestyle, evaluation of the program has not been carried out as yet. The attendance is recorded each week for a fidelity test.

Group 3: Active control/Email only

The active control group or email only group proceed with their normal activities and access health services as required over the trial period. Participants in this group also receive weekly

emails containing links to various websites providing information on lifestyle risk factors and disease management for a duration of 12 weeks. The weekly emails contain several links, and participants are encouraged to spend approximately an hour each week browsing through the material. The material is generally organized around the same themes as the ones included in the BBL-GP program. An effort has been made to include links to relevant information and educational material, but that otherwise does not include the use of identifiable behaviour-change techniques which are the 'active ingredient' of the BBL-GP program. In addition, other than providing participants with the weekly emails, no further contact is made with the participants in this group, such as reminders and prompts that are provided to the BBL-GP group.

Masking

To prevent performance bias, research staff conducting the assessments remain masked to participants' group allocation. The contact person for participants' website queries, access issues, and technical difficulties is independent of all baseline assessment data. All participants are informed that they are being randomly allocated to one of three study groups and that one group may be more effective than others. They are also notified at the start of the study that one of these groups involves face-to-face group sessions which require them to travel to NHC head office. Hence, the research team members who recruit participants, conduct individual diet and physical activity sessions, and professionals who are involved in the LMP are naturally able to tell which group they have been allocated to. Nurses who conduct baseline and follow-up assessments are however masked to group allocation.

Data management and monitoring

A trial management committee is formed by the research team members (chief and co-investigators). Nursing staffs from NHC and research assistants collect, clean and send the study data to the committee on a weekly basis. Most data are automatically entered into excel

files and other data are double-entered to SPSS files to prevent data entry errors. Data management is then handled independently from the researchers who interpret the data. All data are stored electronically and in an independent spreadsheet and SPSS data file, which is only accessible by the researchers involved in this study.

An independent Data Monitoring Committee (DMC) is established independently from the research team who are involved with collecting and managing data. The DMC will provide an independent oversight of the trial and will review general conduct of the trial and study data for participant safety. The DMC is comprised of independent, multidisciplinary experts in dementia research who will make recommendations regarding the continuation, modification or termination of the trial.

Adverse events (minor and serious) will be monitored throughout the trial by the research team and any adverse events will be reported to the trial Data Monitoring Committee. For this trial, an adverse event is defined as an unwanted and usually harmful outcome (e.g. physical injuries). The event may or may not be related to the intervention, but it occurs while the person is participating in the intervention, that is, while they are undertaking physical activities individually prescribed by the exercise physiologist.

There are no formal interim analyses planned, as it is not expected that adverse events will be differentially related to the interventions.

Statistical analyses

Statistical analyses will be based on an intention-to-treat approach. As applied in the previous BBL project (15), multiple imputation and mixed models will be applied to analyse data. We hypothesise that the effectiveness of the intervention programs will be in the following order: BBL-GP> LMP > active control. The hypothesis that BBL-GP will be more effective than LMP is based on research showing that a tailored program is better than a one size fits all

group program in most cases (49). This is also based on the previous BBL project where those in BBL groups improved more than those in the control group. We will also adjust for compliance in completing the online modules and following recommendations provided by the dietitian and exercise physiologist (for BBL-GP group), or for attendance to weekly group sessions (for LMP group).

Ethics and trial registration

The Human Research Ethics Committee at the Australian National University has approved the study protocols and procedures (protocol #2016/157). This project has also been registered at the Australian New Zealand Clinical Trials Registry (ACTRN: 12616000868482).

Adverse events

This study evaluates lifestyle intervention programs to reduce risk factors for AD. The target population is adults in a primary care setting who have some of the known risk factors for dementia, but are at the time of the intervention, healthy and free of any dementia-related symptoms. We do not anticipate that participants will be placed at a greater risk than that associated with self-driven educational activities over the Internet. An adverse event where a participant can get hurt during prescribed exercise can occur. To prevent this, we screen participants using APSS at the baseline assessment to identify individuals with acute/high risk conditions for exercise. In addition, the exercise physiologist individually tailors prescribed exercise to minimise risk of injury. Medical assessments are done by the participants' usual nurses and doctors and if any abnormality is detected in their results, they are required to discuss these abnormalities with participants as usual. To address issues of potential fatigue, the assessments have been kept to a minimum length. In addition, all online and face-to-face sessions are designed in an interactive way and are limited to 1-hour sessions (LMP has 2 themed sessions per week and has a break between sessions). As mentioned

above, all online modules are delivered in an individually tailored fashion to maximize relevance for each individual.

Dissemination plan

Positive, neutral and negative results of the trial will be submitted to international peer-reviewed journals. In addition, results will be presented at national and international conferences relevant to the subject matters. Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors and depends on personal involvement.

Discussion

The project is currently under way as an evaluation of the efficacy of health promotion interventions in adults with risk factors for dementia. The program aims to reduce cardiometabolic risk and promote behaviours shown to protect against dementia. The trial, recruiting from a primary care setting has generated considerable interest, and to date, approximately half of the total target sample has been assessed and randomised into the intervention groups. We anticipate that all data collection will be completed by December 2018. The results of the study are likely to form an evidence base for the feasibility of dementia risk reduction campaigns to lead to lifestyle changes and the reduction of dementia risk factors at the population level. This trial will also support the feasibility of such interventions being applied in primary care settings. Successful outcomes of the current trial may lead to significant public health impact and benefits once the intervention is made available at the population level pending positive results.

Conclusion

Interventions to reduce risk of developing dementia are needed as a cure is not available. This project compares three different approaches to promote healthy lifestyles and to reduce risk of developing dementia applied in a primary care setting. This unique trial demonstrates real

life application of dementia risk reduction intervention rather than more controlled but less ecologically valid interventions typically tested in a research setting.

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Authors' contributions

KJA conceived the study and built relationship with NHC. KJA, NC, SK developed the overall design of the intervention. NL and KC designed the implementation of the physical activity related intervention. CD and KJA designed the statistical analysis plan for the protocol. DP and GR contributed knowledge of primary care setting and advised on implementing the intervention in a GP clinic. ST designed the implementation of the dietary intervention. NC and SK managed the implementation of the online component in the dedicated web portal. SK, MM, ST, KC, NL, GR, DP, IM, NC and KJA wrote the study protocol and critically reviewed the manuscript.

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Competing interests

None declared.

Table 1. Assessment measures at the baseline and follow up evaluations

Assessment measure	Baseline	Immediate follow up (Week 7 for LMP and week 13 for BBL-GP and active control group)	Week 18	Week 36	Week 62
Screening					
APSS	√				
MMSE (if 60+)	√				
Questionnaires					
ANU-ADRI	√	√	√	√	√
Sleep Quality Assessment	√	√	√	√	√
Diet questionnaire	√	√	√	√	√
SF-12	√	√	√	√	√
MHQ	√				

Cognitive measures					
Trails A + B	√		√	√	√
Digit symbol matching	√		√	√	√
Physical and medical evaluation (by doctors and nurses)					
MVPA	√		√	√	√
Blood pressure	√		√	√	√
Height, cm	√				
Weight, kg	√		√	√	√
Waist and hip, cm	√		√	√	√
Body Composition	√		√	√	√
Framingham coronary heart	√		√	√	√
AUSDRISK	√		√	√	√

Note: ANU-ADRI: Australian National University – Alzheimer's Disease Risk Index; SF-12: SF-12 Health Survey; APSS: Adults Pre-exercise Screening System; MHQ: Multidimensional Health Questionnaire; MMSE: Mini-Mental State Examination; MVPA: Moderate-vigorous Physical Activity; AUSDRISK: Australian type 2 diabetes risk assessment tool.

Table 2: Comparison of intervention programs

	LMP	BBL-GP	Active control
Previously applied:	Yes, in primary care. Evaluation has not been carried out.	Yes, with member of general public with concern about developing dementia. Never been tested in primary care setting	Yes, with member of general public with concern about developing dementia.
Duration	6 weeks	12 weeks	12 weeks
Frequency	Weekly	Weekly	Weekly
Number of sessions	12 sessions	8 online sessions, 1 session with dietitian, 1 session with exercise physiologist	12 emails
Format	Face to face group sessions	1 hour individual session with dietitian, 1 hour individual session with exercise physiologist, 8 online modules	Weekly emails containing health information

Table 3: Description of the 12-week online program delivered through the Body Brain Life – GP (BBL-GP) website

Week	Activity	Description
1	Module 1: Dementia literacy	The first module focuses on providing participants with general information about dementia including types, causes, prevalence, social and economic impact, symptoms, brain function, treatment, risk factors (modifiable and non-modifiable), and prevention. This module serves as an introduction to the subsequent modules.
2	Module 2: Dementia risk factors	This module is aimed at building awareness and knowledge of the various health conditions associated with an increased risk of Alzheimer's dementia (AD). Specifically, this module provides details regarding the association between AD and several medical conditions (abnormal weight, high cholesterol, diabetes, hypertension, and depression), as well as lifestyle factors (alcohol use and smoking, physical activity, nutrition, stroke and head injury, mental health, social and cognitive engagement). The module also briefly covers non-modifiable risk factors that contribute to AD, including age and genetics.
3	Module 3: BBL FIT - physical activity	This is a theory-driven, individually-tailored module that aims to help participants incorporate regular physical activity into their daily routine and reduce sedentary behaviour by focusing on increasing endurance, strength, balance, and flexibility. This module targets several barriers to engaging in physical activity, such as increasing motivation, creating opportunities to exercise, and developing a social network that supports physical activity goals.
4	Module 4: BBL nutrition	This is a theory-driven, individually-tailored module aimed at helping people develop healthy dietary habits. This module targets the risk associated with abnormal weight, and the protective effects associated with fish intake and other dietary components.
5	Module 5: BBL health self-management	This is a theory-driven, individually-tailored module aimed at increasing participants' health monitoring and management of chronic health conditions. Because several chronic health conditions such as hypertension, diabetes and high cholesterol, are associated with increased risk for dementia, prevention and appropriate management of such conditions is also likely to be protective against dementia.
6	Module 6: BBL Think – cognitive engagement	This is a theory-driven, individually-tailored module aimed at increasing participants' levels of engagement with mentally stimulating activities such as reading, doing crosswords and visiting museums, which is a protective factor against dementia.

7	Module 7: BBL connect – social engagement	This is a theory-driven, individually-tailored module aimed at increasing participants' levels of social engagement. The module targets the risk factor for dementia associated with loneliness and depression, and the protective effects of regular social engagement.
8	Module 8: BBL mood	This is a theory-driven, individually-tailored module that aims to help participants monitor and maintain good mental health. The module targets risk factors for dementia associated with mental health and mood, focusing on depression and anxiety. Information is provided on symptoms, types, treatment, and tips for managing mood.
9	9 to 12 Self-guided online activities	During these sessions, participants are encouraged to engage in a range of online activities for 1 h, including accessing the many tools they have accumulated during the first 7 weeks. Examples include the goal-setting tool, behaviour-monitoring tool, unhelpful thoughts monitoring tool, videos, and so on.

Figure 1. Study Flowchart

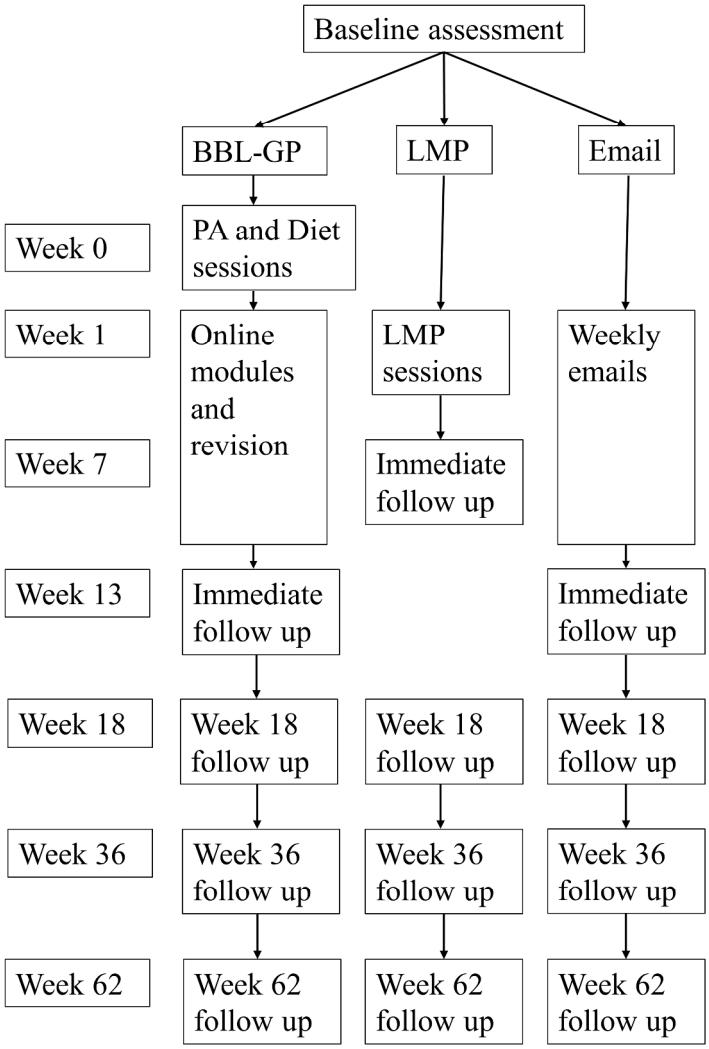

Figure 1: Study Flowchart

225x300mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 18
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-8
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14-17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 27-29

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____13_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____13_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____13_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____17-18_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____17_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ 16-17_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15-17, 18-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle Modification Program to decrease dementia risk exposure in a primary care setting

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Medical education and training
Keywords:	RCT, Dementia < NEUROLOGY, Lifestyle change, online, Australia, General practice

Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle Modification Program to decrease dementia risk exposure in a primary care setting

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Abstract

Introduction: It has been estimated that a 10% to 25% reduction in seven key risk factors could potentially prevent 1.1 to 3.0 million Alzheimer's disease cases globally. In addition, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impact, effective preventative interventions would likely have more extensive benefits. The current study evaluates in primary care a multi-domain risk reduction intervention targeting adults with high risk of developing dementia.

Methods and analysis: A randomised controlled trial (RCT) is being conducted to evaluate three intervention programs using a pragmatic approach suitable to the clinic: 1) A 12-week online and face-to-face dementia risk reduction intervention (BBL-GP); 2) A 6-week face-to-face group lifestyle modification program (LMP); and 3) A 12-week email-only program providing general health information. We aim to recruit 240 participants, aged 18 and over, to undergo a comprehensive cognitive and physical assessment at baseline and follow ups (post intervention, 18, 36 and 62 weeks). The primary outcome is dementia risk measured with the modified version of the ANU-ADRI-Short Form. Secondary outcomes are cognitive function measured with Trail A and B, and the DSMT; physical activity with Moderate-Vigorous Physical Activity and the IPAQ; depression with the CES-D; cost evaluation with the SF-12 health survey, Framingham CHD, and AUSDRISK; diet quality with the ARFS; and sleep quality with the PSQI.

Ethics and dissemination: This RCT is a novel pragmatic intervention applied in a primary care setting to reduce the dementia risk exposure in adults at high risk. If successful, BBL-GP and LMP will provide a versatile, evidence-based package that can be easily and quickly rolled-out to other primary care settings and which can be scaled up at relatively low cost compared to other strategies involving intensive interventions.

Trial registration: Reg. no. ACTRN12616000868482

Keywords: RCT, dementia, lifestyle change, online, physical activity, diet, cardiovascular risk factors, Australia, general practice, primary care.

Strengths and limitations of this study

- BBL-GP program has been built on our dementia prevention research program which has been shown to reduce cognitive decline in older adults at-risk of dementia.
- This pragmatic trial evaluates a multi-domain risk reduction intervention in primary care targeting adults at increased risk of developing dementia.
- A naturalistic approach ensures the program can be adapted efficiently in primary care settings if proven effective.
- We are aware that most of our outcomes are self-reported and therefore can be subjective. Accordingly, we will interpret data conservatively.

Introduction

No cure is available for Alzheimer's disease and other types of dementia. However, it is estimated that an achievable 10% to 25% reduction in seven key risk factors could prevent 1.1 to 3.0 million Alzheimer's disease (AD) cases internationally (1). It is also estimated that if each of seven risk factors was to be reduced by 5%, 10%, 15% and 20% per decade, dementia prevalence would be reduced by between 1.6 and 7.2% in 2020, 3.3-14.9% in 2030, 4-9 – 22.8% in 2040 and 6.6-30.7% in 2050 (2). Furthermore, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impacts, effective preventative interventions would likely have additional benefits.

Increasingly and to afford a greater chance of producing detectable changes during study timeframes, the dementia research community has focused on multi-domain interventions that address multiple risk factors simultaneously (3). Among individuals with high risk factor burden, cognitive decline can be reduced (and possibly reversed) as a result of cardiovascular risk reduction and increase in activities that stimulate and protect the brain including cognitive, social and physical activity and an appropriate diet (4). Alzheimer's disease and cardiovascular disease share cardiometabolic and lifestyle risk factors and cardiovascular risk reduction can be achieved by smoking cessation, increasing physical activities, adopting a healthy diet, reducing abnormally high blood pressure and cholesterol in mid-life, and managing major depression, overweight/obesity in mid-life and diabetes if present (5). Altogether, the literature supports the view that multi-domain interventions aimed at reducing cardiometabolic risk and promoting behaviours shown to protect against dementia will contribute to preventing cognitive decline, reduce overall risk of AD, and lower depressive symptoms.

Insufficient physical activity is the risk factor with the most evidence to support its role as a treatment for Mild Cognitive Impairment (MCI) (6) and more generally cognitive

decline (7). Physical activity has also been shown in RCTs to benefit several other risk factors for dementia including depression (8), and cardiovascular risk factors (9). Physical activity not only modifies multiple risk factors but it has direct benefits for brain health and cognition.

To bring about risk reduction, there needs to be long-lasting behavioural change in multiple areas. Achieving this requires using techniques such as goal setting, decreasing barriers to change, improving self-monitoring, having access to information, and maintaining motivation (10, 11). Therefore, this RCT investigates whether lifestyle management programs that offer not only health promoting information, but also practical behaviour change techniques which can be implemented in daily life can reduce dementia risk.

Recruitment in general practice setting

Primary care is an ideal setting for the implementation of the current program because it is where adults with high risk of developing dementia are identified and early intervention and treatment are provided (12). Assessment of cardiovascular risk factors is common in primary care, as is advice about physical activity and diet. General practitioners (GP) commonly screen for diabetes and increasingly identify depression. GPs are often the first point of contact for patients who are worried that they may have dementia (13).

Although there has been one study conducted in primary care setting with elderly participants (70-78 years old) addressing cardiovascular risk factors (14), the current program is the first of its kind to provide interventions to adults (18 years and above) at the primary care setting, addressing both cardiovascular and lifestyle risk factors of dementia.

Methods and analysis

Study setting and design

This project is a 6-12 week, pragmatic single-blind randomised controlled trial that is designed to assist participants develop and maintain a healthy lifestyle, as well as manage

chronic diseases. The study evaluates the implementation of an evidence-based dementia risk reduction program that we developed and have evaluated previously on volunteers (15) and which has now been adapted for primary care (BBL-GP). The primary care setting in which the study is held already conducted a lifestyle management program (LMP) aimed at helping to manage chronic disease and maintaining a healthy lifestyle. The LMP program was initially developed to consist of 12 sessions over 12 weeks. However, its format was changed prior to this trial to have 12 sessions over 6 weeks. This decision was made by the clinic which provides this program in order for the program to be offered 4 times a year. The current LMP program was chosen as a comparison condition for feasibility and to enable evaluation of an existing program for dementia and cardiovascular risk reduction. The efficacy of the existing LMP program had not previously been evaluated.

The existing LMP program included 6 weeks of face-to-face group education sessions. The BBL-GP program included 12 weeks of individually tailored online education sessions with one hour face-to-face individual sessions with a dietitian and an exercise physiologist. The BBL-GP and LMP are being compared to an active control group receiving weekly email with links to health information. The study is being conducted in Canberra, Australian Capital Territory, Australia. The trial has been designed and is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) statements for non-pharmaceutical (16) and pragmatic (17) trials and is reported according to the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines (18).

Participants

Participants are being recruited from the National Health Co-op (NHC), the largest bulk billing general practice organisation in Canberra comprising of eight clinics. Bulk Billing is a payment option where the doctor bills directly the universal health insurance system (Medicare) in Australia for a medical service that the patients receive. Invitation emails have

been sent to all members excluding members who are inactive (those who did not renew their memberships), those aged less than 18 years, or without email addresses. Posters at the clinics are also being used for the recruitment. Potential participants who express their interest by contacting the LMP coordinator at the NHC or registering on the NHC's website are assessed against the inclusion and exclusion criteria. These are the types of adults who a GP would refer to a dementia risk reduction trial in 'real life' and on whom we are aiming to evaluate our intervention in a naturalistic context. In addition, risk factors for dementia exert their influence over decades and thus the earlier one decreases their risk exposure, the more impact it is likely to have over their lifespan. Therefore, this intervention program is open to anyone aged 18 and older. If criteria are met, information sheets and consent forms are sent to potential participants. Upon return of consent forms via email, each participant is officially registered to the study and allocated a unique identity numbers as well as an online account. Recruitment began in July 2016 for the duration of 13 months.

Inclusion criteria

A naturalistic approach is used in recruitment and the study inclusion criteria being used for this study are those already used by the NHC to refer patients to the LMP program (prior to this research project). The inclusion criteria is pragmatic as the practice already had criteria for referral to their LMP and in developing the protocol, it became clear that introducing a second set of inclusion criteria would make implementation difficult and reduce participant numbers. We therefore decided to use the principle that if a GP would refer the patient to the LMP then they would be eligible for the trial. This is a pragmatic feature of the current trial that significantly differs from our original BBL trial. We aimed to optimise the seamlessness of the intervention in primary care and utilise existing referral pathways to increase the probability that the intervention is conducted in a manner that could lead to implementation in real life. Participants must be aged 18 years and over, reside in the Australian Capital

Territory, be current financial members of the NHC, have access to a computer and internet connection at home, be fluent in English, Australian permanent residents or citizens (for bulk billing eligibility), and must be the only person in their household who is taking part in this study to prevent being randomly assigned to different groups and sharing information about their interventions with each other received. To be eligible for the study, participants are also required to have a chronic health condition (high blood pressure, heart disease, type 2 diabetes or 'pre-diabetes', osteoporosis, osteoarthritis, polycystic ovary syndrome (PCOS), kidney or liver disease, and depression/anxiety) or be overweight or obese (BMI>25). They are also required to agree to commit 1-2 hours a week to complete the program and be interested in obtaining advice on improving their lifestyle to reduce the risk of or better manage chronic disease. Participants are required to complete online assessments and attend NHC at baseline and 18, 36, and 62 weeks after commencement of the intervention for medical and cognitive assessments.

Exclusion criteria

Participants are not eligible to enrol in the trial if they have significant and unstable medical and psychiatric conditions that would prevent participation in the trial. They are also ineligible if they have sensory deficits or mobility limitations that would prevent or substantially restrict the delivery of the assessment or intervention, have cognitive impairment, or are pregnant. Those who have previously participated in the LMP were excluded from participation. However, those who may be/have been participating in other trials, unknown to authors, were not excluded.

Sample size calculations

Sample size calculations were estimated using G*Power (version 3.1.9.2; http://www.gpower.hhu.de/en.html) and have been based on medium effect size as

observed in the previous Body Brain Life project with same primary outcome (19). To detect a medium effect (0.5 standard deviation (SD)) in a 3-group design (1:1:1), 4 measurements with a 5% risk of type 1 error (α) and 80% power, a total sample size of 159 persons is required. To account for a 33% attrition (based on previous lifestyle modification program by NHC using the same inclusion and exclusion criteria and targeting same age group), a baseline sample of 240 is being recruited (80 in BBL-GP group, 80 in LMP group and 80 in control group).

Assessments

Participants who meet all inclusion and no exclusion criteria are invited to complete online surveys and visit NHC for the baseline evaluation, and for week 18, 36, and 62 follow ups. Immediate follow up is also conducted online at week 7 for LMP, and week 13 for BBL-GP and control groups. Table 1 summarises the assessment measures and schedule.

Screening measures and covariate

In addition to the above inclusion and exclusion criteria, further screening measures are conducted to ensure that participants are capable of taking part in the study. The Adult Pre-exercise Screening System (APSS) (20) is used at the baseline assessment to identify individuals with acute/high risk conditions, or who may be at higher risk of an adverse event during exercise. To screen for any cognitive impairment (<25), the Mini-Mental State Examination (MMSE) (21) is administered to participants aged 60 and older.

Health efficacy and motivation for healthiness subscales from the Multidimensional Health Questionnaire (MHQ) (22) is used to measure the extent to which people believe they have the ability, capability, skills and talents to take care of their own physical health, and to measure people's motivation to keep in good physical health.

Primary outcome

The primary outcome is one's exposure profile to demonstrated risk factors for Alzheimer's disease. It is measured with a modified version of the Australian National University Alzheimer's Disease Risk Index – Short form (ANU-ADRI – SF) (23). The ANU-ADRI-SF is comprised of validated scales assessing 15 individual risk and protective factors for Alzheimer's disease and dementia. Intra class correlation coefficients suggested that the reliability of the ANU-ADRI-SF compared to the original ANU-ADRI were moderate to strong (0.77 to 0.99) and statistically significant ($p<.001$) except for cognitive activity. Therefore, for the assessment of engagement in cognitive activities levels only, items from the original ANU-ADRI (19, 24) are used in place of those from the ANU-ADRI-SF due to limitations of the latter.

Secondary outcomes

Secondary outcomes include cognitive function, physical activity level, depressive symptoms, cost of interventions, diet and sleep quality. They are measured as follows: cognitive function is assessed with processing speed, task switching and executive function using Trails A and B, and the Digit Symbol Modalities Test (DSMT). These tests were chosen because the executive function is the most sensitive cognitive domain to physical activity interventions (25) and a decline in processing speed is associated with cardiovascular risk factors (26). Both Trails and DSMT have been used widely and have been reported to have good reliability and validity (27-30). Moderate-vigorous Physical Activity (MVPA) is a continuous measure of activity that registers three or more Metabolic Equivalents (METs) for 10 minutes or longer on an ActiGraph Link activity monitor (http://actigraphcorp.com/products/actigraph-link/), which is worn for 7 days. Self-reported physical activity is also being recorded using the short form of the International Physical Activity Questionnaire (IPAQ) (31), which is part of the ANU-ADRI-SF. Reliability and validity of IPAQ has been tested and confirmed across 12 countries (31). Depression is being

assessed with the Centre for Epidemiological Studies Depression (CES-D) Scale (32), which is also part of the ANU-ADRI. CES-D scale has a very high internal consistency and validity (33).

Health outcomes are assessed with the SF-12 health survey (34), Framingham Coronary Heart Disease (CHD) Risk score (35), and Australian type 2 diabetes risk assessment tool (AUSDRISK) (36) to enable cost effectiveness evaluation of the two health promotion interventions. SF-12 measures both physical and mental health status and has acceptable validity and reliability (37, 38). Framingham CHD is a validated tool to assess cardiovascular diseases (39) and AUSDRISK is a diabetes risk assessment tool based on demographic, lifestyle and simple anthropometric measures (36).

Dietary quality is assessed with a food-based diet quality index, the Australian Recommended Food Score (ARFS) (40). The ARFS is aligned with Australian Dietary Guidelines (41) and the Australian Guide to Healthy Eating (42) recommendations. The ARFS total ranges from 0 to 73 and includes eight subscales: vegetables (0 to 21), fruit (0 to 12), protein (0 to 7), vegetarian alternatives (0 to 6), grains (0 to 13), dairy (0 to 11), water (0 to 1), sauces and condiments (0 to 2). Higher scores indicate greater compliance with the Australian Dietary Guidelines and therefore better diet quality. The ARFS has demonstrated good validity and reproducibility (40).

Lastly, the Pittsburgh Sleep Quality Index (PSQI) (43) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates “poor” from “good” sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. PSQI reports great test-retest reliability (0.87) and high correlations with sleep log data (44).

Randomisation

Upon completion of the baseline assessment, participants are randomly allocated into one of the three groups (see Table 2 and Figure 1). The allocation sequence is computer generated by an independent researcher and is not known to the study team at the time of enrolment and baseline assessment. A permuted block randomisation sequence comprising block sizes of 6 stratified by gender and age group (18-49 vs 50+) is used. The project manager who is not involved with conducting assessments assigns the participants into groups according to the generated sequence and notifies participants of their group allocation via email.

Interventions

Group 1: Body Brain Life – General Practice (BBL-GP)

BBL-GP is an intervention package that builds on our dementia prevention research programs. This includes an online dementia risk reduction program called the Body Brain Life (BBL; Trial ID: ACTRN12612000147886) (15, 45) and the Fitness for the Ageing Brain Study (FABS; Trial ID: ACTRN 12609000755235) (46, 47). Contents for the BBL-GP online modules have been revised after extensive consumer evaluation by members of the Alzheimer's Australia Consumer Dementia Research Network as well as members of the public and from participant feedback after the previous trial. The physical activity program has also been modified for a younger age-group to 18 years and older as previous programs targeted middle aged and older adults. The Actigraph device was introduced to measure the objective amount and intensity of physical activity. This revised program (Body Brain Life – Fit) was piloted with the general public (Trial ID: ACTRN12615000822583; manuscript in preparation).

Participants in the BBL-GP group are required to complete 8 modules (dementia literacy, risk factors, physical activity, nutrition, health, cognitive activity, social activity and

mood) delivered online. Prior to commencing online modules, participants in the BBL-GP group also receive an individually tailored plan/program for both dietary and physical activity interventions developed and delivered by a dietitian and an exercise physiologist, respectively during a face-to-face assessment. This is to ensure the dietary prescription and level of physical activity are suitable and tailored to individual participants.

Physical activity session

The session duration and frequency of the physical activity (PA) program varies between participants based on baseline physical activity levels and individual tailoring. An exercise physiologist designs an individual program for the participant, delivers this in a face-to-face workshop and monitors the physical activity program via the returned diaries and telephone monitoring. For those not doing any regular PA at baseline, the target is 150 minutes/week moderate intensity PA, with moderate intensity defined as a score of 10-12 on the Borg Rating of Perceived Exertion scale (RPE) (48). For those who are doing regular PA but for less than 100 minutes/week, an additional 100 minutes/week is prescribed, and for those meeting the target, an additional 50 minutes/week is prescribed. Printed material guiding participants to increase their activity level with worksheets are also provided. A diary in the format of a calendar returned monthly for 24 weeks is used to record PA and RPE to assess PA and intensity adherence. Participants may develop a medical problem or undergo treatment that can make exercising difficult or impossible. If this happens, prescribed amount of exercise is reviewed and re-prescribed, or stopped.

Dietary session

Participants at baseline who had unintentional weight loss of 5 kg or weight gain of 5 kg over the previous six months were seen by the dietitian. Furthermore, participants whose diets at baseline scored low on one or more of the subscales of the (ARFS) (vegetables <14, fruit <8, protein <4, grains <9, dairy <8, water <1) (40), were also seen by the dietitian. Dietary

counselling was provided by a trained dietitian and overseen by the coordinating dietitian. During the one hour face-to-face counselling session, participants received individually tailored dietary advice and printed material explaining the diet in detail.

Follow ups

Participants in the BBL-GP group are monitored through phone calls at week 4, 12 (14 for PA) and week 20 by the dietitian and exercise physiologist to monitor the progress and for reassurance. In addition, they receive a general booster session at 12 months with a phone call and a mailed-out booklet summarising materials from the online modules. They are being asked to continue being active and follow a healthy eating plan after completion of the intervention.

Online modules

Once participants in the BBL-GP group have received face-to-face PA and dietary counselling sessions, they are asked to log on to the trial website and complete one module per week, each taking approximately 30-40 minutes. The 12-week program is detailed in Table 3. The first 8 weeks include the completion of 8 educational and individually tailored behaviour change modules. In the remaining 4 weeks, participants undertake online activities focused on goal monitoring and revision of the modules materials. Tailoring of the six behaviour change modules (weeks 3-8) is conducted using an automated algorithm that presents content on the basis of whether or not the participant has a relevant risk factor, as well as on the basis of their responses to several questions measuring psychological determinants of behaviour. These questions are presented at the beginning of each of the behaviour change modules. For instance, a person who is classified as having a poor diet (e.g. lack of fish intake) on the basis of their responses on the ANU-ADRI, and who does not regard himself/herself as a role model to others with respect to their diet habits is not presented with information focusing on becoming a role model to others.

The program is built in such a way that participants are only able to access the relevant component of the intervention at a given time. The modules become active, 1 per week, on the same day for the first 8 weeks. Participants are unable to access a newly activated module before completing the previously scheduled module. Each week, participants receive a notification email on the same day of the week alerting them when a new module has become active and a list of already activated modules that they have either not started or completed. Participants who are late completing modules will be followed up with an email from the project manager to identify if there is a reason (e.g. holidays, illness, work commitments) preventing their participation, and encouraging them to continue with the study. Compliance is recorded for each module if they are completed on time, delayed or not completed.

Group 2: Lifestyle Modification Program (LMP)

The lifestyle modification program (LMP), developed by NHC, is designed to provide individuals with tools to help manage chronic disease and maintain a healthy lifestyle. LMP is a six- week group program provided by various health professionals (dietitian, exercise physiologist, nurse practitioner, psychologist, pharmacist, and sleep physician) providing information on basic nutrition, meal planning, physical activity, health conditions, motivation and goals, medications, and sleep. Every week, 2 sessions are provided on the same day with each session lasting an hour. The course is currently run by the NHC for their patients to assist them in improving their lifestyle and management of chronic disease so it is a pragmatic real-life comparison condition. Attendance is recorded for compliance and motivation checking. Although the LMP is a free nationally recognised program that is designed to provide individuals with tools to help manage chronic disease and maintain a healthy lifestyle, evaluation of the program has not been carried out as yet. The attendance is recorded each week to examine intervention fidelity.

Group 3: Active control/Email only

The active control group or email only group proceed with their normal activities and access health services as required over the trial period. Participants in this group also receive weekly emails containing links to various websites providing information on lifestyle risk factors and disease management for a duration of 12 weeks. The weekly emails contain several links, and participants are encouraged to spend approximately an hour each week browsing through the material. The material is generally organised around the same themes as the ones included in the BBL-GP program. An effort has been made to include links to relevant information and educational material, but that otherwise does not include the use of identifiable behaviour-change techniques which are the 'active ingredient' of the BBL-GP program. In addition, other than providing participants with the weekly emails, no further contact is made with the participants in this group, such as reminders and prompts that are provided to the BBL-GP group. Participants in this group receive a face to face, 1 hour risk reduction workshop that provides the information contained in the BBL-GP intervention as a mean of debriefing at the end of the intervention.

Masking

To prevent performance bias, research staff conducting the assessments remain masked to participants' group allocation. The contact person for participants' website queries, access issues, and technical difficulties is independent of all baseline assessment data. All participants are informed that they are being randomly allocated to one of three study groups and that one group may be more effective than others. They are also notified at the start of the study that one of these groups involves face-to-face group sessions which require them to travel to NHC head office. Hence, the research team members who recruit participants, conduct individual diet and physical activity sessions, and professionals who are involved in the LMP are naturally able to tell which group they have been allocated to. Nurses who

conduct baseline and follow-up assessments are however masked to group allocation.

Data management and monitoring

A trial management committee is formed by the research team members (chief and co-investigators). Nursing staffs from NHC and research assistants collect, clean and send the study data to the committee on a weekly basis. Most data are automatically entered into excel files and other data are double-entered to SPSS files to prevent data entry errors. Data management is then handled independently from the researchers who interpret the data. All data are stored electronically and in an independent spreadsheet and SPSS data file, which is only accessible by the researchers involved in this study.

An independent Data Monitoring Committee (DMC) is established independently from the research team who are involved with collecting and managing data. The DMC provides an independent oversight of the trial and reviews general conduct of the trial and study data for participant safety. The DMC is comprised of independent, multidisciplinary experts in dementia research who makes recommendations regarding the continuation, modification or termination of the trial.

Adverse events (minor and serious) are monitored throughout the trial by the research team and any adverse events would be reported to the trial DMC. For this trial, an adverse event is defined as an unwanted and usually harmful outcome (e.g. physical injuries). The event may or may not be related to the intervention, but it occurs while the person is participating in the intervention, that is, while they are undertaking physical activities individually prescribed by the exercise physiologist.

There are no formal interim analyses planned, as it is not expected that adverse events would be differentially related to the interventions.

Statistical analyses

Statistical analyses will be based on an intention-to-treat approach. As applied in the previous

BBL project (15), multiple imputation and mixed models will be applied to analyse data. We hypothesise that the effectiveness of the intervention programs will be in the following order: BBL-GP> LMP > active control. The hypothesis that BBL-GP will be more effective than LMP is based on research showing that a tailored program is better than a one size fits all group program in most cases (49). This is also based on the previous BBL project where those in BBL groups improved more than those in the control group. We will also adjust for compliance in completing the online modules and following recommendations provided by the dietitian and exercise physiologist (for BBL-GP group), or for attendance to weekly group sessions (for LMP group).

Ethics and trial registration

The Human Research Ethics Committee at the Australian National University has approved the study protocols and procedures (protocol #2016/157). This project has also been registered at the Australian New Zealand Clinical Trials Registry (ACTRN: 12616000868482).

Adverse events

This study evaluates lifestyle intervention programs to reduce risk factors for AD. The target population is adults in a primary care setting who have some of the known risk factors for dementia, but are at the time of the intervention, healthy and free of any dementia-related symptoms. We do not anticipate that participants are placed at a greater risk than that associated with self-driven educational activities over the Internet. An adverse event where a participant can get hurt during prescribed exercise can occur. To prevent this, we screen participants using APSS at the baseline assessment to identify individuals with acute/high risk conditions for exercise. In addition, the exercise physiologist individually tailors prescribed exercise to minimise risk of injury. Medical assessments are done by the participants' usual nurses and doctors and if any abnormality is detected in their results, they

are required to discuss these abnormalities with participants as usual. To address issues of potential fatigue, the assessments have been kept to a minimum length. In addition, all online and face-to-face sessions are designed in an interactive way and are limited to 1-hour sessions (LMP has 2 themed sessions per week and has a break between sessions). As mentioned above, all online modules are delivered in an individually tailored fashion to maximise relevance for each individual.

Dissemination plan

Positive, neutral and negative results of the trial will be submitted to international peer-reviewed journals. In addition, results will be presented at national and international conferences relevant to the subject matters. Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors and depends on personal involvement.

Discussion

The project is currently under way as an evaluation of the efficacy of health promotion interventions in adults with risk factors for dementia. The program aims to reduce cardiometabolic risk and promote behaviours shown to protect against dementia. The trial, recruiting from a primary care setting has generated considerable interest, and to date, approximately half of the total target sample has been assessed and randomised into the intervention groups. We anticipate that all data collection will be completed by December 2018. The results of the study are likely to form an evidence base for the feasibility of dementia risk reduction campaigns to lead to lifestyle changes and the reduction of dementia risk factors at the population level. This trial will also support the feasibility of such interventions being applied in primary care settings. Successful outcomes of the current trial may lead to significant public health impact and benefits once the intervention is made available at the population level pending positive results.

Conclusion

Interventions to reduce risk of developing dementia are needed as a cure is not available. This project compares three different approaches to promote healthy lifestyles and to reduce risk of developing dementia applied in a primary care setting. This unique trial demonstrates real life application of dementia risk reduction intervention rather than more controlled but less ecologically valid interventions typically tested in a research setting.

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Authors' contributions

KJA conceived the study and built relationship with NHC. KJA, NC, SK developed the overall design of the intervention. NL and KC designed the implementation of the physical activity related intervention. CD and KJA designed the statistical analysis plan for the protocol. DP and GR contributed knowledge of primary care setting and advised on implementing the intervention in a GP clinic. ST designed the implementation of the dietary intervention. NC and SK managed the implementation of the online component in the dedicated web portal. SK, MM, ST, KC, NL, GR, DP, IM, NC and KJA wrote the study protocol and critically reviewed the manuscript.

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Competing interests

None declared.

Table 1. Assessment measures at the baseline and follow up evaluations

Assessment measure	Baseline	Immediate follow up (Week 7 for LMP and week 13 for BBL-GP and active control group)	Week 18	Week 36	Week 62
Screening					
APSS	√				
MMSE (if 60+)	√				
Questionnaires					
ANU-ADRI	√	√	√	√	√
PSQI	√	√	√	√	√
ARFS	√	√	√	√	√
SF-12	√	√	√	√	√
MHQ	√				

Cognitive measures					
Trails A + B	√		√	√	√
DSMT	√		√	√	√
Physical and medical evaluation (by doctors and nurses)					
MVPA	√		√	√	√
Blood pressure	√		√	√	√
Height, cm	√				
Weight, kg	√		√	√	√
Waist and hip, cm	√		√	√	√
Body Composition	√		√	√	√
Framingham CHD	√		√	√	√
AUSDRISK	√		√	√	√

Note: APSS: Adults Pre-exercise Screening System; MMSE: Mini-Mental State Examination; ANU-ADRI: Australian National University – Alzheimer's Disease Risk Index; PSQI: Pittsburgh Sleep Quality Index; ARFS: Australian Recommended Food Score; SF-12: SF-12 Health

Survey;; MHQ: Multidimensional Health Questionnaire; DSMT: Digit Symbol Modalities Test; MVPA: Moderate-vigorous Physical Activity; Framingham CHD: Framingham Coronary Heart Disease Risk score; AUSDRISK: Australian type 2 diabetes risk assessment tool.

Table 2: Comparison of intervention programs

	LMP	BBL-GP	Active control
Previously applied:	Yes, in primary care. Evaluation has not been carried out.	Yes, with member of general public with concern about developing dementia. Never been tested in primary care setting.	Yes, with member of general public with concern about developing dementia.
Duration	6 weeks	12 weeks	12 weeks
Frequency	Weekly	Weekly	Weekly
Number of sessions	12 sessions (2 sessions per week)	8 online sessions, 1 session with dietitian, 1 session with exercise physiologist	12 emails containing links to various websites providing information on lifestyle risk factors and disease management
Format	Face to face group sessions	1 hour individual session with dietitian, 1 hour individual session with exercise physiologist, 8 online modules	Weekly emails containing health information such as health status of Australians, physical activity and nutrition, alcohol and tobacco, and mental health.

Table 3: Description of the 12-week online program delivered through the Body Brain Life – GP (BBL-GP) website

Week	Activity	Description
1	Module 1: Dementia literacy	The first module focuses on providing participants with general information about dementia including types, causes, prevalence, social and economic impact, symptoms, brain function, treatment, risk factors (modifiable and non-modifiable), and prevention. This module serves as an introduction to the subsequent modules.
2	Module 2: Dementia risk factors	This module is aimed at building awareness and knowledge of the various health conditions associated with an increased risk of Alzheimer's dementia (AD). Specifically, this module provides details regarding the association between AD and several medical conditions (abnormal weight, high cholesterol, diabetes, hypertension, and depression), as well as lifestyle factors (alcohol use and smoking, physical activity, nutrition, stroke and head injury, mental health, social and cognitive engagement). The module also briefly covers non-modifiable risk factors that contribute to AD, including age and genetics.
3	Module 3: BBL FIT - physical activity	This is a theory-driven, individually-tailored module that aims to help participants incorporate regular physical activity into their daily routine and reduce sedentary behaviour by focusing on increasing endurance, strength, balance, and flexibility. This module targets several barriers to engaging in physical activity, such as increasing motivation, creating opportunities to exercise, and developing a social network that supports physical activity goals.
4	Module 4: BBL nutrition	This is a theory-driven, individually-tailored module aimed at helping people develop healthy dietary habits. This module targets the risk associated with abnormal weight, and the protective effects associated with fish intake and other dietary components.
5	Module 5: BBL health self-management	This is a theory-driven, individually-tailored module aimed at increasing participants' health monitoring and management of chronic health conditions. Because several chronic health conditions such as hypertension, diabetes and high cholesterol, are associated with increased risk for dementia, prevention and appropriate management of such conditions is also likely to be protective against dementia.
6	Module 6: BBL Think – cognitive engagement	This is a theory-driven, individually-tailored module aimed at increasing participants' levels of engagement with mentally stimulating activities such as reading, doing crosswords and visiting museums, which is a protective factor against dementia.

7	Module 7: BBL connect – social engagement	This is a theory-driven, individually-tailored module aimed at increasing participants' levels of social engagement. The module targets the risk factor for dementia associated with loneliness and depression, and the protective effects of regular social engagement.
8	Module 8: BBL mood	This is a theory-driven, individually-tailored module that aims to help participants monitor and maintain good mental health. The module targets risk factors for dementia associated with mental health and mood, focusing on depression and anxiety. Information is provided on symptoms, types, treatment, and tips for managing mood.
9	9 to 12 Self-guided online activities	During these sessions, participants are encouraged to engage in a range of online activities for 1 h, including accessing the many tools they have accumulated during the first 7 weeks. Examples include the goal-setting tool, behaviour-monitoring tool, unhelpful thoughts monitoring tool, videos, and so on.

Figure 1. Study Flowchart

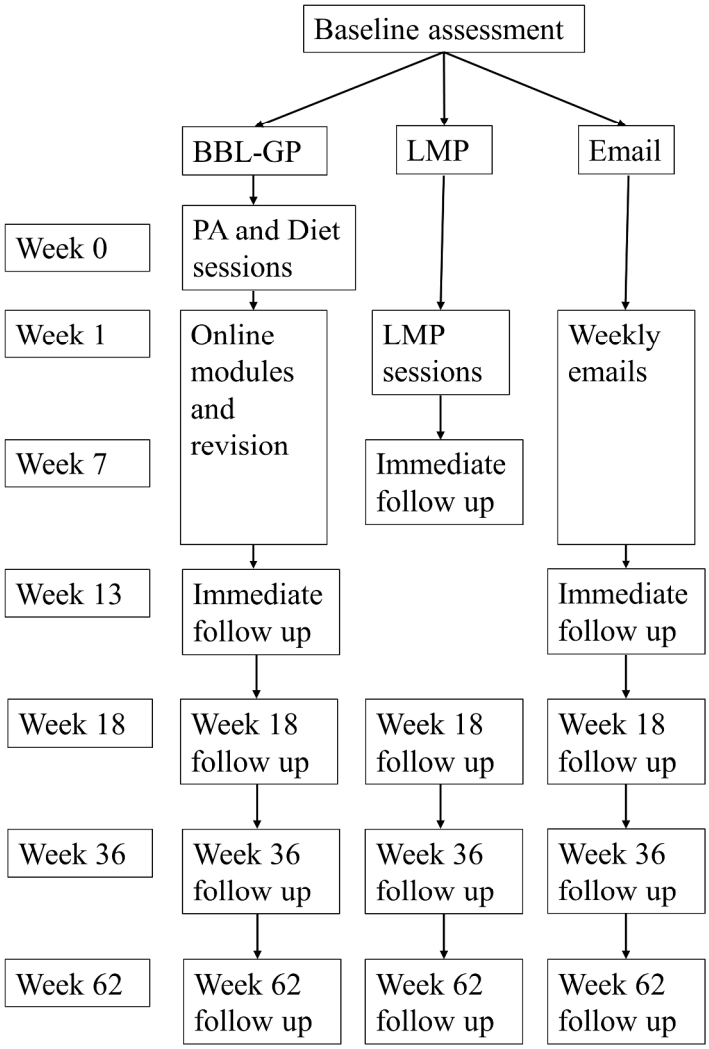

Figure 1: Study Flowchart

225x300mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 18
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-8
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14-17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 27-29

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____13_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____13_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____13_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____17-18_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____17_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ 16-17_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15-17, 18-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle Modification Program to decrease dementia risk exposure in a primary care setting

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Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle Modification Program to decrease dementia risk exposure in a primary care setting

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Abstract

Introduction: It has been estimated that a 10% to 25% reduction in seven key risk factors could potentially prevent 1.1 to 3.0 million Alzheimer's disease cases globally. In addition, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impact, effective preventative interventions would likely have more extensive benefits. The current study evaluates in primary care a multi-domain risk reduction intervention targeting adults with high risk of developing dementia.

Methods and analysis: A randomised controlled trial (RCT) is being conducted to evaluate three intervention programs using a pragmatic approach suitable to the clinic: 1) A 12-week online and face-to-face dementia risk reduction intervention (BBL-GP); 2) A 6-week face-to-face group lifestyle modification program (LMP); and 3) A 12-week email-only program providing general health information. We aim to recruit 240 participants, aged 18 and over, to undergo a comprehensive cognitive and physical assessment at baseline and follow ups (post intervention, 18, 36 and 62 weeks). The primary outcome is dementia risk measured with the modified version of the ANU-ADRI-Short Form. Secondary outcomes are cognitive function measured with Trail A and B, and the DSMT; physical activity with Moderate-Vigorous Physical Activity and the IPAQ; depression with the CES-D; cost evaluation with the SF-12 health survey, Framingham CHD, and AUSDRISK; diet quality with the ARFS; and sleep quality with the PSQI.

Ethics and dissemination: This RCT is a novel pragmatic intervention applied in a primary care setting to reduce the dementia risk exposure in adults at high risk. If successful, BBL-GP and LMP will provide a versatile, evidence-based package that can be easily and quickly rolled-out to other primary care settings and which can be scaled up at relatively low cost compared to other strategies involving intensive interventions.

Trial registration: Reg. no. ACTRN12616000868482

Keywords: RCT, dementia, lifestyle change, online, physical activity, diet, cardiovascular risk factors, Australia, general practice, primary care.

Strengths and limitations of this study

- BBL-GP program has been built on our dementia prevention research program which has been shown to reduce cognitive decline in older adults at-risk of dementia.
- This pragmatic trial evaluates a multi-domain risk reduction intervention in primary care targeting adults at increased risk of developing dementia.
- A naturalistic approach ensures the program can be adapted efficiently in primary care settings if proven effective.
- We are aware that most of our outcomes are self-reported and therefore can be subjective. Accordingly, we will interpret data conservatively.

Introduction

No cure is available for Alzheimer's disease (AD) and other types of dementia. However, it is estimated that an achievable 10% to 25% reduction in seven key risk factors could prevent 1.1 to 3.0 million AD cases internationally (1). It is also estimated that if each of seven risk factors was to be reduced by 5%, 10%, 15% and 20% per decade, dementia prevalence would be reduced by between 1.6 and 7.2% in 2020, 3.3-14.9% in 2030, 4-9 – 22.8% in 2040 and 6.6-30.7% in 2050 (2). Furthermore, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impacts, effective preventative interventions would likely have additional benefits.

Increasingly and to afford a greater chance of producing detectable changes during study timeframes, the dementia research community has focused on multi-domain interventions that address multiple risk factors simultaneously (3). Among individuals with high risk factor burden, cognitive decline can be reduced (and possibly reversed) as a result of cardiovascular risk reduction and increase in activities that stimulate and protect the brain including cognitive, social and physical activity (PA) and an appropriate diet (4). AD and cardiovascular disease share cardiometabolic and lifestyle risk factors and cardiovascular risk reduction can be achieved by smoking cessation, increasing physical activities, adopting a healthy diet, reducing abnormally high blood pressure and cholesterol in mid-life, and managing major depression, overweight/obesity in mid-life and diabetes if present (5). Altogether, the literature supports the view that multi-domain interventions aimed at reducing cardiometabolic risk and promoting behaviours shown to protect against dementia will contribute to preventing cognitive decline, reduce overall risk of AD, and lower depressive symptoms.

Insufficient PA is the risk factor with the most evidence to support its role as a treatment for Mild Cognitive Impairment (MCI) (6) and more generally cognitive decline (7).

PA has also been shown in RCTs to benefit several other risk factors for dementia including depression (8), and cardiovascular risk factors (9). PA not only modifies multiple risk factors but it has direct benefits for brain health and cognition.

To bring about risk reduction, there needs to be long-lasting behavioural change in multiple areas. Achieving this requires using techniques such as goal setting, decreasing barriers to change, improving self-monitoring, having access to information, and maintaining motivation (10, 11). Therefore, this RCT investigates whether lifestyle management programs that offer not only health promoting information, but also practical behaviour change techniques which can be implemented in daily life can reduce dementia risk.

Recruitment in general practice setting

Primary care is an ideal setting for the implementation of the current program because it is where adults with high risk of developing dementia are identified and early intervention and treatment are provided (12). Assessment of cardiovascular risk factors is common in primary care, as is advice about PA and diet. General practitioners (GP) commonly screen for diabetes and increasingly identify depression. GPs are often the first point of contact for patients who are worried that they may have dementia (13).

Although there has been one study conducted in primary care setting with elderly participants (70-78 years old) addressing cardiovascular risk factors (14), the current program is the first of its kind to provide interventions to adults (18 years and above) at the primary care setting, addressing both cardiovascular and lifestyle risk factors of dementia.

Methods and analysis

Study setting and design

This project is a 6-12 week, pragmatic single-blind randomised controlled trial that is designed to assist participants develop and maintain a healthy lifestyle, as well as manage chronic diseases. The study evaluates the implementation of an evidence-based dementia risk

reduction program that we developed and have evaluated previously on volunteers (15) and which has now been adapted for primary care (BBL-GP). The primary care setting in which the study is held already conducted a lifestyle management program (LMP) aimed at helping to manage chronic disease and maintaining a healthy lifestyle. The LMP program was initially developed to consist of 12 sessions over 12 weeks. However, its format was changed prior to this trial to have 12 sessions over 6 weeks. This decision was made by the clinic which provides this program in order for the program to be offered 4 times a year. The current LMP program was chosen as a comparison condition for feasibility and to enable evaluation of an existing program for dementia and cardiovascular risk reduction. The efficacy of the existing LMP program had not previously been evaluated.

The existing LMP program included 6 weeks of face-to-face group education sessions. The BBL-GP program included 12 weeks of individually tailored online education sessions with one hour face-to-face individual sessions with a dietitian and an exercise physiologist. The BBL-GP and LMP are being compared to an active control group receiving weekly email with links to health information. The study is being conducted in Canberra, Australian Capital Territory, Australia. The trial has been designed and is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) statements for non-pharmaceutical (16) and pragmatic (17) trials and is reported according to the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines (18).

Participants

Participants are being recruited from the National Health Co-op (NHC), the largest bulk billing general practice organisation in Canberra comprising of eight clinics. Bulk Billing is a payment option where the doctor bills directly the universal health insurance system (Medicare) in Australia for a medical service that the patients receive. Invitation emails have been sent to all members excluding members who are inactive (those who did not renew their

memberships), those aged less than 18 years, or without email addresses. Posters at the clinics are also being used for the recruitment. Potential participants who express their interest by contacting the LMP coordinator at the NHC or registering on the NHC's website are assessed against the inclusion and exclusion criteria. These are the types of adults who a GP would refer to a dementia risk reduction trial in 'real life' and on whom we are aiming to evaluate our intervention in a naturalistic context. In addition, risk factors for dementia exert their influence over decades and thus the earlier one decreases their risk exposure, the more impact it is likely to have over their lifespan. Therefore, this intervention program is open to anyone aged 18 and older. If criteria are met, information sheets and consent forms are sent to potential participants. Upon return of consent forms via email, each participant is officially registered to the study and allocated a unique identity number as well as an online account. Recruitment began in July 2016 for the duration of 13 months.

Inclusion criteria

A naturalistic approach is used in recruitment and the study inclusion criteria being used for this study are those already used by the NHC to refer patients to the LMP program (prior to this research project). The inclusion criteria is pragmatic as the practice already had criteria for referral to their LMP and in developing the protocol, it became clear that introducing a second set of inclusion criteria would make implementation difficult and reduce participant numbers. We therefore decided to use the principle that if a GP would refer the patient to the LMP then they would be eligible for the trial. This is a pragmatic feature of the current trial that significantly differs from our original BBL trial. We aimed to optimise the seamlessness of the intervention in primary care and utilise existing referral pathways to increase the probability that the intervention is conducted in a manner that could lead to implementation in real life. Participants must be aged 18 years and over, reside in the Australian Capital Territory, be current financial members of the NHC, have access to a computer and internet

connection at home, be fluent in English, Australian permanent residents or citizens (for bulk billing eligibility), and must be the only person in their household who is taking part in this study to prevent being randomly assigned to different groups and sharing information about their interventions with each other received. To be eligible for the study, participants are also required to have a chronic health condition (high blood pressure, heart disease, type 2 diabetes or 'pre-diabetes', osteoporosis, osteoarthritis, polycystic ovary syndrome (PCOS), kidney or liver disease, and depression/anxiety) or be overweight or obese (BMI>25). They are also required to agree to commit 1-2 hours a week to complete the program and be interested in obtaining advice on improving their lifestyle to reduce the risk of or better manage chronic disease. Participants are required to complete online assessments and attend NHC at baseline and 18, 36, and 62 weeks after commencement of the intervention for medical and cognitive assessments.

Exclusion criteria

Participants are not eligible to enrol in the trial if they have significant and unstable medical and psychiatric conditions that would prevent participation in the trial. They are also ineligible if they have sensory deficits or mobility limitations that would prevent or substantially restrict the delivery of the assessment or intervention, have cognitive impairment, or are pregnant. Those who have previously participated in the LMP were excluded from participation. However, those who may be/have been participating in other trials, unknown to authors, were not excluded.

Sample size calculations

Sample size calculations were estimated using G*Power (version 3.1.9.2; http://www.gpower.hhu.de/en.html) and have been based on medium effect size as observed in the previous Body Brain Life project with same primary outcome (19). To

detect a medium effect (0.5 standard deviation (SD)) in a 3-group design (1:1:1), 4 measurements with a 5% risk of type 1 error (α) and 80% power, a total sample size of 159 persons is required. To account for a 33% attrition (based on previous lifestyle modification program by NHC using the same inclusion and exclusion criteria and targeting same age group), a baseline sample of 240 is being recruited (80 in BBL-GP group, 80 in LMP group and 80 in control group).

Assessments

Participants who meet all inclusion and no exclusion criteria are invited to complete online surveys and visit NHC for the baseline evaluation, and for week 18, 36, and 62 follow ups. Immediate follow up is also conducted online at week 7 for LMP, and week 13 for BBL-GP and control groups. Table 1 summarises the assessment measures and schedule.

Screening measures and covariate

In addition to the above inclusion and exclusion criteria, further screening measures are conducted to ensure that participants are capable of taking part in the study. The Adult Pre-exercise Screening System (APSS) (20) is used at the baseline assessment to identify individuals with acute/high risk conditions, or who may be at higher risk of an adverse event during exercise. To screen for any cognitive impairment (<25), the Mini-Mental State Examination (MMSE) (21) is administered to participants aged 60 and older.

Health efficacy and motivation for healthiness subscales from the Multidimensional Health Questionnaire (MHQ) (22) is used to measure the extent to which people believe they have the ability, capability, skills and talents to take care of their own physical health, and to measure people's motivation to keep in good physical health.

Primary outcome

The primary outcome is one's exposure profile to demonstrated risk factors for AD. It is measured with a modified version of the Australian National University Alzheimer's Disease Risk Index – Short form (ANU-ADRI – SF) (23). The ANU-ADRI-SF is comprised of validated scales assessing 15 individual risk and protective factors for AD and dementia. Intra class correlation coefficients suggested that the reliability of the ANU-ADRI-SF compared to the original ANU-ADRI were moderate to strong (0.77 to 0.99) and statistically significant ($p<.001$) except for cognitive activity. Therefore, for the assessment of engagement in cognitive activities levels only, items from the original ANU-ADRI (19, 24) are used in place of those from the ANU-ADRI-SF due to limitations of the latter.

Secondary outcomes

Secondary outcomes include cognitive function, PA level, depressive symptoms, cost of interventions, diet and sleep quality. They are measured as follows: cognitive function is assessed with processing speed, task switching and executive function using Trails A and B, and the Digit Symbol Modalities Test (DSMT). These tests were chosen because the executive function is the most sensitive cognitive domain to PA interventions (25) and a decline in processing speed is associated with cardiovascular risk factors (26). Both Trails and DSMT have been used widely and have been reported to have good reliability and validity (27-30). Moderate-vigorous Physical Activity (MVPA) is a continuous measure of activity that registers three or more Metabolic Equivalents (METs) for 10 minutes or longer on an ActiGraph Link activity monitor (http://actigraphcorp.com/products/actigraph-link/), which is worn for 7 days. Self-reported PA is also being recorded using the short form of the International Physical Activity Questionnaire (IPAQ) (31), which is part of the ANU-ADRI-SF. Reliability and validity of IPAQ has been tested and confirmed across 12 countries (31). Depression is being assessed with the Centre for Epidemiological Studies Depression (CES-

D) Scale (32), which is also part of the ANU-ADRI. CES-D scale has a very high internal consistency and validity (33).

Health outcomes are assessed with the SF-12 health survey (34), Framingham Coronary Heart Disease (CHD) Risk score (35), and Australian type 2 diabetes risk assessment tool (AUSDRISK) (36) to enable cost effectiveness evaluation of the two health promotion interventions. SF-12 measures both physical and mental health status and has acceptable validity and reliability (37, 38). Framingham CHD is a validated tool to assess cardiovascular diseases (39) and AUSDRISK is a diabetes risk assessment tool based on demographic, lifestyle and simple anthropometric measures (36).

Dietary quality is assessed with a food-based diet quality index, the Australian Recommended Food Score (ARFS) (40). The ARFS is aligned with Australian Dietary Guidelines (41) and the Australian Guide to Healthy Eating (42) recommendations. The ARFS total ranges from 0 to 73 and includes eight subscales: vegetables (0 to 21), fruit (0 to 12), protein (0 to 7), vegetarian alternatives (0 to 6), grains (0 to 13), dairy (0 to 11), water (0 to 1), sauces and condiments (0 to 2). Higher scores indicate greater compliance with the Australian Dietary Guidelines and therefore better diet quality. The ARFS has demonstrated good validity and reproducibility (40).

Lastly, the Pittsburgh Sleep Quality Index (PSQI) (43) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. PSQI reports great test-retest reliability (0.87) and high correlations with sleep log data (44).

Randomisation

Upon completion of the baseline assessment, participants are randomly allocated into one of the three groups (see Table 2 and Figure 1). The allocation sequence is computer generated by an independent researcher and is not known to the study team at the time of enrolment and baseline assessment. A permuted block randomisation sequence comprising block sizes of 6 stratified by gender and age group (18-49 vs 50+) is used. The project manager who is not involved with conducting assessments assigns the participants into groups according to the generated sequence and notifies participants of their group allocation via email.

Interventions

Group 1: Body Brain Life – General Practice (BBL-GP)

BBL-GP is an intervention package that builds on our dementia prevention research programs. This includes an online dementia risk reduction program called the Body Brain Life (BBL; Trial ID: ACTRN12612000147886) (15, 45) and the Fitness for the Ageing Brain Study (FABS; Trial ID: ACTRN 12609000755235) (46, 47). Contents for the BBL-GP online modules have been revised after extensive consumer evaluation by members of the Alzheimer's Australia Consumer Dementia Research Network as well as members of the public and from participant feedback after the previous trial. The PA program has also been modified for a younger age-group to 18 years and older as previous programs targeted middle aged and older adults. The Actigraph device was introduced to measure the objective amount and intensity of PA. This revised program (Body Brain Life – Fit) was piloted with the general public (Trial ID: ACTRN12615000822583; manuscript in preparation).

Participants in the BBL-GP group are required to complete 8 modules (dementia literacy, risk factors, PA, nutrition, health, cognitive activity, social activity and mood) delivered online. Prior to commencing online modules, participants in the BBL-GP group also receive an individually tailored plan/program for both dietary and PA interventions

developed and delivered by a dietitian and an exercise physiologist, respectively during a face-to-face assessment. This is to ensure the dietary prescription and level of PA are suitable and tailored to individual participants.

Physical activity session

The session duration and frequency of the PA program varies between participants based on baseline PA levels and individual tailoring. An exercise physiologist designs an individual program for the participant, delivers this in a face-to-face workshop and monitors the PA program via the returned diaries and telephone monitoring. For those not doing any regular PA at baseline, the target is 150 minutes/week moderate intensity PA, with moderate intensity defined as a score of 10-12 on the Borg Rating of Perceived Exertion scale (RPE) (48). For those who are doing regular PA but for less than 100 minutes/week, an additional 100 minutes/week is prescribed, and for those meeting the target, an additional 50 minutes/week is prescribed. Printed material guiding participants to increase their activity level with worksheets are also provided. A diary in the format of a calendar returned monthly for 24 weeks is used to record PA and RPE to assess PA and intensity adherence. Participants may develop a medical problem or undergo treatment that can make exercising difficult or impossible. If this happens, prescribed amount of exercise is reviewed and re-prescribed, or stopped.

Dietary session

Participants at baseline who had unintentional weight loss of 5 kg or weight gain of 5 kg over the previous six months were seen by the dietitian. Furthermore, participants whose diets at baseline scored low on one or more of the subscales of the (ARFS) (vegetables <14, fruit <8, protein <4, grains <9, dairy <8, water <1) (40), were also seen by the dietitian. Dietary counselling was provided by a trained dietitian and overseen by the coordinating dietitian. During the one hour face-to-face counselling session, participants received individually

tailored dietary advice and printed material explaining the diet in detail.

Follow ups

Participants in the BBL-GP group are monitored through phone calls at week 4, 12 (14 for PA) and week 20 by the dietitian and exercise physiologist to monitor the progress and for reassurance. In addition, they receive a general booster session at 12 months with a phone call and a mailed-out booklet summarising materials from the online modules. They are being asked to continue being active and follow a healthy eating plan after completion of the intervention.

Online modules

Once participants in the BBL-GP group have received face-to-face PA and dietary counselling sessions, they are asked to log on to the trial website and complete one module per week, each taking approximately 30-40 minutes. The 12-week program is detailed in Table 3. The first 8 weeks include the completion of 8 educational and individually tailored behaviour change modules. In the remaining 4 weeks, participants undertake online activities focused on goal monitoring and revision of the modules materials. Tailoring of the six behaviour change modules (weeks 3-8) is conducted using an automated algorithm that presents content on the basis of whether or not the participant has a relevant risk factor, as well as on the basis of their responses to several questions measuring psychological determinants of behaviour. These questions are presented at the beginning of each of the behaviour change modules. For instance, a person who is classified as having a poor diet (e.g. lack of fish intake) on the basis of their responses on the ANU-ADRI, and who does not regard himself/herself as a role model to others with respect to their diet habits is not presented with information focusing on becoming a role model to others.

The program is built in such a way that participants are only able to access the relevant component of the intervention at a given time. The modules become active, 1 per

week, on the same day for the first 8 weeks. Participants are unable to access a newly activated module before completing the previously scheduled module. Each week, participants receive a notification email on the same day of the week alerting them when a new module has become active and a list of already activated modules that they have either not started or completed. Participants who are late completing modules will be followed up with an email from the project manager to identify if there is a reason (e.g. holidays, illness, work commitments) preventing their participation, and encouraging them to continue with the study. Compliance is recorded for each module if they are completed on time, delayed or not completed.

Group 2: Lifestyle Modification Program (LMP)

The lifestyle modification program (LMP), developed by NHC, is designed to provide individuals with tools to help manage chronic disease and maintain a healthy lifestyle. LMP is a six- week group program provided by various health professionals (dietitian, exercise physiologist, nurse practitioner, psychologist, pharmacist, and sleep physician) providing information on basic nutrition, meal planning, PA, health conditions, motivation and goals, medications, and sleep. Every week, 2 sessions are provided on the same day with each session lasting an hour. The course is currently run by the NHC for their patients to assist them in improving their lifestyle and management of chronic disease so it is a pragmatic real-life comparison condition. Attendance is recorded for compliance and motivation checking. Although the LMP is a free nationally recognised program that is designed to provide individuals with tools to help manage chronic disease and maintain a healthy lifestyle, evaluation of the program has not been carried out as yet. The attendance is recorded each week to examine intervention fidelity.

Group 3: Active control/Email only

The active control group or email only group proceed with their normal activities and access health services as required over the trial period. Participants in this group also receive weekly emails containing links to various websites providing information on lifestyle risk factors and disease management for a duration of 12 weeks. The weekly emails contain several links, and participants are encouraged to spend approximately an hour each week browsing through the material. The material is generally organised around the same themes as the ones included in the BBL-GP program. An effort has been made to include links to relevant information and educational material, but that otherwise does not include the use of identifiable behaviour-change techniques which are the 'active ingredient' of the BBL-GP program. In addition, other than providing participants with the weekly emails, no further contact is made with the participants in this group, such as reminders and prompts that are provided to the BBL-GP group. Participants in this group receive a face-to-face, 1 hour risk reduction workshop that provides the information contained in the BBL-GP intervention as a mean of debriefing at the end of the intervention.

Masking

To prevent performance bias, research staff conducting the assessments remain masked to participants' group allocation. The contact person for participants' website queries, access issues, and technical difficulties is independent of all baseline assessment data. All participants are informed that they are being randomly allocated to one of three study groups and that one group may be more effective than others. They are also notified at the start of the study that one of these groups involves face-to-face group sessions which require them to travel to NHC head office. Hence, the research team members who recruit participants, conduct individual diet and PA sessions, and professionals who are involved in the LMP are naturally able to tell which group they have been allocated to. Nurses who conduct baseline and follow-up assessments are however masked to group allocation.

Data management and monitoring

A trial management committee is formed by the research team members (chief and co-investigators). Nursing staffs from NHC and research assistants collect, clean and send the study data to the committee on a weekly basis. Most data are automatically entered into excel files and other data are double-entered to SPSS files to prevent data entry errors. Data management is then handled independently from the researchers who interpret the data. All data are stored electronically and in an independent spreadsheet and SPSS data file, which is only accessible by the researchers involved in this study.

An independent Data Monitoring Committee (DMC) is established independently from the research team who are involved with collecting and managing data. The DMC provides an independent oversight of the trial and reviews general conduct of the trial and study data for participant safety. The DMC is comprised of independent, multidisciplinary experts in dementia research who makes recommendations regarding the continuation, modification or termination of the trial.

Adverse events (minor and serious) are monitored throughout the trial by the research team and any adverse events would be reported to the trial DMC. For this trial, an adverse event is defined as an unwanted and usually harmful outcome (e.g. physical injuries). The event may or may not be related to the intervention, but it occurs while the person is participating in the intervention, that is, while they are undertaking physical activities individually prescribed by the exercise physiologist.

There are no formal interim analyses planned, as it is not expected that adverse events would be differentially related to the interventions.

Statistical analyses

Statistical analyses will be based on an intention-to-treat approach. As applied in the previous BBL project (15), multiple imputation and mixed models will be applied to analyse data. We

hypothesise that the effectiveness of the intervention programs will be in the following order: BBL-GP> LMP > active control. The hypothesis that BBL-GP will be more effective than LMP is based on research showing that a tailored program is better than a one size fits all group program in most cases (49). This is also based on the previous BBL project where those in BBL groups improved more than those in the control group. We will also adjust for compliance in completing the online modules and following recommendations provided by the dietitian and exercise physiologist (for BBL-GP group), or for attendance to weekly group sessions (for LMP group).

Ethics and trial registration

The Human Research Ethics Committee at the Australian National University has approved the study protocols and procedures (protocol #2016/157). This project has also been registered at the Australian New Zealand Clinical Trials Registry (ACTRN: 12616000868482).

Adverse events

This study evaluates lifestyle intervention programs to reduce risk factors for AD. The target population is adults in a primary care setting who have some of the known risk factors for dementia, but are at the time of the intervention, healthy and free of any dementia-related symptoms. We do not anticipate that participants are placed at a greater risk than that associated with self-driven educational activities over the Internet. An adverse event where a participant can get hurt during prescribed exercise can occur. To prevent this, we screen participants using APSS at the baseline assessment to identify individuals with acute/high risk conditions for exercise. In addition, the exercise physiologist individually tailors prescribed exercise to minimise risk of injury. Medical assessments are done by the participants' usual nurses and doctors and if any abnormality is detected in their results, they are required to discuss these abnormalities with participants as usual. To address issues of

potential fatigue, the assessments have been kept to a minimum length. In addition, all online and face-to-face sessions are designed in an interactive way and are limited to 1-hour sessions (LMP has 2 themed sessions per week and has a break between sessions). As mentioned above, all online modules are delivered in an individually tailored fashion to maximise relevance for each individual.

Dissemination plan

Positive, neutral and negative results of the trial will be submitted to international peer-reviewed journals. In addition, results will be presented at national and international conferences relevant to the subject matters. Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors and depends on personal involvement.

Discussion

The project is currently under way as an evaluation of the efficacy of health promotion interventions in adults with risk factors for dementia. The program aims to reduce cardiometabolic risk and promote behaviours shown to protect against dementia. The trial, recruiting from a primary care setting has generated considerable interest, and to date, approximately half of the total target sample has been assessed and randomised into the intervention groups. We anticipate that all data collection will be completed by December 2018. The results of the study are likely to form an evidence base for the feasibility of dementia risk reduction campaigns to lead to lifestyle changes and the reduction of dementia risk factors at the population level. This trial will also support the feasibility of such interventions being applied in primary care settings. Successful outcomes of the current trial may lead to significant public health impact and benefits once the intervention is made available at the population level pending positive results.

Conclusion

Interventions to reduce risk of developing dementia are needed as a cure is not available. This project compares three different approaches to promote healthy lifestyles and to reduce risk of developing dementia applied in a primary care setting. This unique trial demonstrates real life application of dementia risk reduction intervention rather than more controlled but less ecologically valid interventions typically tested in a research setting.

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Authors' contributions

KJA conceived the study and built relationship with NHC. KJA, NC, SK developed the overall design of the intervention. NL and KC designed the implementation of the PA related intervention. CD and KJA designed the statistical analysis plan for the protocol. DP and GR contributed knowledge of primary care setting and advised on implementing the intervention in a GP clinic. ST designed the implementation of the dietary intervention. NC and SK managed the implementation of the online component in the dedicated web portal. SK, MM, ST, KC, NL, GR, DP, IM, NC and KJA wrote the study protocol and critically reviewed the manuscript.

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Competing interests

None declared.

Table 1. Assessment measures at the baseline and follow up evaluations

Assessment measure	Baseline	Immediate follow up (Week 7 for LMP and week 13 for BBL-GP and active control group)	Week 18	Week 36	Week 62
Screening					
APSS	√				
MMSE (if 60+)	√				
Questionnaires					
ANU-ADRI	√	√	√	√	√
PSQI	√	√	√	√	√
ARFS	√	√	√	√	√
SF-12	√	√	√	√	√
MHQ	√				

Cognitive measures					
Trails A + B	√		√	√	√
DSMT	√		√	√	√
Physical and medical evaluation (by doctors and nurses)					
MVPA	√		√	√	√
Blood pressure	√		√	√	√
Height, cm	√				
Weight, kg	√		√	√	√
Waist and hip, cm	√		√	√	√
Body Composition	√		√	√	√
Framingham CHD	√		√	√	√
AUSDRISK	√		√	√	√

Note: APSS: Adults Pre-exercise Screening System; MMSE: Mini-Mental State Examination; ANU-ADRI: Australian National University – Alzheimer's Disease Risk Index; PSQI: Pittsburgh Sleep Quality Index; ARFS: Australian Recommended Food Score; SF-12: SF-12 Health

Survey;; MHQ: Multidimensional Health Questionnaire; DSMT: Digit Symbol Modalities Test; MVPA: Moderate-Vigorous Physical Activity; Framingham CHD: Framingham Coronary Heart Disease Risk score; AUSDRISK: Australian type 2 diabetes risk assessment tool.

Table 2: Comparison of intervention programs

	LMP	BBL-GP	Active control
Previously applied:	Yes, in primary care. Evaluation has not been carried out.	Yes, with member of general public with concern about developing dementia. Never been tested in primary care setting.	Yes, with member of general public with concern about developing dementia.
Duration	6 weeks	12 weeks	12 weeks
Frequency	Weekly	Weekly	Weekly
Number of sessions	12 sessions (2 sessions per week)	8 online sessions, 1 session with dietitian, 1 session with exercise physiologist	12 emails containing links to various websites providing information on lifestyle risk factors and disease management
Format	Face-to-face group sessions	1 hour individual session with dietitian, 1 hour individual session with exercise physiologist, 8 online modules	Weekly emails containing health information such as health status of Australians, PA and nutrition, alcohol and tobacco, and mental health.

Table 3: Description of the 12-week online program delivered through the Body Brain Life – GP (BBL-GP) website

Week	Activity	Description
1	Module 1: Dementia literacy	The first module focuses on providing participants with general information about dementia including types, causes, prevalence, social and economic impact, symptoms, brain function, treatment, risk factors (modifiable and non-modifiable), and prevention. This module serves as an introduction to the subsequent modules.
2	Module 2: Dementia risk factors	This module is aimed at building awareness and knowledge of the various health conditions associated with an increased risk of AD. Specifically, this module provides details regarding the association between AD and several medical conditions (abnormal weight, high cholesterol, diabetes, hypertension, and depression), as well as lifestyle factors (alcohol use and smoking, PA, nutrition, stroke and head injury, mental health, social and cognitive engagement). The module also briefly covers non-modifiable risk factors that contribute to AD, including age and genetics.
3	Module 3: BBL FIT - PA	This is a theory-driven, individually-tailored module that aims to help participants incorporate regular PA into their daily routine and reduce sedentary behaviour by focusing on increasing endurance, strength, balance, and flexibility. This module targets several barriers to engaging in PA, such as increasing motivation, creating opportunities to exercise, and developing a social network that supports PA goals.
4	Module 4: BBL nutrition	This is a theory-driven, individually-tailored module aimed at helping people develop healthy dietary habits. This module targets the risk associated with abnormal weight, and the protective effects associated with fish intake and other dietary components.
5	Module 5: BBL health self-management	This is a theory-driven, individually-tailored module aimed at increasing participants' health monitoring and management of chronic health conditions. Because several chronic health conditions such as hypertension, diabetes and high cholesterol, are associated with increased risk for dementia, prevention and appropriate management of such conditions is also likely to be protective against dementia.
6	Module 6: BBL Think – cognitive engagement	This is a theory-driven, individually-tailored module aimed at increasing participants' levels of engagement with mentally stimulating activities such as reading, doing crosswords and visiting museums, which is a protective factor against dementia.
7	Module 7: BBL connect – social engagement	This is a theory-driven, individually-tailored module aimed at increasing participants' levels of social engagement. The module targets the risk factor for dementia associated

		with loneliness and depression, and the protective effects of regular social engagement.
8	Module 8: BBL mood	This is a theory-driven, individually-tailored module that aims to help participants monitor and maintain good mental health. The module targets risk factors for dementia associated with mental health and mood, focusing on depression and anxiety. Information is provided on symptoms, types, treatment, and tips for managing mood.
9	9 to 12 Self-guided online activities	During these sessions, participants are encouraged to engage in a range of online activities for 1 h, including accessing the many tools they have accumulated during the first 7 weeks. Examples include the goal-setting tool, behaviour-monitoring tool, unhelpful thoughts monitoring tool, videos, and so on.

Figure 1. Study Flowchart

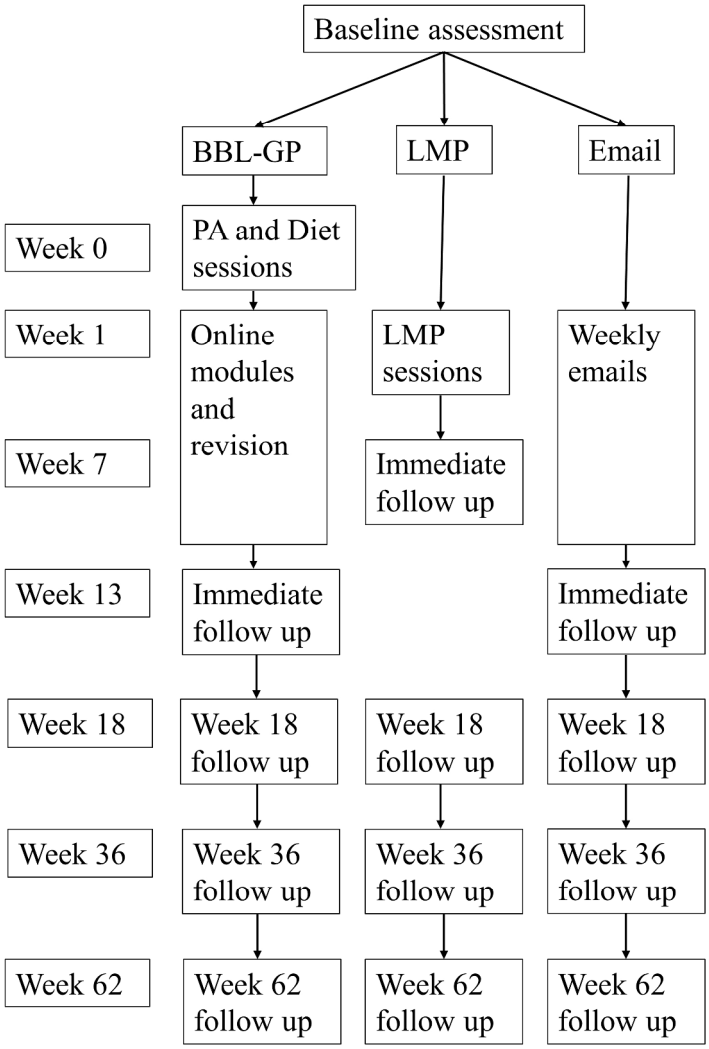

Figure 1: Study Flowchart

225x300mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 18
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-8
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14-17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 27-29

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____13_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____13_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____13_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____17-18_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____17_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ 16-17_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15-17, 18-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.