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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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Manuscripts

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5 Protocol for a randomised controlled trial of Body Brain Life – GP and a Lifestyle
6 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.

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6 Trial registration: Reg. no. ACTRN12616000868482
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11 Keywords: RCT, dementia, lifestyle change, online, physical activity, diet, cardiovascular
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13 risk factors, Australia, general practice, primary care.
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For peer review only

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

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2
3 role as a treatment for Mild Cognitive Impairment (MCI; Blondell, Hammersley-Mather, &
4 Veerman, 2014) and more generally cognitive decline (Northey, Cherbuin, Pampa, Smee, &
5 Rattray, 2017). Physical activity has also been shown in RCTs to benefit several other risk
6 factors for dementia including depression (Mammen & Faulkner, 2013), and cardiovascular
7 risk factors (Brouwer, van der Graaf, Soedamah-Muthu, Wassink, & Visseren, 2010).
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9 Physical activity not only modifies multiple risk factors but it has direct benefits for brain
10 health and cognition.
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18 To bring about risk reduction, there needs to be long-lasting behavioural change in
19 multiple areas. Achieving this requires using techniques such as goal setting, decreasing
20 barriers to change, improving self-monitoring, having access to information, and maintaining
21 motivation (Locke, 1996; Middleton, Anton, & Perri, 2013). Therefore, this RCT investigates
22 whether lifestyle management programs that offer not only health promoting information, but
23 also practical behaviour change techniques which can be implemented in daily life can reduce
24 dementia risk.
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32 33 *Recruitment in general practice setting*

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35 Primary care is an ideal setting for the implementation of the current program because
36 it is where adults with high risk of developing dementia are identified and early intervention
37 and treatment are provided (The Department of Health, 2013). Assessment of cardiovascular
38 risk factors is common in primary care, as is advice about physical activity and diet. General
39 practitioners (GP) commonly screen for diabetes and increasingly identify depression. GPs
40 are often the first point of contact for patients who are worried that they may have dementia
41 (Robinson, Tang, & Taylor, 2015).
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50 Although there has been one study conducted in primary care setting with elderly
51 participants (70-78 years old; Richard et al., 2009), the current program is the first of its kind
52 to provide interventions to adults (18 years and above) at the primary care setting, addressing
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3 both cardiovascular and lifestyle risk factors of dementia.

4 **Methods and analysis**

5 *Study setting and design*

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10 This project is a 6-12 week, single-blind randomised controlled trial that is designed to assist
11 participants develop and maintain a healthy lifestyle, as well as manage chronic diseases. The
12 study evaluates the implementation of an evidence-based dementia risk reduction program
13 that we developed and have evaluated previously on volunteers and which has now been
14 adapted for primary care (BBL-GP). The primary care setting in which the study is held
15 already conducted a lifestyle management program (LMP) aimed to reduce vascular risk
16 factors. The LMP program was initially developed to consist of 12 sessions over 12 weeks.
17 However, its format was changed prior to this trial to have 12 sessions over 6 weeks. This
18 decision was made by the clinic which provides this program in order for the program to be
19 offered 4 times a year. The current LMP program was chosen as a comparison condition for
20 feasibility and to enable evaluation of an existing program for dementia and cardiovascular
21 risk reduction. The efficacy of the existing program had not previously been evaluated.
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36 The existing LMP program included 6 weeks of face-to-face group education sessions.
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38 The BBL-GP program included 12 weeks of individually tailored online education sessions
39 with one hour face-to-face individual sessions with a dietitian and an exercise physiologist.
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41 The BBL-GP and LMP are being compared to an active control group receiving weekly email
42 with links to health information. The study is being conducted in Canberra, Australian
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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

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3 the only person in their household who is taking part in this study. To be eligible for the study,
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5 participants are also required to have a chronic health condition (high blood pressure, heart
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7 disease, type 2 diabetes or 'pre-diabetes', osteoporosis, osteoarthritis, polycystic ovary
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9 syndrome (PCOS), kidney or liver disease, and depression/anxiety) or be overweight or obese
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11 (BMI>25). They are also required to agree to commit 1-2 hours a week to complete the
12
13 program and be interested in obtaining advice on improving their lifestyle to reduce the risk
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15 of or better manage chronic disease. Participants are required to complete online assessments
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17 and attend NHC at baseline and 18, 36, and 62 weeks after commencement of the
18
19 intervention for medical and cognitive assessments.
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22 23 *Exclusion criteria*

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25 Participants are not eligible to enrol in the trial if they have significant and unstable medical
26
27 and psychiatric conditions that would prevent participation in the trial. They are also
28
29 ineligible if they have sensory deficits or mobility limitations that would prevent or
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31 substantially restrict the delivery of the assessment or intervention, have cognitive
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33 impairment, or are pregnant.
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36 37 *Sample size calculations*

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39 Sample size calculations were estimated using G*Power (version 3.1.9.2;
40
41 <http://www.gpower.hhu.de/en.html>) and have been based on medium effect size as
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43 observed in the previous Body Brain Life project. To detect a medium effect in a 3-
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45 group design (1:1:1), 4 measurements with a 5% risk of type 1 error (α) and 80%
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47 power, a total sample size of 159 persons is required. To account for a 33% attrition
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49 (based on previous lifestyle modification program by NHC), a baseline sample of 240
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51 is being recruited (80 in BBL-GP group, 80 in LMP group and 80 in control group).
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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,

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

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10 Secondary outcomes include cognitive function, physical activity level, depressive symptoms,
11 cost of interventions, diet and sleep quality. They are measured as follows: cognitive function
12 is assessed with processing speed and task switching using Trails A and B, and the Digit
13 Symbol Modalities Test. Moderate-vigorous Physical Activity (MVPA) is a continuous
14 measure of activity that registers three or more Metabolic Equivalents (METs) for 10 minutes
15 or longer on an ActiGraph Link activity monitor
16 (<http://actigraphcorp.com/products/actigraph-link/>), which is worn for 7 days. Self-reported
17 physical activity is also being recorded using the short form of IPAQ (Craig et al., 2003),
18 which is part of the ANU-ADRI-SF. Depression is being assessed with the Centre for
19 Epidemiological Studies Depression Scale (Radloff, 1977), which is also part of the ANU-
20 ADRI.
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35 Health outcomes are assessed with the SF-12 health survey (Ware, Kosinski, & Keller,
36 1996), Framingham coronary heart disease risk score (Wilson et al., 1998), and Australian
37 type 2 diabetes risk assessment tool (AUSDRISK; Chen et al., 2010) to enable cost
38 effectiveness evaluation of the two health promotion interventions.
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44 Dietary quality is assessed with a food-based diet quality index, the Australian
45 Recommended Food Score (ARFS; Collins et al., 2015). The ARFS is aligned with
46 Australian Dietary Guidelines (National Health and Medical Research Council, 2013) and the
47 Australian Guide to Healthy Eating (National Health and Medical Research Council, 2003)
48 recommendations. The ARFS total ranges from 0 to 73 and includes eight subscales:
49 vegetables (0 to 21), fruit (0 to 12), protein (0 to 7), vegetarian alternatives (0 to 6), grains (0
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3 to 13), dairy (0 to 11), water (0 to 1), sauces and condiments (0 to 2). Higher scores indicate
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5 greater compliance with the Australian Dietary Guidelines and therefore better diet quality.
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7 The ARFS has demonstrated good validity and reproducibility (Collins et al., 2015).
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10 Lastly, the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman,
11 & Kupfer, 1989) is an effective instrument used to measure the quality and patterns of sleep
12 in adults. It differentiates “poor” from “good” sleep quality by measuring seven areas
13 (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency,
14 sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.
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20 21 *Randomization*

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24 Upon completion of the baseline assessment, participants are randomly allocated into one of
25 the three groups. The allocation sequence is generated by an independent researcher and is
26 not known to the study team at the time of enrolment and baseline assessment. A permuted
27 block randomization sequence comprising block sizes of 6 stratified by gender and age group
28 (18-49 vs 50+) is used.
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34 35 *Interventions*

36 37 38 *Group 1: Body Brain Life – General Practice (BBL-GP)*

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41 BBL-GP is an intervention package that builds on our dementia prevention research programs.
42 This includes an online dementia risk reduction program called the Body Brain Life (BBL;
43 Trial ID: ACTRN12612000147886) (Anstey et al., 2015; Anstey, Bahar-Fuchs, Herath,
44 Rebok, & Cherbuin, 2013) and the Fitness for the Ageing Brain Study (FABS; Trial ID:
45 ACTRN 12609000755235) (Cyarto et al., 2010; Lautenschlager et al., 2008). Contents for the
46 BBL-GP online modules have been revised after extensive consumer evaluation by members
47 of the Alzheimer’s Australia Consumer Dementia Research Network as well as members of
48 the public and from participant feedback after the previous trial. The physical activity
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3 program has also been modified for a younger age-group to 18 years and older. The
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5 Actigraph device was introduced to measure the objective amount and intensity of physical
6
7 activity. This revised program (Body Brain Life – Fit) was piloted with the general public
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9 (Trial ID: ACTRN12615000822583).
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11 Participants in the BBL-GP group are required to complete 8 modules (dementia
12
13 literacy, risk factors, physical activity, nutrition, health, cognitive activity, social activity and
14
15 mood) delivered online. Prior to commencing online modules, participants in the BBL-GP
16
17 group also receive an individually tailored plan/program for both dietary and physical activity
18
19 interventions developed and delivered by a dietitian and an exercise physiologist, respectively
20
21 during a face-to-face assessment. This is to ensure the dietary prescription and level of
22
23 physical activity are suitable and tailored to individual participants.
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26 *Physical activity session*

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28 The session duration and frequency of the physical activity (PA) program varies between
29
30 participants based on baseline physical activity levels and individual tailoring. An exercise
31
32 physiologist designs an individual program for the participant, delivers this in a face-to-face
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34 workshop and monitors the physical activity program via the returned diaries and telephone
35
36 monitoring. For those not doing any regular PA at baseline, the target is 150 minutes/week
37
38 moderate intensity PA, with moderate intensity defined as a score of 10-12 on the Borg
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40 Rating of Perceived Exertion scale (RPE; Borg, 1982). For those who are doing regular PA
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42 but for less than 100 minutes/week, an additional 100 minutes/week is prescribed, and for
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44 those meeting the target, an additional 50 minutes/week is prescribed. Printed material
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46 guiding participants to increase their activity level with worksheets are also provided. A diary
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48 in the format of a calendar returned monthly for 24 weeks is used to record PA and RPE to
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50 assess PA and intensity adherence.
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54 *Dietary session*

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3 Participants at baseline who had unintentional weight loss of 5 kg or weight gain of 5 kg over
4 the previous six months were seen by the dietitian. Furthermore, participants whose diets at
5 baseline scored low on one or more of the subscales of the (ARFS) (vegetables <14, fruit <8,
6 protein <4, grains <9, dairy <8, water <1) (Collins et al., 2015), were also seen by the
7 dietitian. Dietary counselling was provided by a trained dietitian and overseen by the
8 coordinating dietitian. During the one hour face-to-face counselling session, participants
9 received individually tailored dietary advice and printed material explaining the diet in detail.
10
11

12 *Follow ups*

13
14 Participants in the BBL-GP group are monitored through phone calls at week 4, 12 (14 for
15 PA) and week 20 by the dietitian and exercise physiologist to monitor the progress and for
16 reassurance. In addition, they receive a general booster session at 12 months with a phone
17 call and a mailed out booklet summarising materials from the online modules. They are being
18 asked to continue being active and follow a healthy eating plan after completion of the
19 intervention.
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22 *Online modules*

23
24 Once participants in the BBL-GP group have received face-to-face PA and dietary
25 counselling sessions, they are asked to log on to the trial website and complete one module
26 per week, each taking approximately 30-40 minutes. The 12-week program is detailed in
27 Table 2. The first 8 weeks include the completion of 8 educational and individually tailored
28 behaviour change modules. In the remaining 4 weeks, participants undertake online activities
29 focused on goal monitoring and revision of the modules materials. Tailoring of the six
30 behaviour change modules (weeks 3-8) is conducted using an automated algorithm that
31 presents content on the basis of whether or not the participant has a relevant risk factor, as
32 well as on the basis of their responses to several questions measuring psychological
33 determinants of behaviour. These questions are presented at the beginning of each of the
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3 behaviour change modules. For instance, a person who is classified as having a poor diet (e.g.
4 lack of fish intake) on the basis of their responses on the ANU-ADRI, and who does not
5 regard himself/herself as a role model to others with respect to their diet habits will not be
6 presented with information focusing on becoming a role model to others.
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11 The program is built in such a way that participants are only able to access the
12 relevant component of the intervention at a given time. The modules become active, 1 per
13 week, on the same day for the first 8 weeks. Participants are unable to access a newly
14 activated module before completing the previously scheduled module. Each week,
15 participants receive a notification email on the same day of the week alerting them when a
16 new module has become active and a list of already activated modules that they have either
17 not started or completed. Participants who are late completing modules will be followed up
18 with an email from the project manager to identify if there is a reason (e.g. holidays, illness,
19 work commitments) preventing their participation, and encouraging them to continue with the
20 study. Compliance is recorded for each module if they are completed on time, delayed or not
21 completed.
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36 *Group 2: Lifestyle Modification Program (LMP)*

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38 The lifestyle modification program (LMP), developed by NHC, is designed to enhance
39 general wellbeing and improve lifestyle to reduce the risk of chronic disease. LMP is a six-
40 week group program provided by various health professionals (dietitian, exercise physiologist,
41 nurse practitioner, psychologist, pharmacist and sleep physician) providing information on
42 basic nutrition, meal planning, physical activity, health conditions, motivation and goals,
43 medications, and sleep. Every week, 2 sessions are provided on the same day with each
44 session lasting an hour. The course is currently run by the NHC for their patients to assist
45 them in improving their lifestyle and management of chronic disease so it is a real-life
46 comparison condition. Attendance is recorded for compliance and motivation checking.
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3 Although the LMP is a free nationally recognized program that is designed to provide
4 individuals with tools to help manage chronic disease and maintain a healthy lifestyle,
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6 evaluation of the program has not been carried out as yet.
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10 *Group 3: Active control/Email only*

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12 The active control group or email only group proceed with their normal activities and access
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14 health services as required over the trial period. Participants in this group also receive weekly
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16 emails containing links to various websites providing information on lifestyle risk factors and
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18 disease management for a duration of 12 weeks. The weekly emails contain several links, and
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20 participants are encouraged to spend approximately an hour each week browsing through the
21
22 material. The material is generally organized around the same themes as the ones included in
23
24 the BBL-GP program. An effort has been made to include links to relevant information and
25
26 educational material, but that otherwise does not include the use of identifiable behaviour-
27
28 change techniques which are the ‘active ingredient’ of the BBL-GP program. In addition,
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30 other than providing participants with the weekly emails, no further contact is made with the
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32 participants in this group, such as reminders and prompts that are provided to the BBL-GP
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34 group.
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37 *Masking*

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40 To prevent performance bias, research staff conducting the assessments remain masked to
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42 participants’ group allocation. The contact person for participants’ website queries, access
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44 issues, and technical difficulties is independent of all baseline assessment data. All
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46 participants are informed that they are being randomly allocated to one of three study groups
47
48 and that one group may be more effective than others. They are also notified at the start of the
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50 study that one of these groups involves face-to-face group sessions which require them to
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52 travel to NHC head office. Hence, the research team members who recruit participants,
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54 conduct individual diet and physical activity sessions, and professionals who are involved in
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3 the LMP are naturally able to tell which group they have been allocated to. Nurses who
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5 conduct baseline and follow-up assessments are however masked to group allocation.
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7 *Data management and monitoring*

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

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17 Statistical analyses will be based on an intention-to-treat approach. As applied in the previous
18
19 BBL project (Anstey et al., 2015), multiple imputation and mixed models will be applied to
20
21 analyse data. We hypothesise that the effectiveness of the intervention programs will be in
22
23 the following order: BBL-GP > LMP > active control. The hypothesis that BBL-GP will be
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25 more effective than LMP is based on research showing that a tailored program is better than a
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27 one size fits all group program in most cases (Kreuter, Oswald, Bull, & Clark, 2000). This is
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29 also based on the previous BBL project where those in BBL groups improved more than
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31 those in the control group. We will also adjust for compliance in completing the online
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33 modules and following recommendations provided by the dietitian and exercise physiologist
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35 (for BBL-GP group), or for attendance to weekly group sessions (for LMP group).
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39 *Ethics and trial registration*

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41 The Human Research Ethics Committee at the Australian National University has approved
42
43 the study protocols and procedures (protocol #2016/157). This project has also been
44
45 registered at the Australian New Zealand Clinical Trials Registry (ACTRN:
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47 12616000868482).
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50 *Adverse events*

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52 This study evaluates lifestyle intervention programs to reduce risk factors for AD. The target
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54 population is adults in a primary care setting who have some of the known risk factors for
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3 dementia, but are at the time of the intervention, healthy and free of any dementia-related
4 symptoms. We do not anticipate that participants will be placed at a greater risk than that
5 associated with self-driven educational activities over the Internet. Medical assessments are
6 done by the participants' usual nurses and doctors and if any abnormality is detected in their
7 results, they are required to discuss these abnormalities with participants as usual. To address
8 issues of potential fatigue, the assessments have been kept to a minimum length. In addition,
9 all online and face-to-face sessions are designed in an interactive way and are limited to 1-
10 hour sessions (LMP has 2 themed sessions per week and has a break between sessions). As
11 mentioned above, all online modules are delivered in an individually tailored fashion to
12 maximize relevance for each individual.
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24 *Dissemination plan*

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

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39 The project is currently under way as an evaluation of the efficacy of health promotion
40 interventions in adults with risk factors for dementia. The program aims to reduce
41 cardiometabolic risk and promote behaviours shown to protect against dementia. The trial,
42 recruiting from a primary care setting has generated considerable interest, and to date,
43 approximately half of the total target sample has been assessed and randomised into the
44 intervention groups. We anticipate that all data collection will be completed by December
45 2018. The results of the study are likely to form an evidence base for the feasibility of
46 dementia risk reduction campaigns to lead to lifestyle changes and the reduction of dementia
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3 risk factors at the population level. This trial will also support the feasibility of such
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5 interventions being applied in primary care settings. Successful outcomes of the current trial
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7 may lead to significant public health impact and benefits once the intervention is made
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9 available at the population level pending positive results.
10

11 **Conclusion**

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13 Interventions to reduce risk of developing dementia are needed as a cure is not available. This
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15 project compares three different approaches to promote healthy lifestyles and to reduce risk
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17 of developing dementia applied in a primary care setting. This unique trial demonstrates real
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19 life application of dementia risk reduction intervention rather than more controlled but less
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21 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.

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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	√		√	√	√

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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.

For peer review only

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.

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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.

For peer review only



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___

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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

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3	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___
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5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___9___
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8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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12	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___
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17	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___
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___13___
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___17-18___
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___17___
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31 **Methods: Data collection, management, and analysis**

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33	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___
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38		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___
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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_____



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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___9___
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A___
7				
8	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___
9				
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___26___
12				
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14	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___
15				
16				
17	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___
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20	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___
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	___19___
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___N/A___
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___N/A___
32				
33				
34	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___
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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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

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Manuscripts

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5 Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle
6 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

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2
3 rolled-out to other primary care settings and which can be scaled up at relatively low cost
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5 compared to other strategies involving intensive interventions.
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10 Trial registration: Reg. no. ACTRN12616000868482
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16 Keywords: RCT, dementia, lifestyle change, online, physical activity, diet, cardiovascular
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18 risk factors, Australia, general practice, primary care.
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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

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3 decline (7). Physical activity has also been shown in RCTs to benefit several other risk
4 factors for dementia including depression (8), and cardiovascular risk factors (9). Physical
5 activity not only modifies multiple risk factors but it has direct benefits for brain health and
6 cognition.
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11 To bring about risk reduction, there needs to be long-lasting behavioural change in
12 multiple areas. Achieving this requires using techniques such as goal setting, decreasing
13 barriers to change, improving self-monitoring, having access to information, and maintaining
14 motivation (10, 11). Therefore, this RCT investigates whether lifestyle management
15 programs that offer not only health promoting information, but also practical behaviour
16 change techniques which can be implemented in daily life can reduce dementia risk.
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20 21 22 *Recruitment in general practice setting*

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26 Primary care is an ideal setting for the implementation of the current program because
27 it is where adults with high risk of developing dementia are identified and early intervention
28 and treatment are provided (12). Assessment of cardiovascular risk factors is common in
29 primary care, as is advice about physical activity and diet. General practitioners (GP)
30 commonly screen for diabetes and increasingly identify depression. GPs are often the first
31 point of contact for patients who are worried that they may have dementia (13).
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40 Although there has been one study conducted in primary care setting with elderly
41 participants (70-78 years old) addressing cardiovascular risk factors (14), the current program
42 is the first of its kind to provide interventions to adults (18 years and above) at the primary
43 care setting, addressing both cardiovascular and lifestyle risk factors of dementia.
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48 49 **Methods and analysis**

50 51 *Study setting and design*

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

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27 The existing LMP program included 6 weeks of face-to-face group education sessions.
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29 The BBL-GP program included 12 weeks of individually tailored online education sessions
30 with one hour face-to-face individual sessions with a dietitian and an exercise physiologist.
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32 The BBL-GP and LMP are being compared to an active control group receiving weekly email
33 with links to health information. The study is being conducted in Canberra, Australian
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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

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

28 29 *Inclusion criteria*

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

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3 connection at home, be fluent in English, Australian permanent residents or citizens (for bulk
4 billing eligibility), and must be the only person in their household who is taking part in this
5 study to prevent being randomly assigned to different groups and sharing information about
6 their interventions with each other received. To be eligible for the study, participants are also
7 required to have a chronic health condition (high blood pressure, heart disease, type 2
8 diabetes or 'pre-diabetes', osteoporosis, osteoarthritis, polycystic ovary syndrome (PCOS),
9 kidney or liver disease, and depression/anxiety) or be overweight or obese (BMI>25). They
10 are also required to agree to commit 1-2 hours a week to complete the program and be
11 interested in obtaining advice on improving their lifestyle to reduce the risk of or better
12 manage chronic disease. Participants are required to complete online assessments and attend
13 NHC at baseline and 18, 36, and 62 weeks after commencement of the intervention for
14 medical and cognitive assessments.
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28 29 *Exclusion criteria*

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

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46 Sample size calculations were estimated using G*Power (version 3.1.9.2;
47 <http://www.gpower.hhu.de/en.html>) and have been based on medium effect size as
48 observed in the previous Body Brain Life project with same primary outcome (19). To
49 detect a medium effect (0.5 standard deviation (SD)) in a 3-group design (1:1:1), 4
50 measurements with a 5% risk of type 1 error (α) and 80% power, a total sample size of
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3 159 persons is required. To account for a 33% attrition (based on previous lifestyle
4 modification program by NHC using the same inclusion and exclusion criteria and
5 targeting same age group), a baseline sample of 240 is being recruited (80 in BBL-GP
6 group, 80 in LMP group and 80 in control group).
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10 11 12 *Assessments*

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14 Participants who meet all inclusion and no exclusion criteria are invited to complete online
15 surveys and visit NHC for the baseline evaluation, and for week 18, 36, and 62 follow ups.
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17 Immediate follow up is also conducted online at week 7 for LMP, and week 13 for BBL-GP
18 and control groups. Table 1 summarizes the assessment measures and schedule.
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23 24 *Screening measures and covariate*

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26 In addition to the above inclusion and exclusion criteria, further screening measures are
27 conducted to ensure that participants are capable of taking part in the study. The Adult Pre-
28 exercise Screening System (APSS) (20) is used at the baseline assessment to identify
29 individuals with acute/high risk conditions, or who may be at higher risk of an adverse event
30 during exercise. To screen for any cognitive impairment (<25), the Mini-Mental State
31 Examination (MMSE) (21) is administered to participants aged 60 and older.
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40 Health efficacy and motivation for healthiness subscales from the Multidimensional
41 Health Questionnaire (MHQ) (22) is used to measure the extent to which people believe they
42 have the ability, capability, skills and talents to take care of their own physical health, and to
43 measure people's motivation to keep in good physical health.
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49 50 *Primary outcome*

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52 The primary outcome is one's exposure profile to demonstrated risk factors for Alzheimer's
53 disease. It is measured with a modified version of the Australian National University
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3 Alzheimer's Disease Risk Index – Short form (ANU-ADRI – SF) (23). The ANU-ADRI-SF
4 is comprised of validated scales assessing 15 individual risk and protective factors for
5
6 Alzheimer's disease and dementia. Intra class correlation coefficients suggested that the
7
8 reliability of the ANU-ADRI-SF compared to the original ANU-ADRI were moderate to
9
10 strong (0.77 to 0.99) and statistically significant ($p < .001$) except for cognitive activity.
11
12 Therefore, for the assessment of engagement in cognitive activities levels only, items from
13
14 the original ANU-ADRI (19, 24) are used in place of those from the ANU-ADRI-SF due to
15
16 limitations of the latter.
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19 20 21 *Secondary outcomes*

22
23 Secondary outcomes include cognitive function, physical activity level, depressive symptoms,
24
25 cost of interventions, diet and sleep quality. They are measured as follows: cognitive function
26
27 is assessed with processing speed, task switching and executive function using Trails A and B,
28
29 and the Digit Symbol Modalities Test (DSMT). These tests were chosen because the
30
31 executive function is the most sensitive cognitive domain to physical activity interventions
32
33 (25) and a decline in processing speed is associated with cardiovascular risk factors (26).
34
35 Both Trails and DSMT have been used widely and have been reported to have good
36
37 reliability and validity (27-30). Moderate-vigorous Physical Activity (MVPA) is a continuous
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39 measure of activity that registers three or more Metabolic Equivalents (METs) for 10 minutes
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41 or longer on an ActiGraph Link activity monitor
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43 (<http://actigraphcorp.com/products/actigraph-link/>), which is worn for 7 days. Self-reported
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45 physical activity is also being recorded using the short form of IPAQ (31), which is part of
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47 the ANU-ADRI-SF. Reliability and validity of IPAQ has been tested and confirmed across 12
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49 countries (31). Depression is being assessed with the Centre for Epidemiological Studies
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51 Depression (CES-D) Scale (32), which is also part of the ANU-ADRI. CES-D scale has a
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53 very high internal consistency and validity (33).
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3 Health outcomes are assessed with the SF-12 health survey (34), Framingham
4 coronary heart disease (CHD) risk score (35), and Australian type 2 diabetes risk assessment
5 tool (AUSDRISK) (36) to enable cost effectiveness evaluation of the two health promotion
6 interventions. SF-12 measures both physical and mental health status and has acceptable
7 validity and reliability (37, 38). Framingham CHD is a validated tool to assess cardiovascular
8 diseases (39) and AUSDRISK is a diabetes risk assessment tool based on demographic,
9 lifestyle and simple anthropometric measures (36).
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18 Dietary quality is assessed with a food-based diet quality index, the Australian
19 Recommended Food Score (ARFS) (40). The ARFS is aligned with Australian Dietary
20 Guidelines (41) and the Australian Guide to Healthy Eating (42) recommendations. The
21 ARFS total ranges from 0 to 73 and includes eight subscales: vegetables (0 to 21), fruit (0 to
22 12), protein (0 to 7), vegetarian alternatives (0 to 6), grains (0 to 13), dairy (0 to 11), water (0
23 to 1), sauces and condiments (0 to 2). Higher scores indicate greater compliance with the
24 Australian Dietary Guidelines and therefore better diet quality. The ARFS has demonstrated
25 good validity and reproducibility (40).
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36 Lastly, the Pittsburgh Sleep Quality Index (PSQI) (43) is an effective instrument used
37 to measure the quality and patterns of sleep in adults. It differentiates “poor” from “good”
38 sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency,
39 sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and
40 daytime dysfunction over the last month. PSQI reports great test-retest reliability (0.87) and
41 high correlations with sleep log data (44).
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50 *Randomization*

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53 Upon completion of the baseline assessment, participants are randomly allocated into one of
54 the three groups (see Table 2 and Figure 1). The allocation sequence is computer generated
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3 by an independent researcher and is not known to the study team at the time of enrolment and
4
5 baseline assessment. A permuted block randomization sequence comprising block sizes of 6
6
7 stratified by gender and age group (18-49 vs 50+) is used. The project manager who is not
8
9 involved with conducting assessments assigns the participants into groups according to the
10
11 generated sequence and notifies participants of their group allocation via email.
12

13 14 *Interventions*

15 16 17 *Group 1: Body Brain Life – General Practice (BBL-GP)*

18
19 BBL-GP is an intervention package that builds on our dementia prevention research programs.
20
21 This includes an online dementia risk reduction program called the Body Brain Life (BBL;
22
23 Trial ID: ACTRN12612000147886) (15, 45) and the Fitness for the Ageing Brain Study
24
25 (FABS; Trial ID: ACTRN 12609000755235) (46, 47). Contents for the BBL-GP online
26
27 modules have been revised after extensive consumer evaluation by members of the
28
29 Alzheimer’s Australia Consumer Dementia Research Network as well as members of the
30
31 public and from participant feedback after the previous trial. The physical activity program
32
33 has also been modified for a younger age-group to 18 years and older as previous programs
34
35 targeted middle aged and older adults. The Actigraph device was introduced to measure the
36
37 objective amount and intensity of physical activity. This revised program (Body Brain Life –
38
39 Fit) was piloted with the general public (Trial ID: ACTRN12615000822583).
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44 Participants in the BBL-GP group are required to complete 8 modules (dementia
45
46 literacy, risk factors, physical activity, nutrition, health, cognitive activity, social activity and
47
48 mood) delivered online. Prior to commencing online modules, participants in the BBL-GP
49
50 group also receive an individually tailored plan/program for both dietary and physical activity
51
52 interventions developed and delivered by a dietitian and an exercise physiologist, respectively
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54 during a face-to-face assessment. This is to ensure the dietary prescription and level of
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3 physical activity are suitable and tailored to individual participants.
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5 *Physical activity session*

6
7 The session duration and frequency of the physical activity (PA) program varies between
8 participants based on baseline physical activity levels and individual tailoring. An exercise
9 physiologist designs an individual program for the participant, delivers this in a face-to-face
10 workshop and monitors the physical activity program via the returned diaries and telephone
11 monitoring. For those not doing any regular PA at baseline, the target is 150 minutes/week
12 moderate intensity PA, with moderate intensity defined as a score of 10-12 on the Borg
13 Rating of Perceived Exertion scale (RPE) (48). For those who are doing regular PA but for
14 less than 100 minutes/week, an additional 100 minutes/week is prescribed, and for those
15 meeting the target, an additional 50 minutes/week is prescribed. Printed material guiding
16 participants to increase their activity level with worksheets are also provided. A diary in the
17 format of a calendar returned monthly for 24 weeks is used to record PA and RPE to assess
18 PA and intensity adherence. Participants may develop a medical problem or undergo
19 treatment that can make exercising difficult or impossible. If this happens, prescribed amount
20 of exercise is reviewed and re-prescribed, or stopped.
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37 *Dietary session*

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39 Participants at baseline who had unintentional weight loss of 5 kg or weight gain of 5 kg over
40 the previous six months were seen by the dietitian. Furthermore, participants whose diets at
41 baseline scored low on one or more of the subscales of the (ARFS) (vegetables <14, fruit <8,
42 protein <4, grains <9, dairy <8, water <1) (40), were also seen by the dietitian. Dietary
43 counselling was provided by a trained dietitian and overseen by the coordinating dietitian.
44
45 During the one hour face-to-face counselling session, participants received individually
46 tailored dietary advice and printed material explaining the diet in detail.
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54 *Follow ups*

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

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18 Once participants in the BBL-GP group have received face-to-face PA and dietary
19 counselling sessions, they are asked to log on to the trial website and complete one module
20 per week, each taking approximately 30-40 minutes. The 12-week program is detailed in
21 Table 3. The first 8 weeks include the completion of 8 educational and individually tailored
22 behaviour change modules. In the remaining 4 weeks, participants undertake online activities
23 focused on goal monitoring and revision of the modules materials. Tailoring of the six
24 behaviour change modules (weeks 3-8) is conducted using an automated algorithm that
25 presents content on the basis of whether or not the participant has a relevant risk factor, as
26 well as on the basis of their responses to several questions measuring psychological
27 determinants of behaviour. These questions are presented at the beginning of each of the
28 behaviour change modules. For instance, a person who is classified as having a poor diet (e.g.
29 lack of fish intake) on the basis of their responses on the ANU-ADRI, and who does not
30 regard himself/herself as a role model to others with respect to their diet habits will not be
31 presented with information focusing on becoming a role model to others.
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48 The program is built in such a way that participants are only able to access the
49 relevant component of the intervention at a given time. The modules become active, 1 per
50 week, on the same day for the first 8 weeks. Participants are unable to access a newly
51 activated module before completing the previously scheduled module. Each week,
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3 participants receive a notification email on the same day of the week alerting them when a
4
5 new module has become active and a list of already activated modules that they have either
6
7 not started or completed. Participants who are late completing modules will be followed up
8
9 with an email from the project manager to identify if there is a reason (e.g. holidays, illness,
10
11 work commitments) preventing their participation, and encouraging them to continue with the
12
13 study. Compliance is recorded for each module if they are completed on time, delayed or not
14
15 completed.

16 17 18 *Group 2: Lifestyle Modification Program (LMP)*

19
20
21 The lifestyle modification program (LMP), developed by NHC, is designed to provide
22
23 individuals with tools to help manage chronic disease and maintain a healthy lifestyle. LMP
24
25 is a six- week group program provided by various health professionals (dietitian, exercise
26
27 physiologist, nurse practitioner, psychologist, pharmacist and sleep physician) providing
28
29 information on basic nutrition, meal planning, physical activity, health conditions, motivation
30
31 and goals, medications, and sleep. Every week, 2 sessions are provided on the same day with
32
33 each session lasting an hour. The course is currently run by the NHC for their patients to
34
35 assist them in improving their lifestyle and management of chronic disease so it is a
36
37 pragmatic real-life comparison condition. Attendance is recorded for compliance and
38
39 motivation checking. Although the LMP is a free nationally recognized program that is
40
41 designed to provide individuals with tools to help manage chronic disease and maintain a
42
43 healthy lifestyle, evaluation of the program has not been carried out as yet. The attendance is
44
45 recorded each week for a fidelity test.

46 47 48 *Group 3: Active control/Email only*

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51 The active control group or email only group proceed with their normal activities and access
52
53 health services as required over the trial period. Participants in this group also receive weekly
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3 emails containing links to various websites providing information on lifestyle risk factors and
4 disease management for a duration of 12 weeks. The weekly emails contain several links, and
5
6
7 participants are encouraged to spend approximately an hour each week browsing through the
8
9 material. The material is generally organized around the same themes as the ones included in
10
11 the BBL-GP program. An effort has been made to include links to relevant information and
12
13 educational material, but that otherwise does not include the use of identifiable behaviour-
14
15 change techniques which are the 'active ingredient' of the BBL-GP program. In addition,
16
17 other than providing participants with the weekly emails, no further contact is made with the
18
19 participants in this group, such as reminders and prompts that are provided to the BBL-GP
20
21 group.
22
23

24 *Masking*

25
26 To prevent performance bias, research staff conducting the assessments remain masked to
27
28 participants' group allocation. The contact person for participants' website queries, access
29
30 issues, and technical difficulties is independent of all baseline assessment data. All
31
32 participants are informed that they are being randomly allocated to one of three study groups
33
34 and that one group may be more effective than others. They are also notified at the start of the
35
36 study that one of these groups involves face-to-face group sessions which require them to
37
38 travel to NHC head office. Hence, the research team members who recruit participants,
39
40 conduct individual diet and physical activity sessions, and professionals who are involved in
41
42 the LMP are naturally able to tell which group they have been allocated to. Nurses who
43
44 conduct baseline and follow-up assessments are however masked to group allocation.
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48 *Data management and monitoring*

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50 A trial management committee is formed by the research team members (chief and co-
51
52 investigators). Nursing staffs from NHC and research assistants collect, clean and send the
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54 study data to the committee on a weekly basis. Most data are automatically entered into excel
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3 files and other data are double-entered to SPSS files to prevent data entry errors. Data
4
5 management is then handled independently from the researchers who interpret the data. All
6
7 data are stored electronically and in an independent spreadsheet and SPSS data file, which is
8
9 only accessible by the researchers involved in this study.
10

11 An independent Data Monitoring Committee (DMC) is established independently
12
13 from the research team who are involved with collecting and managing data. The DMC will
14
15 provide an independent oversight of the trial and will review general conduct of the trial and
16
17 study data for participant safety. The DMC is comprised of independent, multidisciplinary
18
19 experts in dementia research who will make recommendations regarding the continuation,
20
21 modification or termination of the trial.
22
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24 Adverse events (minor and serious) will be monitored throughout the trial by the
25
26 research team and any adverse events will be reported to the trial Data Monitoring
27
28 Committee. For this trial, an adverse event is defined as an unwanted and usually
29
30 harmful outcome (e.g. physical injuries). The event may or may not be related to the
31
32 intervention, but it occurs while the person is participating in the intervention, that is,
33
34 while they are undertaking physical activities individually prescribed by the exercise
35
36 physiologist.
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39 There are no formal interim analyses planned, as it is not expected that adverse events
40
41 will be differentially related to the interventions.
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43

44 *Statistical analyses*

45
46 Statistical analyses will be based on an intention-to-treat approach. As applied in the previous
47
48 BBL project (15), multiple imputation and mixed models will be applied to analyse data. We
49
50 hypothesise that the effectiveness of the intervention programs will be in the following order:
51
52 BBL-GP > LMP > active control. The hypothesis that BBL-GP will be more effective than
53
54 LMP is based on research showing that a tailored program is better than a one size fits all
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3 group program in most cases (49). This is also based on the previous BBL project where
4
5 those in BBL groups improved more than those in the control group. We will also adjust for
6
7 compliance in completing the online modules and following recommendations provided by
8
9 the dietitian and exercise physiologist (for BBL-GP group), or for attendance to weekly group
10
11 sessions (for LMP group).
12

13 *Ethics and trial registration*

14
15 The Human Research Ethics Committee at the Australian National University has approved
16
17 the study protocols and procedures (protocol #2016/157). This project has also been
18
19 registered at the Australian New Zealand Clinical Trials Registry (ACTRN:
20
21 12616000868482).
22
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24 *Adverse events*

25
26 This study evaluates lifestyle intervention programs to reduce risk factors for AD. The target
27
28 population is adults in a primary care setting who have some of the known risk factors for
29
30 dementia, but are at the time of the intervention, healthy and free of any dementia-related
31
32 symptoms. We do not anticipate that participants will be placed at a greater risk than that
33
34 associated with self-driven educational activities over the Internet. An adverse event where a
35
36 participant can get hurt during prescribed exercise can occur. To prevent this, we screen
37
38 participants using APSS at the baseline assessment to identify individuals with acute/high
39
40 risk conditions for exercise. In addition, the exercise physiologist individually tailors
41
42 prescribed exercise to minimise risk of injury. Medical assessments are done by the
43
44 participants' usual nurses and doctors and if any abnormality is detected in their results, they
45
46 are required to discuss these abnormalities with participants as usual. To address issues of
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48 potential fatigue, the assessments have been kept to a minimum length. In addition, all online
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50 and face-to-face sessions are designed in an interactive way and are limited to 1-hour sessions
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52 (LMP has 2 themed sessions per week and has a break between sessions). As mentioned
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2
3 above, all online modules are delivered in an individually tailored fashion to maximize
4
5 relevance for each individual.

6 7 *Dissemination plan*

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9 Positive, neutral and negative results of the trial will be submitted to international peer-
10
11 reviewed journals. In addition, results will be presented at national and international
12
13 conferences relevant to the subject matters. Authorship will be allocated using the guidelines
14
15 for authorship defined by the International Committees of Medical Journal Editors and
16
17 depends on personal involvement.
18

19 20 **Discussion**

21
22 The project is currently under way as an evaluation of the efficacy of health promotion
23
24 interventions in adults with risk factors for dementia. The program aims to reduce
25
26 cardiometabolic risk and promote behaviours shown to protect against dementia. The trial,
27
28 recruiting from a primary care setting has generated considerable interest, and to date,
29
30 approximately half of the total target sample has been assessed and randomised into the
31
32 intervention groups. We anticipate that all data collection will be completed by December
33
34 2018. The results of the study are likely to form an evidence base for the feasibility of
35
36 dementia risk reduction campaigns to lead to lifestyle changes and the reduction of dementia
37
38 risk factors at the population level. This trial will also support the feasibility of such
39
40 interventions being applied in primary care settings. Successful outcomes of the current trial
41
42 may lead to significant public health impact and benefits once the intervention is made
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44 available at the population level pending positive results.
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48 49 **Conclusion**

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

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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	√				

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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	√		√	√	√

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

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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.

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3 Figure 1. Study Flowchart
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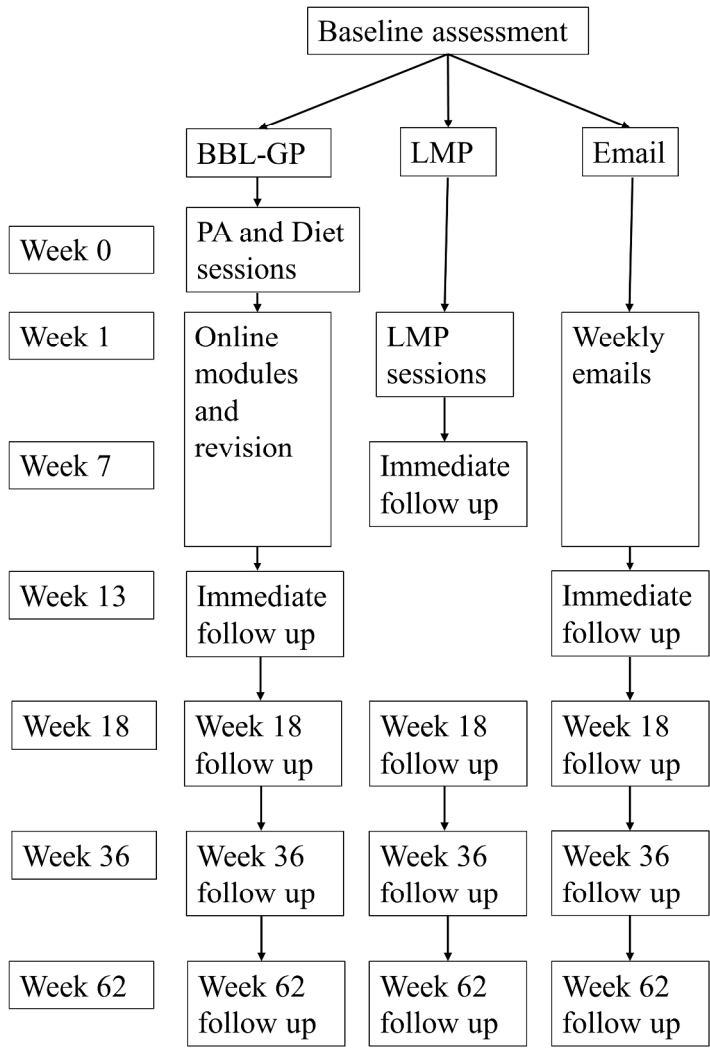


Figure 1: Study Flowchart

225x300mm (300 x 300 DPI)



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___

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47**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 ___

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3	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___
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5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___9___
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8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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12	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___
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17	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___
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___13___
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___17-18___
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___17___
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31 **Methods: Data collection, management, and analysis**

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33	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___
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38		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___
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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___
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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___
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	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___18___
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	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___
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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___
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	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___
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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___
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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___
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Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___18___
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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___
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___9___
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A___
7				
8	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___
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___26___
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14	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___
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17	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___
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20	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___
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	___19___
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___N/A___
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___N/A___
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34	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___
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019329.R2
Article Type:	Protocol
Date Submitted by the Author:	23-Jan-2018
Complete List of Authors:	Kim, Sarang; Australian National University, Centre for Research on Ageing, Health and Wellbeing McMaster, Mitchell; Australian National University, Centre for Research on Ageing, Health and Wellbeing Torres, Susan ; Deakin University Cox, Kay L. Lautenschlager, Nicola; University of Melbourne, Academic Unit of Psychiatry of Old Age Rebok, George; Johns Hopkins Bloomberg School of Public Health, Psychiatry and Behavioral Sciences Pond, Dimity; University of Newcastle Australia, General Practice D'Este, Catherine; ANU College of Medicine, Biology and Environment The Australian National University, National Centre for Epidemiology and Population Health (NCEPH) McRae, Ian; Australian National University, School of Population Health Cherbuin, Nicolas; Australian National University, Centre for Research on Ageing, Health and Wellbing Anstey, Kaarin
Primary Subject Heading:	Public health
Secondary Subject Heading:	Medical education and training
Keywords:	RCT, Dementia < NEUROLOGY, Lifestyle change, online, Australia, General practice

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Manuscripts

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6 Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle
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8 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.

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3 Trial registration: Reg. no. ACTRN12616000868482
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8 Keywords: RCT, dementia, lifestyle change, online, physical activity, diet, cardiovascular
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10 risk factors, Australia, general practice, primary care.
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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

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3 decline (7). Physical activity has also been shown in RCTs to benefit several other risk
4 factors for dementia including depression (8), and cardiovascular risk factors (9). Physical
5 activity not only modifies multiple risk factors but it has direct benefits for brain health and
6 cognition.
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11 To bring about risk reduction, there needs to be long-lasting behavioural change in
12 multiple areas. Achieving this requires using techniques such as goal setting, decreasing
13 barriers to change, improving self-monitoring, having access to information, and maintaining
14 motivation (10, 11). Therefore, this RCT investigates whether lifestyle management
15 programs that offer not only health promoting information, but also practical behaviour
16 change techniques which can be implemented in daily life can reduce dementia risk.
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20 21 22 *Recruitment in general practice setting*

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26 Primary care is an ideal setting for the implementation of the current program because
27 it is where adults with high risk of developing dementia are identified and early intervention
28 and treatment are provided (12). Assessment of cardiovascular risk factors is common in
29 primary care, as is advice about physical activity and diet. General practitioners (GP)
30 commonly screen for diabetes and increasingly identify depression. GPs are often the first
31 point of contact for patients who are worried that they may have dementia (13).
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40 Although there has been one study conducted in primary care setting with elderly
41 participants (70-78 years old) addressing cardiovascular risk factors (14), the current program
42 is the first of its kind to provide interventions to adults (18 years and above) at the primary
43 care setting, addressing both cardiovascular and lifestyle risk factors of dementia.
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48 49 **Methods and analysis**

50 51 *Study setting and design*

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

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27 The existing LMP program included 6 weeks of face-to-face group education sessions.
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29 The BBL-GP program included 12 weeks of individually tailored online education sessions
30 with one hour face-to-face individual sessions with a dietitian and an exercise physiologist.
31
32 The BBL-GP and LMP are being compared to an active control group receiving weekly email
33 with links to health information. The study is being conducted in Canberra, Australian
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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

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

31 *Inclusion criteria*

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34 A naturalistic approach is used in recruitment and the study inclusion criteria being used for
35 this study are those already used by the NHC to refer patients to the LMP program (prior to
36 this research project). The inclusion criteria is pragmatic as the practice already had criteria
37 for referral to their LMP and in developing the protocol, it became clear that introducing a
38 second set of inclusion criteria would make implementation difficult and reduce participant
39 numbers. We therefore decided to use the principle that if a GP would refer the patient to the
40 LMP then they would be eligible for the trial. This is a pragmatic feature of the current trial
41 that significantly differs from our original BBL trial. We aimed to optimise the seamlessness
42 of the intervention in primary care and utilise existing referral pathways to increase the
43 probability that the intervention is conducted in a manner that could lead to implementation
44 in real life. Participants must be aged 18 years and over, reside in the Australian Capital
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3 Territory, be current financial members of the NHC, have access to a computer and internet
4 connection at home, be fluent in English, Australian permanent residents or citizens (for bulk
5 billing eligibility), and must be the only person in their household who is taking part in this
6 study to prevent being randomly assigned to different groups and sharing information about
7 their interventions with each other received. To be eligible for the study, participants are also
8 required to have a chronic health condition (high blood pressure, heart disease, type 2
9 diabetes or 'pre-diabetes', osteoporosis, osteoarthritis, polycystic ovary syndrome (PCOS),
10 kidney or liver disease, and depression/anxiety) or be overweight or obese (BMI>25). They
11 are also required to agree to commit 1-2 hours a week to complete the program and be
12 interested in obtaining advice on improving their lifestyle to reduce the risk of or better
13 manage chronic disease. Participants are required to complete online assessments and attend
14 NHC at baseline and 18, 36, and 62 weeks after commencement of the intervention for
15 medical and cognitive assessments.
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30 31 *Exclusion criteria*

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

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53 Sample size calculations were estimated using G*Power (version 3.1.9.2;
54 <http://www.gpower.hhu.de/en.html>) and have been based on medium effect size as
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3 observed in the previous Body Brain Life project with same primary outcome (19). To
4 detect a medium effect (0.5 standard deviation (SD)) in a 3-group design (1:1:1), 4
5 measurements with a 5% risk of type 1 error (α) and 80% power, a total sample size of
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7 159 persons is required. To account for a 33% attrition (based on previous lifestyle
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9 modification program by NHC using the same inclusion and exclusion criteria and
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11 targeting same age group), a baseline sample of 240 is being recruited (80 in BBL-GP
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13 group, 80 in LMP group and 80 in control group).
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16 17 18 *Assessments*

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21 Participants who meet all inclusion and no exclusion criteria are invited to complete online
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23 surveys and visit NHC for the baseline evaluation, and for week 18, 36, and 62 follow ups.
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25 Immediate follow up is also conducted online at week 7 for LMP, and week 13 for BBL-GP
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27 and control groups. Table 1 summarises the assessment measures and schedule.
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30 31 *Screening measures and covariate*

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33 In addition to the above inclusion and exclusion criteria, further screening measures are
34
35 conducted to ensure that participants are capable of taking part in the study. The Adult Pre-
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37 exercise Screening System (APSS) (20) is used at the baseline assessment to identify
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39 individuals with acute/high risk conditions, or who may be at higher risk of an adverse event
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41 during exercise. To screen for any cognitive impairment (<25), the Mini-Mental State
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43 Examination (MMSE) (21) is administered to participants aged 60 and older.
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47 Health efficacy and motivation for healthiness subscales from the Multidimensional
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49 Health Questionnaire (MHQ) (22) is used to measure the extent to which people believe they
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51 have the ability, capability, skills and talents to take care of their own physical health, and to
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53 measure people's motivation to keep in good physical health.
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56 57 *Primary outcome*

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3 The primary outcome is one's exposure profile to demonstrated risk factors for Alzheimer's
4 disease. It is measured with a modified version of the Australian National University
5 Alzheimer's Disease Risk Index – Short form (ANU-ADRI – SF) (23). The ANU-ADRI-SF
6 is comprised of validated scales assessing 15 individual risk and protective factors for
7 Alzheimer's disease and dementia. Intra class correlation coefficients suggested that the
8 reliability of the ANU-ADRI-SF compared to the original ANU-ADRI were moderate to
9 strong (0.77 to 0.99) and statistically significant ($p < .001$) except for cognitive activity.
10 Therefore, for the assessment of engagement in cognitive activities levels only, items from
11 the original ANU-ADRI (19, 24) are used in place of those from the ANU-ADRI-SF due to
12 limitations of the latter.
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24 25 *Secondary outcomes*

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27 Secondary outcomes include cognitive function, physical activity level, depressive symptoms,
28 cost of interventions, diet and sleep quality. They are measured as follows: cognitive function
29 is assessed with processing speed, task switching and executive function using Trails A and B,
30 and the Digit Symbol Modalities Test (DSMT). These tests were chosen because the
31 executive function is the most sensitive cognitive domain to physical activity interventions
32 (25) and a decline in processing speed is associated with cardiovascular risk factors (26).
33 Both Trails and DSMT have been used widely and have been reported to have good
34 reliability and validity (27-30). Moderate-vigorous Physical Activity (MVPA) is a continuous
35 measure of activity that registers three or more Metabolic Equivalents (METs) for 10 minutes
36 or longer on an ActiGraph Link activity monitor
37 (<http://actigraphcorp.com/products/actigraph-link/>), which is worn for 7 days. Self-reported
38 physical activity is also being recorded using the short form of the International Physical
39 Activity Questionnaire (IPAQ) (31), which is part of the ANU-ADRI-SF. Reliability and
40 validity of IPAQ has been tested and confirmed across 12 countries (31). Depression is being
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3 assessed with the Centre for Epidemiological Studies Depression (CES-D) Scale (32), which
4 is also part of the ANU-ADRI. CES-D scale has a very high internal consistency and validity
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7 (33).
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10 Health outcomes are assessed with the SF-12 health survey (34), Framingham
11 Coronary Heart Disease (CHD) Risk score (35), and Australian type 2 diabetes risk
12 assessment tool (AUSDRISK) (36) to enable cost effectiveness evaluation of the two health
13 promotion interventions. SF-12 measures both physical and mental health status and has
14 acceptable validity and reliability (37, 38). Framingham CHD is a validated tool to assess
15 cardiovascular diseases (39) and AUSDRISK is a diabetes risk assessment tool based on
16 demographic, lifestyle and simple anthropometric measures (36).
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25 Dietary quality is assessed with a food-based diet quality index, the Australian
26 Recommended Food Score (ARFS) (40). The ARFS is aligned with Australian Dietary
27 Guidelines (41) and the Australian Guide to Healthy Eating (42) recommendations. The
28 ARFS total ranges from 0 to 73 and includes eight subscales: vegetables (0 to 21), fruit (0 to
29 12), protein (0 to 7), vegetarian alternatives (0 to 6), grains (0 to 13), dairy (0 to 11), water (0
30 to 1), sauces and condiments (0 to 2). Higher scores indicate greater compliance with the
31 Australian Dietary Guidelines and therefore better diet quality. The ARFS has demonstrated
32 good validity and reproducibility (40).
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43 Lastly, the Pittsburgh Sleep Quality Index (PSQI) (43) is an effective instrument used
44 to measure the quality and patterns of sleep in adults. It differentiates “poor” from “good”
45 sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency,
46 sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and
47 daytime dysfunction over the last month. PSQI reports great test-retest reliability (0.87) and
48 high correlations with sleep log data (44).
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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

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

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

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48 Participants at baseline who had unintentional weight loss of 5 kg or weight gain of 5 kg over
49 the previous six months were seen by the dietitian. Furthermore, participants whose diets at
50 baseline scored low on one or more of the subscales of the (ARFS) (vegetables <14, fruit <8,
51 protein <4, grains <9, dairy <8, water <1) (40), were also seen by the dietitian. Dietary
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3 counselling was provided by a trained dietitian and overseen by the coordinating dietitian.
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5 During the one hour face-to-face counselling session, participants received individually
6
7 tailored dietary advice and printed material explaining the diet in detail.
8

9 *Follow ups*

10
11 Participants in the BBL-GP group are monitored through phone calls at week 4, 12 (14 for
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13 PA) and week 20 by the dietitian and exercise physiologist to monitor the progress and for
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15 reassurance. In addition, they receive a general booster session at 12 months with a phone
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17 call and a mailed-out booklet summarising materials from the online modules. They are being
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19 asked to continue being active and follow a healthy eating plan after completion of the
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21 intervention.
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24 *Online modules*

25
26 Once participants in the BBL-GP group have received face-to-face PA and dietary
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28 counselling sessions, they are asked to log on to the trial website and complete one module
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30 per week, each taking approximately 30-40 minutes. The 12-week program is detailed in
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32 Table 3. The first 8 weeks include the completion of 8 educational and individually tailored
33
34 behaviour change modules. In the remaining 4 weeks, participants undertake online activities
35
36 focused on goal monitoring and revision of the modules materials. Tailoring of the six
37
38 behaviour change modules (weeks 3-8) is conducted using an automated algorithm that
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40 presents content on the basis of whether or not the participant has a relevant risk factor, as
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42 well as on the basis of their responses to several questions measuring psychological
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44 determinants of behaviour. These questions are presented at the beginning of each of the
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46 behaviour change modules. For instance, a person who is classified as having a poor diet (e.g.
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48 lack of fish intake) on the basis of their responses on the ANU-ADRI, and who does not
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50 regard himself/herself as a role model to others with respect to their diet habits is not
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52 presented with information focusing on becoming a role model to others.
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3 The program is built in such a way that participants are only able to access the
4 relevant component of the intervention at a given time. The modules become active, 1 per
5 week, on the same day for the first 8 weeks. Participants are unable to access a newly
6 activated module before completing the previously scheduled module. Each week,
7 participants receive a notification email on the same day of the week alerting them when a
8 new module has become active and a list of already activated modules that they have either
9 not started or completed. Participants who are late completing modules will be followed up
10 with an email from the project manager to identify if there is a reason (e.g. holidays, illness,
11 work commitments) preventing their participation, and encouraging them to continue with the
12 study. Compliance is recorded for each module if they are completed on time, delayed or not
13 completed.

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27 *Group 2: Lifestyle Modification Program (LMP)*

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29 The lifestyle modification program (LMP), developed by NHC, is designed to provide
30 individuals with tools to help manage chronic disease and maintain a healthy lifestyle. LMP
31 is a six- week group program provided by various health professionals (dietitian, exercise
32 physiologist, nurse practitioner, psychologist, pharmacist, and sleep physician) providing
33 information on basic nutrition, meal planning, physical activity, health conditions, motivation
34 and goals, medications, and sleep. Every week, 2 sessions are provided on the same day with
35 each session lasting an hour. The course is currently run by the NHC for their patients to
36 assist them in improving their lifestyle and management of chronic disease so it is a
37 pragmatic real-life comparison condition. Attendance is recorded for compliance and
38 motivation checking. Although the LMP is a free nationally recognised program that is
39 designed to provide individuals with tools to help manage chronic disease and maintain a
40 healthy lifestyle, evaluation of the program has not been carried out as yet. The attendance is
41 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

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

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5 *Data management and monitoring*

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7 A trial management committee is formed by the research team members (chief and co-
8 investigators). Nursing staffs from NHC and research assistants collect, clean and send the
9 study data to the committee on a weekly basis. Most data are automatically entered into excel
10 files and other data are double-entered to SPSS files to prevent data entry errors. Data
11 management is then handled independently from the researchers who interpret the data. All
12 data are stored electronically and in an independent spreadsheet and SPSS data file, which is
13 only accessible by the researchers involved in this study.
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22 An independent Data Monitoring Committee (DMC) is established independently
23 from the research team who are involved with collecting and managing data. The DMC
24 provides an independent oversight of the trial and reviews general conduct of the trial and
25 study data for participant safety. The DMC is comprised of independent, multidisciplinary
26 experts in dementia research who makes recommendations regarding the continuation,
27 modification or termination of the trial.
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35 Adverse events (minor and serious) are monitored throughout the trial by the
36 research team and any adverse events would be reported to the trial DMC. For this trial,
37 an adverse event is defined as an unwanted and usually harmful outcome (e.g. physical
38 injuries). The event may or may not be related to the intervention, but it occurs while
39 the person is participating in the intervention, that is, while they are undertaking
40 physical activities individually prescribed by the exercise physiologist.
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48 There are no formal interim analyses planned, as it is not expected that adverse events
49 would be differentially related to the interventions.
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52 *Statistical analyses*

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54 Statistical analyses will be based on an intention-to-treat approach. As applied in the previous
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3 BBL project (15), multiple imputation and mixed models will be applied to analyse data. We
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5 hypothesise that the effectiveness of the intervention programs will be in the following order:
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7 BBL-GP > LMP > active control. The hypothesis that BBL-GP will be more effective than
8
9 LMP is based on research showing that a tailored program is better than a one size fits all
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11 group program in most cases (49). This is also based on the previous BBL project where
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13 those in BBL groups improved more than those in the control group. We will also adjust for
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15 compliance in completing the online modules and following recommendations provided by
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17 the dietitian and exercise physiologist (for BBL-GP group), or for attendance to weekly group
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19 sessions (for LMP group).
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22 *Ethics and trial registration*

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24 The Human Research Ethics Committee at the Australian National University has approved
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26 the study protocols and procedures (protocol #2016/157). This project has also been
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28 registered at the Australian New Zealand Clinical Trials Registry (ACTRN:
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30 12616000868482).
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33 *Adverse events*

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35 This study evaluates lifestyle intervention programs to reduce risk factors for AD. The target
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37 population is adults in a primary care setting who have some of the known risk factors for
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39 dementia, but are at the time of the intervention, healthy and free of any dementia-related
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41 symptoms. We do not anticipate that participants are placed at a greater risk than that
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43 associated with self-driven educational activities over the Internet. An adverse event where a
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45 participant can get hurt during prescribed exercise can occur. To prevent this, we screen
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47 participants using APSS at the baseline assessment to identify individuals with acute/high
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49 risk conditions for exercise. In addition, the exercise physiologist individually tailors
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51 prescribed exercise to minimise risk of injury. Medical assessments are done by the
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53 participants' usual nurses and doctors and if any abnormality is detected in their results, they
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3 are required to discuss these abnormalities with participants as usual. To address issues of
4 potential fatigue, the assessments have been kept to a minimum length. In addition, all online
5 and face-to-face sessions are designed in an interactive way and are limited to 1-hour sessions
6 (LMP has 2 themed sessions per week and has a break between sessions). As mentioned
7 above, all online modules are delivered in an individually tailored fashion to maximise
8 relevance for each individual.
9

10 *Dissemination plan*

11 Positive, neutral and negative results of the trial will be submitted to international peer-
12 reviewed journals. In addition, results will be presented at national and international
13 conferences relevant to the subject matters. Authorship will be allocated using the guidelines
14 for authorship defined by the International Committees of Medical Journal Editors and
15 depends on personal involvement.
16

17 **Discussion**

18 The project is currently under way as an evaluation of the efficacy of health promotion
19 interventions in adults with risk factors for dementia. The program aims to reduce
20 cardiometabolic risk and promote behaviours shown to protect against dementia. The trial,
21 recruiting from a primary care setting has generated considerable interest, and to date,
22 approximately half of the total target sample has been assessed and randomised into the
23 intervention groups. We anticipate that all data collection will be completed by December
24 2018. The results of the study are likely to form an evidence base for the feasibility of
25 dementia risk reduction campaigns to lead to lifestyle changes and the reduction of dementia
26 risk factors at the population level. This trial will also support the feasibility of such
27 interventions being applied in primary care settings. Successful outcomes of the current trial
28 may lead to significant public health impact and benefits once the intervention is made
29 available at the population level pending positive results.
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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.

For peer review only

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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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This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

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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	√				

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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

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

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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.

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3 Figure 1. Study Flowchart
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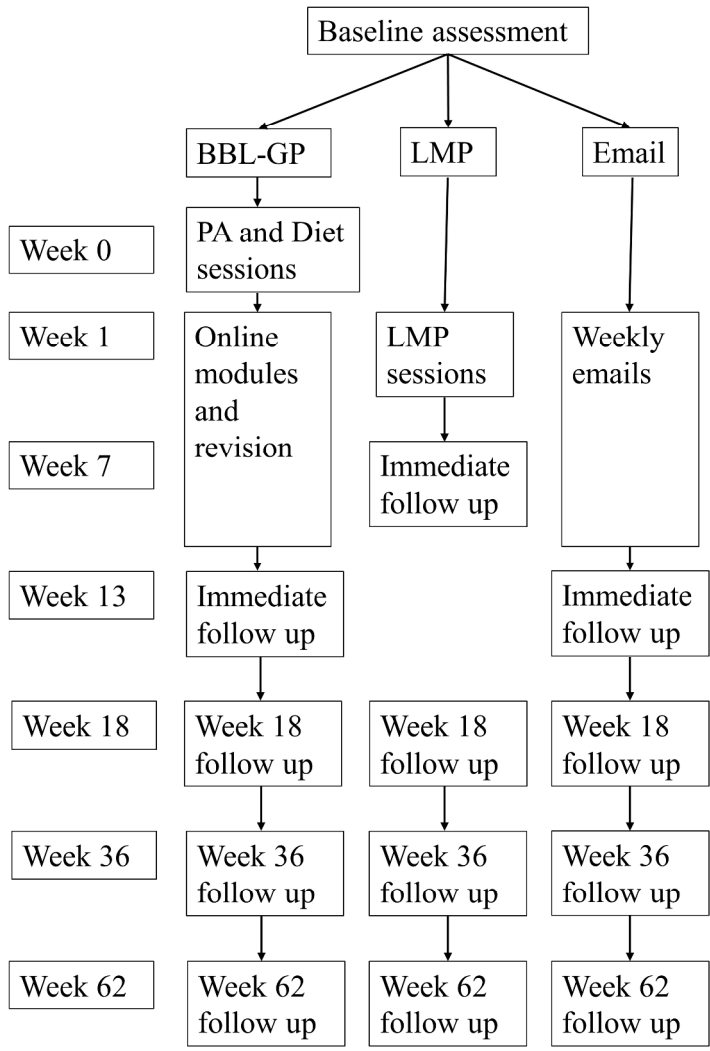


Figure 1: Study Flowchart

225x300mm (300 x 300 DPI)



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___

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47**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 ___

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3	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___
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5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___9___
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8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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12	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___
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17	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___
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___13___
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___17-18___
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___17___
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31 **Methods: Data collection, management, and analysis**

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33	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___
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38		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___
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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_____



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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___9___
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A___
7				
8	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___
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___26___
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14	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___
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17	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___
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20	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___
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	___19___
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___N/A___
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___N/A___
32				
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34	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___
35				
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019329.R3
Article Type:	Protocol
Date Submitted by the Author:	09-Feb-2018
Complete List of Authors:	Kim, Sarang; Australian National University, Centre for Research on Ageing, Health and Wellbeing McMaster, Mitchell; Australian National University, Centre for Research on Ageing, Health and Wellbeing Torres, Susan ; Deakin University Cox, Kay L. Lautenschlager, Nicola; University of Melbourne, Academic Unit of Psychiatry of Old Age Rebok, George; Johns Hopkins Bloomberg School of Public Health, Psychiatry and Behavioral Sciences Pond, Dimity; University of Newcastle Australia, General Practice D'Este, Catherine; ANU College of Medicine, Biology and Environment The Australian National University, National Centre for Epidemiology and Population Health (NCEPH) McRae, Ian; Australian National University, School of Population Health Cherbuin, Nicolas; Australian National University, Centre for Research on Ageing, Health and Wellbeing Anstey, Kaarin
Primary Subject Heading:	Public health
Secondary Subject Heading:	Medical education and training
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Manuscripts

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6 Protocol for a pragmatic randomised controlled trial of Body Brain Life – GP and a Lifestyle
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8 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.

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3 Trial registration: Reg. no. ACTRN12616000868482
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8 Keywords: RCT, dementia, lifestyle change, online, physical activity, diet, cardiovascular
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10 risk factors, Australia, general practice, primary care.
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For peer review only

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).

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3 PA has also been shown in RCTs to benefit several other risk factors for dementia including
4 depression (8), and cardiovascular risk factors (9). PA not only modifies multiple risk factors
5 but it has direct benefits for brain health and cognition.
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9 To bring about risk reduction, there needs to be long-lasting behavioural change in
10 multiple areas. Achieving this requires using techniques such as goal setting, decreasing
11 barriers to change, improving self-monitoring, having access to information, and maintaining
12 motivation (10, 11). Therefore, this RCT investigates whether lifestyle management
13 programs that offer not only health promoting information, but also practical behaviour
14 change techniques which can be implemented in daily life can reduce dementia risk.
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22 *Recruitment in general practice setting*

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24 Primary care is an ideal setting for the implementation of the current program because
25 it is where adults with high risk of developing dementia are identified and early intervention
26 and treatment are provided (12). Assessment of cardiovascular risk factors is common in
27 primary care, as is advice about PA and diet. General practitioners (GP) commonly screen for
28 diabetes and increasingly identify depression. GPs are often the first point of contact for
29 patients who are worried that they may have dementia (13).
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37 Although there has been one study conducted in primary care setting with elderly
38 participants (70-78 years old) addressing cardiovascular risk factors (14), the current program
39 is the first of its kind to provide interventions to adults (18 years and above) at the primary
40 care setting, addressing both cardiovascular and lifestyle risk factors of dementia.
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46 **Methods and analysis**

47 *Study setting and design*

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

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24 The existing LMP program included 6 weeks of face-to-face group education sessions.
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26 The BBL-GP program included 12 weeks of individually tailored online education sessions
27 with one hour face-to-face individual sessions with a dietitian and an exercise physiologist.
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29 The BBL-GP and LMP are being compared to an active control group receiving weekly email
30 with links to health information. The study is being conducted in Canberra, Australian
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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

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3 memberships), those aged less than 18 years, or without email addresses. Posters at the
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5 clinics are also being used for the recruitment. Potential participants who express their
6
7 interest by contacting the LMP coordinator at the NHC or registering on the NHC's website
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9 are assessed against the inclusion and exclusion criteria. These are the types of adults who a
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11 GP would refer to a dementia risk reduction trial in 'real life' and on whom we are aiming to
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13 evaluate our intervention in a naturalistic context. In addition, risk factors for dementia exert
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15 their influence over decades and thus the earlier one decreases their risk exposure, the more
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17 impact it is likely to have over their lifespan. Therefore, this intervention program is open to
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19 anyone aged 18 and older. If criteria are met, information sheets and consent forms are sent to
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21 potential participants. Upon return of consent forms via email, each participant is officially
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23 registered to the study and allocated a unique identity number as well as an online account.
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25 Recruitment began in July 2016 for the duration of 13 months.
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28 29 *Inclusion criteria*

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32 A naturalistic approach is used in recruitment and the study inclusion criteria being used for
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34 this study are those already used by the NHC to refer patients to the LMP program (prior to
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36 this research project). The inclusion criteria is pragmatic as the practice already had criteria
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38 for referral to their LMP and in developing the protocol, it became clear that introducing a
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40 second set of inclusion criteria would make implementation difficult and reduce participant
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42 numbers. We therefore decided to use the principle that if a GP would refer the patient to the
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44 LMP then they would be eligible for the trial. This is a pragmatic feature of the current trial
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46 that significantly differs from our original BBL trial. We aimed to optimise the seamlessness
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48 of the intervention in primary care and utilise existing referral pathways to increase the
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50 probability that the intervention is conducted in a manner that could lead to implementation
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52 in real life. Participants must be aged 18 years and over, reside in the Australian Capital
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54 Territory, be current financial members of the NHC, have access to a computer and internet
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3 connection at home, be fluent in English, Australian permanent residents or citizens (for bulk
4 billing eligibility), and must be the only person in their household who is taking part in this
5 study to prevent being randomly assigned to different groups and sharing information about
6 their interventions with each other received. To be eligible for the study, participants are also
7 required to have a chronic health condition (high blood pressure, heart disease, type 2
8 diabetes or 'pre-diabetes', osteoporosis, osteoarthritis, polycystic ovary syndrome (PCOS),
9 kidney or liver disease, and depression/anxiety) or be overweight or obese (BMI>25). They
10 are also required to agree to commit 1-2 hours a week to complete the program and be
11 interested in obtaining advice on improving their lifestyle to reduce the risk of or better
12 manage chronic disease. Participants are required to complete online assessments and attend
13 NHC at baseline and 18, 36, and 62 weeks after commencement of the intervention for
14 medical and cognitive assessments.
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28 29 *Exclusion criteria*

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

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50 Sample size calculations were estimated using G*Power (version 3.1.9.2;
51 <http://www.gpower.hhu.de/en.html>) and have been based on medium effect size as
52 observed in the previous Body Brain Life project with same primary outcome (19). To
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3 detect a medium effect (0.5 standard deviation (SD)) in a 3-group design (1:1:1), 4
4 measurements with a 5% risk of type 1 error (α) and 80% power, a total sample size of
5 159 persons is required. To account for a 33% attrition (based on previous lifestyle
6 modification program by NHC using the same inclusion and exclusion criteria and
7 targeting same age group), a baseline sample of 240 is being recruited (80 in BBL-GP
8 group, 80 in LMP group and 80 in control group).

16 *Assessments*

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

28 *Screening measures and covariate*

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

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

54 *Primary outcome*

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

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25 Secondary outcomes include cognitive function, PA level, depressive symptoms, cost of
26 interventions, diet and sleep quality. They are measured as follows: cognitive function is
27 assessed with processing speed, task switching and executive function using Trails A and B,
28 and the Digit Symbol Modalities Test (DSMT). These tests were chosen because the
29 executive function is the most sensitive cognitive domain to PA interventions (25) and a
30 decline in processing speed is associated with cardiovascular risk factors (26). Both Trails
31 and DSMT have been used widely and have been reported to have good reliability and
32 validity (27-30). Moderate-vigorous Physical Activity (MVPA) is a continuous measure of
33 activity that registers three or more Metabolic Equivalents (METs) for 10 minutes or longer
34 on an ActiGraph Link activity monitor (<http://actigraphcorp.com/products/actigraph-link/>),
35 which is worn for 7 days. Self-reported PA is also being recorded using the short form of the
36 International Physical Activity Questionnaire (IPAQ) (31), which is part of the ANU-ADRI-
37 SF. Reliability and validity of IPAQ has been tested and confirmed across 12 countries (31).
38 Depression is being assessed with the Centre for Epidemiological Studies Depression (CES-
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3 D) Scale (32), which is also part of the ANU-ADRI. CES-D scale has a very high internal
4 consistency and validity (33).
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8 Health outcomes are assessed with the SF-12 health survey (34), Framingham
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10 Coronary Heart Disease (CHD) Risk score (35), and Australian type 2 diabetes risk
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12 assessment tool (AUSDRISK) (36) to enable cost effectiveness evaluation of the two health
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14 promotion interventions. SF-12 measures both physical and mental health status and has
15
16 acceptable validity and reliability (37, 38). Framingham CHD is a validated tool to assess
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18 cardiovascular diseases (39) and AUSDRISK is a diabetes risk assessment tool based on
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20 demographic, lifestyle and simple anthropometric measures (36).
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24 Dietary quality is assessed with a food-based diet quality index, the Australian
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26 Recommended Food Score (ARFS) (40). The ARFS is aligned with Australian Dietary
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28 Guidelines (41) and the Australian Guide to Healthy Eating (42) recommendations. The
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30 ARFS total ranges from 0 to 73 and includes eight subscales: vegetables (0 to 21), fruit (0 to
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32 12), protein (0 to 7), vegetarian alternatives (0 to 6), grains (0 to 13), dairy (0 to 11), water (0
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34 to 1), sauces and condiments (0 to 2). Higher scores indicate greater compliance with the
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36 Australian Dietary Guidelines and therefore better diet quality. The ARFS has demonstrated
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38 good validity and reproducibility (40).
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42 Lastly, the Pittsburgh Sleep Quality Index (PSQI) (43) is an effective instrument used
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44 to measure the quality and patterns of sleep in adults. It differentiates “poor” from “good”
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46 sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency,
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48 sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and
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50 daytime dysfunction over the last month. PSQI reports great test-retest reliability (0.87) and
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52 high correlations with sleep log data (44).
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55 *Randomisation*

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

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

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21 BBL-GP is an intervention package that builds on our dementia prevention research programs.
22 This includes an online dementia risk reduction program called the Body Brain Life (BBL;
23 Trial ID: ACTRN12612000147886) (15, 45) and the Fitness for the Ageing Brain Study
24 (FABS; Trial ID: ACTRN 12609000755235) (46, 47). Contents for the BBL-GP online
25 modules have been revised after extensive consumer evaluation by members of the
26 Alzheimer’s Australia Consumer Dementia Research Network as well as members of the
27 public and from participant feedback after the previous trial. The PA program has also been
28 modified for a younger age-group to 18 years and older as previous programs targeted middle
29 aged and older adults. The Actigraph device was introduced to measure the objective amount
30 and intensity of PA. This revised program (Body Brain Life – Fit) was piloted with the
31 general public (Trial ID: ACTRN12615000822583; manuscript in preparation).
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48 Participants in the BBL-GP group are required to complete 8 modules (dementia
49 literacy, risk factors, PA, nutrition, health, cognitive activity, social activity and mood)
50 delivered online. Prior to commencing online modules, participants in the BBL-GP group
51 also receive an individually tailored plan/program for both dietary and PA interventions
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3 developed and delivered by a dietitian and an exercise physiologist, respectively during a
4 face-to-face assessment. This is to ensure the dietary prescription and level of PA are suitable
5 and tailored to individual participants.
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8 9 *Physical activity session*

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11 The session duration and frequency of the PA program varies between participants based on
12 baseline PA levels and individual tailoring. An exercise physiologist designs an individual
13 program for the participant, delivers this in a face-to-face workshop and monitors the PA
14 program via the returned diaries and telephone monitoring. For those not doing any regular
15 PA at baseline, the target is 150 minutes/week moderate intensity PA, with moderate
16 intensity defined as a score of 10-12 on the Borg Rating of Perceived Exertion scale (RPE)
17 (48). For those who are doing regular PA but for less than 100 minutes/week, an additional
18 100 minutes/week is prescribed, and for those meeting the target, an additional 50
19 minutes/week is prescribed. Printed material guiding participants to increase their activity
20 level with worksheets are also provided. A diary in the format of a calendar returned monthly
21 for 24 weeks is used to record PA and RPE to assess PA and intensity adherence. Participants
22 may develop a medical problem or undergo treatment that can make exercising difficult or
23 impossible. If this happens, prescribed amount of exercise is reviewed and re-prescribed, or
24 stopped.
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41 *Dietary session*

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

4 5 *Follow ups*

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7 Participants in the BBL-GP group are monitored through phone calls at week 4, 12 (14 for
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9 PA) and week 20 by the dietitian and exercise physiologist to monitor the progress and for
10
11 reassurance. In addition, they receive a general booster session at 12 months with a phone
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13 call and a mailed-out booklet summarising materials from the online modules. They are being
14
15 asked to continue being active and follow a healthy eating plan after completion of the
16
17 intervention.
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19 20 *Online modules*

21
22 Once participants in the BBL-GP group have received face-to-face PA and dietary
23
24 counselling sessions, they are asked to log on to the trial website and complete one module
25
26 per week, each taking approximately 30-40 minutes. The 12-week program is detailed in
27
28 Table 3. The first 8 weeks include the completion of 8 educational and individually tailored
29
30 behaviour change modules. In the remaining 4 weeks, participants undertake online activities
31
32 focused on goal monitoring and revision of the modules materials. Tailoring of the six
33
34 behaviour change modules (weeks 3-8) is conducted using an automated algorithm that
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36 presents content on the basis of whether or not the participant has a relevant risk factor, as
37
38 well as on the basis of their responses to several questions measuring psychological
39
40 determinants of behaviour. These questions are presented at the beginning of each of the
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42 behaviour change modules. For instance, a person who is classified as having a poor diet (e.g.
43
44 lack of fish intake) on the basis of their responses on the ANU-ADRI, and who does not
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46 regard himself/herself as a role model to others with respect to their diet habits is not
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48 presented with information focusing on becoming a role model to others.
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52 The program is built in such a way that participants are only able to access the
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54 relevant component of the intervention at a given time. The modules become active, 1 per
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3 week, on the same day for the first 8 weeks. Participants are unable to access a newly
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5 activated module before completing the previously scheduled module. Each week,
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7 participants receive a notification email on the same day of the week alerting them when a
8
9 new module has become active and a list of already activated modules that they have either
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11 not started or completed. Participants who are late completing modules will be followed up
12
13 with an email from the project manager to identify if there is a reason (e.g. holidays, illness,
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15 work commitments) preventing their participation, and encouraging them to continue with the
16
17 study. Compliance is recorded for each module if they are completed on time, delayed or not
18
19 completed.
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22 23 *Group 2: Lifestyle Modification Program (LMP)*

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25 The lifestyle modification program (LMP), developed by NHC, is designed to provide
26
27 individuals with tools to help manage chronic disease and maintain a healthy lifestyle. LMP
28
29 is a six- week group program provided by various health professionals (dietitian, exercise
30
31 physiologist, nurse practitioner, psychologist, pharmacist, and sleep physician) providing
32
33 information on basic nutrition, meal planning, PA, health conditions, motivation and goals,
34
35 medications, and sleep. Every week, 2 sessions are provided on the same day with each
36
37 session lasting an hour. The course is currently run by the NHC for their patients to assist
38
39 them in improving their lifestyle and management of chronic disease so it is a pragmatic real-
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41 life comparison condition. Attendance is recorded for compliance and motivation checking.
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45 Although the LMP is a free nationally recognised program that is designed to provide
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47 individuals with tools to help manage chronic disease and maintain a healthy lifestyle,
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49 evaluation of the program has not been carried out as yet. The attendance is recorded each
50
51 week to examine intervention fidelity.
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54 55 *Group 3: Active control/Email only*

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

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

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

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22 The Human Research Ethics Committee at the Australian National University has approved
23 the study protocols and procedures (protocol #2016/157). This project has also been
24 registered at the Australian New Zealand Clinical Trials Registry (ACTRN:
25 12616000868482).
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30 *Adverse events*

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

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

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28 The project is currently under way as an evaluation of the efficacy of health promotion
29 interventions in adults with risk factors for dementia. The program aims to reduce
30 cardiometabolic risk and promote behaviours shown to protect against dementia. The trial,
31 recruiting from a primary care setting has generated considerable interest, and to date,
32 approximately half of the total target sample has been assessed and randomised into the
33 intervention groups. We anticipate that all data collection will be completed by December
34 2018. The results of the study are likely to form an evidence base for the feasibility of
35 dementia risk reduction campaigns to lead to lifestyle changes and the reduction of dementia
36 risk factors at the population level. This trial will also support the feasibility of such
37 interventions being applied in primary care settings. Successful outcomes of the current trial
38 may lead to significant public health impact and benefits once the intervention is made
39 available at the population level pending positive results.
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54 **Conclusion**

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

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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	√				

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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

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

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		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.

For peer review only

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3 Figure 1. Study Flowchart
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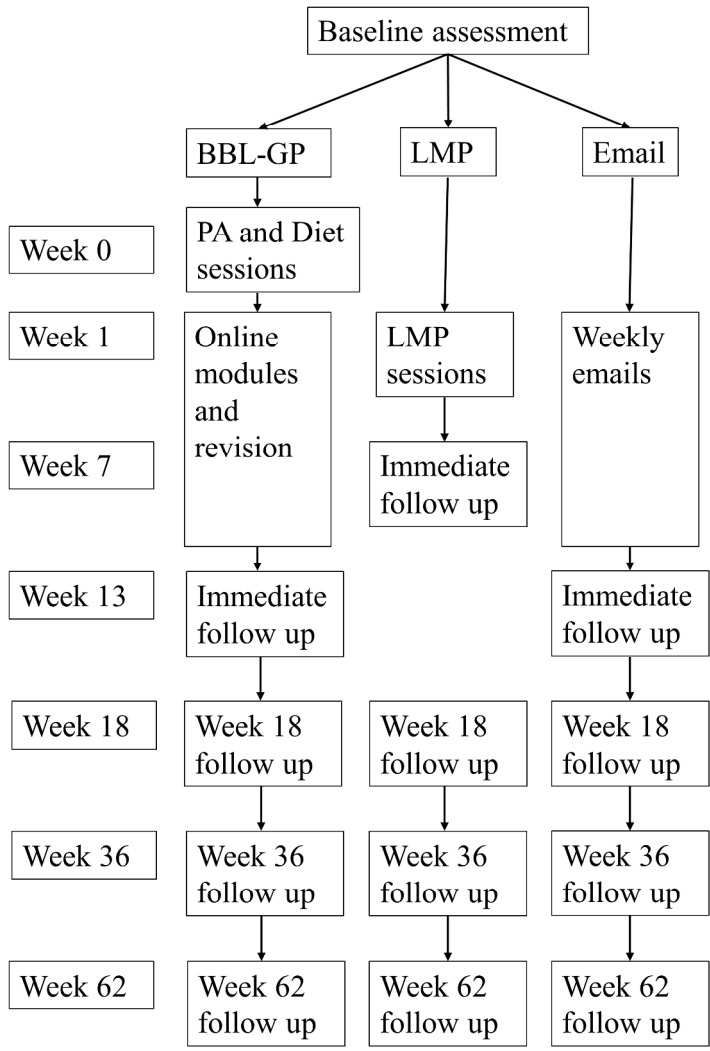


Figure 1: Study Flowchart

225x300mm (300 x 300 DPI)



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___

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47**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 ___

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3	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___
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5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___9___
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8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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12	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___
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17	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___
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___13___
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___17-18___
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___17___
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31 **Methods: Data collection, management, and analysis**

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33	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___
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38		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___
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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_____



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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___9___
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A___
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8	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___
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___26___
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14	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___
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17	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___
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20	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___
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	___19___
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___N/A___
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___N/A___
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34	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___
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
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