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ABORIGINAL DEMENTIA PREVENTION STUDY

STUDY PROTOCOL

Version 7

May 2024

CONTENTS

Details of protocol modifications

Date	Version	Modification
02/05/2024	7	Minor amendments for HREC - Added reference to evaluation under objectives (1.2)
11/04/2024	6	Major amendments for HREC - Updated primary outcome from binary elevated blood pressure to two continuous blood pressure measurements. - Updated sample size calculation and statistical analysis plan sections to correspond with changes to the primary outcomes. - Study timetable in Section 11 updated to reflect reduced follow-up time for participants. Minor amendments for HREC - Added elevated blood pressure (original primary outcome) as secondary outcome. - Added titles to Table 1 and Table 2 and updated incorrect table numbers for Table 3 and Table 4. - Updated reference section to include all references included in the protocol. - Order of secondary endpoints changed in Section 8.2 to be consistent with order of secondary outcomes listed earlier.
10/7/2023	5	Major amendments - Removal of some of the blood tests – specifically, the bloods that are collected to test selected biomarkers of cognition (inflammatory cytokine panel, oxidative stress, apolipoprotein B, neurofilament light chain) and destruction of associated blood samples. The collection and analysis of these were approved by WAAHEC on 18/8/2021. WAAHEC approved the addition to the protocol although it was noted in this amendment that the PIF and Consent form had not been changed. Subsequently, after some concerns raised by study staff, we re-reviewed the PIF and consent form and believed that they were deficient with respect to informing participants that the study was collecting bloods to test these biomarkers. As such, we decided to discontinue the collection of the bloods for these biomarkers and destroy all collected samples (without analysing them). - Reduction of follow-up, from 24 months to 12 months, as a result of financial limitations (COVID impacts). - Removal of questionnaires: physical activity survey and Australian Dietary Survey, to reduce participant burden. Secondary outcomes pertaining to physical activity and diet will still be assessed using data collected as part of the nutrition program intervention.
23/9/2021	4	Major amendments - Removal of cognitive function assessment at 6 months to reduce participant burden. - Removal of the apolipoprotein E genotype test on the basis of ethical concerns.

4/8/2021	3	Major amendments - Change to the wording of the primary outcome to reflect that measurement is ‘greater than or equal to’ not ‘greater than’ the stipulated thresholds. - Addition of blood tests: now including inflammatory cytokine panel, oxidative stress, apolipoprotein B, neurofilament light chain and apolipoprotein E genotype. - Additional note that blood samples are taken from venepuncture.
27/5/2021	2	Major amendments - Included prior diagnosis of dementia as an exclusion criteria for recruitment. Minor amendments - Minor change to the wording of the primary outcome. - Change to the technology used in the randomisation of participants. - Minor changes to the articulation of the objectives.

1. EXECUTIVE SUMMARY

1.1 BACKGROUND

Limited data that are available indicate that Indigenous Australians have a dementia prevalence three times higher than the general Australian population. The major risk factors for dementia and cognitive decline – the slowing of brain function and memory – are known and are elevated in older Indigenous Australians. Many of these risk factors can be targeted for prevention. During the recent two decades, several studies have shown a relationship between the development of cognitive decline and dementia with lifestyle-related risk factors, such as: physical inactivity, tobacco use, unhealthy diets, and harmful use of alcohol. Certain chronic conditions are also associated with an increased risk of cognitive decline and developing dementia, including hypertension, diabetes, hypercholesterolemia, obesity and depression. Other potentially modifiable risk factors are social isolation and cognitive inactivity. The existence of potentially modifiable risk factors means that prevention of cognitive decline and dementia is possible through a public health approach, including the implementation of key interventions that delay or slow cognitive decline.

Prevention of dementia and cognitive decline requires the management of cardiovascular risk factors and dementia-specific risk factors, as well as building on current primary care interventions. Rather than address individual risk factors in isolation, our study is planning to adopt a multi-domain approach that targets multiple risk factors simultaneously to maximise the potential for risk reduction.

1.2 OBJECTIVES

Our primary objective is to examine the efficacy of an Aboriginal health practitioner (AHP) led cardiovascular risk management and lifestyle modification program on blood pressure among Aboriginal and Torres Strait Islander people with elevated risk for cardiovascular disease onset or complications.

Our secondary objectives are to examine the impact of an Aboriginal health practitioner led cardiovascular risk management and lifestyle modification program on cardio-metabolic disease risk factors, cognitive function and achieving the recommended Australian dietary and physical activity guidelines.

An evaluation of the implementation of the intervention will also be undertaken, examining factors that may affect its acceptability, appropriateness, feasibility and the extent of its adoption within health services and by intended recipients.

1.3 STUDY POPULATION

Participants will include Aboriginal and Torres Strait Islander people aged 35 to 60 years of age from Perth and Bunbury in Western Australia at high risk of cardiovascular disease. Participants will be classified as ‘high risk’ if they: have a previous history of atherosclerotic cardiovascular disease (e.g. stroke, coronary artery disease, peripheral vascular disease, heart

failure) or are current regular smoker or have any two of the following risk factors diagnosed within the past 3 months: elevated blood pressure, elevated waist circumference, reduced high density lipoprotein (HDL) C, elevated low density lipoprotein (LDL) C or elevated HbA_1C. Participants with a prior diagnosis of dementia and/or cognitive impairment, assessed as not being able to participate in the proposed intervention or enrolled in another clinical trial will not be eligible to participate.

1.4 Study Interventions

The one-year intervention program will be guided and led by the Aboriginal health practitioners (AHPs) at each site and will involve a cardiovascular risk management program, including the pharmacologic treatment of cardio-metabolic risk factors (hypertension, diabetes, hyperlipidaemia), lifestyle program targeting diet and physical activity, targeted advice and coaching for smoking cessation (for current smokers) and depression (for those at high risk of depression). All intervention protocols will be developed in consultation with AHPs and relevant staff from the Aboriginal community-controlled health services. Participants will be invited to join weekly sessions over the year of the intervention.

1.5 Outcomes

The two primary outcomes are change in systolic blood pressure (mmHg) and change in diastolic blood pressure (mmHg) from baseline to 12-months follow-up.

The primary outcome was originally defined as elevated blood pressure (either systolic pressure greater than or equal to 140mmHg or diastolic pressure greater than or equal to 90 mmHg) at 24-month follow-up in the trial registration and when recruitment commenced. This was subsequently amended to change in blood pressure. This major protocol change was based on revisiting the study inclusion criteria. As not all participants will have elevated blood pressure at the commencement of the trial, change in continuous blood pressure was deemed a more appropriate primary outcome (see Section 6.2 Participation Criteria). The primary time point was changed from 24 months to 12 months due to funding issues which limited participant follow-up. Planned participant follow-up at 18 and 24 months was no longer possible; these time points were excluded as secondary and primary endpoints, respectively.

Secondary outcomes include:

(1) Elevated blood pressure (either systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg) at 6- and 12-months follow-up.

(2) Change in other cardio-metabolic risk markers (absolute cardiovascular risk score, waist circumference, HDL-C and HbA_1C) at 6- and 12-months follow-up.

(3) Change in cognitive function at 12-months follow-up.

(4) Change in the proportion of participants meeting the recommended Australian dietary and physical activity guidelines at 6- and 12-months follow-up.

1.6 Design and Power

The sample size calculation was undertaken for the binary outcome outlined in the original trial protocol and registration at the commencement of the study. A total sample size of 300 (150 intervention subjects and 150 control subjects) will provide 80% power to detect a difference of 0.13 in the proportion of participants with elevated blood pressure at follow-up between the intervention and control arm with two-sided α=0.05. This is based on the continuity-corrected comparison of two proportions using the chi-squared statistic, assuming 25% of the control group have elevated blood pressure based on estimates from Calabria et al. (2018).[1] Accounting for potential loss-to-follow up of 15%, overall the trial would require 177 participants randomized in each group (i.e., a total of 354 participants).

The target sample size remained 354 since the trial had commenced recruitment when the decision was made to alter the primary outcome. Assuming a 15% loss to follow-up, this sample size provides 80% power to detect a minimum clinically important difference of 4mmHg in mean change in diastolic blood pressure at 12-months follow-up between the intervention and control arm with two-sided α=0.05 divided between the two primary outcomes. This assumes equal standard deviations of 11mmHg in both groups based on estimates at 24-month follow-up from Carrington et al. (2021) and no correlation between baseline and follow-up diastolic blood pressure (conservative assumption).[2] This sample size provides >95% power to detect a minimum clinically important difference of 8mmHg in the other primary outcome, mean change in systolic blood pressure, between the two study arms, assuming a standard deviation of 15mmHg.[2] Changes of 4mmHg in diastolic blood pressure and 8mmHg systolic blood pressure have been used as clinically significant minimum changes elsewhere.[3]

1.7 Analyses

A detailed statistical analysis plan will be developed while biostatisticians are blinded to treatment allocation and approved prior to database lock. The analysis will be undertaken on an intention-to-treat basis, with all randomised participants included according to the treatment they were randomised to receive. Constrained longitudinal data analysis will be used to examine the change in primary outcomes (systolic and diastolic blood pressure), with the response consisting of all measures (baseline, 6 months, 12 months) and the model including factors representing group (intervention/control), time, intervention by time interaction and the strata (site and age group), with the restriction of a common baseline mean across interventions. The mean change in each of systolic and diastolic blood pressure from baseline to each follow-up time point between the two treatment arms will be obtained. The primary research question will be evaluated by obtaining the estimated differences between the two treatment arms in mean change in systolic and diastolic blood pressure from

baseline to 12 months follow-up (primary time point), two-sided 97.5% confidence intervals and p-values. A similar approach will be used for continuous secondary outcomes. For binary outcomes, logistic regression models will be fitted using generalised estimating equations to account for clustering of time within participants, with risk differences and 95% confidence intervals calculated.

2. OBJECTIVES

2.1 Primary Research Question

What is the efficacy of an Aboriginal health practitioner led cardiovascular risk management and lifestyle modification program on blood pressure among Aboriginal and Torres Strait Islander people with elevated risk for cardiovascular disease onset or complications?

2.2 Secondary Research Question

What is the impact of an Aboriginal health practitioner led cardiovascular risk management and lifestyle modification program on cardio-metabolic disease risk factors, cognitive function and achieving the recommended Australian dietary and physical activity guidelines?

3. BACKGROUND AND RATIONALE

Dementia describes a collection of symptoms that are caused by disorders affecting the brain.[4] It is not one specific disease. Dementia affects thinking, behaviour and the ability to perform everyday tasks, enough to interfere with a person's normal social or working life. It is important to know that not all older people get dementia — it is not a normal part of ageing and it may be delayed and/or prevented. Most people with dementia are generally older; people in their 40s and 50s can have dementia, but it is more common after the age of 65 years.[4]

Prevalence of dementia among Australian Aboriginal people

Data from Western Australia, New South Wales (NSW), and the Northern Territory show that the age-standardised prevalence for dementia ranges from 21-28% among men and women aged 60 years and older.[5] Alzheimer's disease (AD) is the most common type of dementia (making up 44% of all cases in urban and regional parts of NSW), followed by stroke-related 'vascular' dementia (17% of all cases).

Modifiable and non-modifiable risk factors for dementia

It is estimated that one-third of all Alzheimer's disease cases globally are due to potentially modifiable risk factors.[6] A recent systematic review of the risk factors for Alzheimer's disease and related dementia in Indigenous populations found that 5 out of 10 cross sectional studies had been conducted in Australia.[7] The findings of these studies (plus an additional one that was not included in the review) are summarised in Table 1.

Table 1. Summary of studies examining risk factors for Alzheimer's disease and dementia in Indigenous populations in Australia.

Study	Main Findings
Smith 2008[8]	Aboriginal adults aged 70+ ($p < 0.0001$) were more frequently diagnosed with dementia relative to non-Aboriginal adults aged 70+. Male Aboriginal Australians were more frequently diagnosed with dementia relative to female Aboriginal Australians (17% vs 9%, 95% CI of the difference: 0.4%–15.6%).
Smith 2010[9]	Age 80+ (40.3, 95% CI: 10.3–156.8), male gender (3.1, 1.4–6.8), no education (2.7, 1.1–6.7), smoking (4.5, 1.1–18.6); stroke (17.2, 5.9–49.7), epilepsy (33.5, 4.8–232.3), head injury (4.0, 1.7–9.4), falls (2.7, 1.2–6.1), poor mobility (13.3, 4.1–43.9), daytime urinary incontinence (116.8, 21.9–622.8), night-time urinary incontinence (87.4, 18.4–15.7)
Lo Giudice 2015[10]	Age (1.12, 95% CI: 1.06–1.17), head injury (5.22, 1.85–14.70), analgesic medication (3.60, 1.35–9.62), poor mobility (3.08, 1.09, 8.72) and BMI (0.90, 0.82–0.98) were associated with dementia.
Radford 2017[11]	Childhood adversity - Each SD increase in childhood adversity score was associated with all-cause dementia (1.70, 95% CI: 1.14–2.54) and Alzheimer dementia (1.77, 1.08–2.91)
Radford 2019[12]	Age (1.96, 95% CI: 1.43–2.68), childhood trauma (1.63, 1.11–2.39), high-risk alcohol use (2.6, 1.09–6.21), unskilled job (2.25, 1.14–4.44), stroke (4.36, 2.16–8.77), head injury with loss of consciousness (2.87, 1.44–5.74), and epilepsy (4.65, 1.62–13.34) were associated with dementia.
Cations 2018[13]	Young onset dementia (having symptoms prior to 65 years of age) was associated with poor educational attainment, low participation in cognitive leisure activity, stroke, transient ischemic attack and self-reported very heavy alcohol use

Longitudinal studies have shown that the risk factors associated with cognitive decline included age, head injury, stroke, non-aspirin analgesics, lower BMI and higher systolic blood pressure.[10] A recent longitudinal study by Derrig and colleagues (2020) found that mild cognitive decline among Aboriginal Australians aged 60 years and over was associated with older age, head injury, symptoms of depression and lower blood pressure. 44% of the cohort remained stable after 6 years of follow-up, 15% reverted to intact and 41% had died.[14]

In summary, through mostly cross-sectional and a few longitudinal studies, cognitive decline has been shown to be associated with lifestyle related factors (smoking, physical activity, unhealthy diet, tobacco and alcohol use). Chronic diseases such as hypertension, diabetes, hypercholesterolemia, obesity and depression have also been shown to be linked with increased risk of dementia.

Hypertension and dementia risk

A recently published systematic review and meta-analysis showed the strong association between hypertension and risk of dementia. 12 out of 14 randomised controlled trials found

that blood pressure lowering with antihypertensives was significantly associated with a reduced risk of dementia or cognitive impairment.[15] Using data from two longitudinal studies among Indigenous people, Cations and colleagues showed that in terms of young onset dementia (having symptoms of dementia prior to 60 years of age), the effect of hypertension was time dependent (significant risk when occurring more than 10 years prior to dementia onset, it had no effect within 10 years of dementia onset) (Cations 2018).[13]

Rather than address individual risk factors in isolation, our study is planning to adopt a multi-domain approach that targets multiple risk factors simultaneously to maximise the potential for risk reduction. Key to the prevention of dementia and cognitive decline is the modification of risk factors through lifestyle changes and adherence to medications. Amongst individuals with conditions such as dementia and heart failure with long term risk exposures, such as hypertension, self-care maintenance behaviours were significantly lower in Indigenous compared to non-Indigenous individuals. Implementation of behavioural change techniques are needed to achieve real changes in risk profile.

Intervention Components

1) Cardiovascular risk factor management. An Aboriginal health practitioner (AHP) will assess and guide the participant through a care plan to reduce their cardiovascular disease risk factors which can include prescription of medications to manage chronic diseases, regular health checks and other procedures. This care plan will be tailored to individual needs and requirements.

2) Lifestyle behavioural intervention targeting nutrition and physical activity. In recent years, there has been a shift both in nutritional epidemiology and the neurosciences from a "single nutrient" to a "whole diet" approach, more broadly aimed at capturing the food synergy of the cumulative effects of overall diet patterns on the health status of the individual. Recent reviews of cohort and experimental studies indicate that several dietary patterns and nutritional components (e.g. Mediterranean diet, unsaturated fatty acids, vitamin D, vitamin B) are associated with a significantly reduced risk of dementia.[16] For example, the evidence for protective effects from the Mediterranean diet against diabetes and CVD – precursors to vascular cognitive decline – is well established.[16] Such nutritional components may exert a protective function in multiple and convergent ways – accordingly, our intervention includes both individual and group dietary counselling sessions throughout the follow-up period. All sessions will be run by a qualified dietitian, with group sessions also supported by an AHP. Group physical activity sessions will be conducted by a qualified exercise physiologist.

3) Smoking cessation. Regular smokers will be asked about their previous attempts to quit smoking in order to develop a tailored smoking cessation plan with an AHP. The AHP will provide regular follow-up to the participants to monitor progress and provide encouragement to action the care plan.

4) Mental health care plan for those at high risk of depression. Participants who return a PHQ-9 score of greater than 9 will receive a referral and advice to see their GP for treatment.

Those in the Intervention group will be followed-up at regular one-month intervals and further supported to attend visits with their GP for management of depression by the study AHPs and nurses.

Interventions delivered for prevention through primary healthcare clinics are more likely to be effective when they are delivered in combination with other lifestyle change and disease prevention programs. The intervention in our study will be coordinated by local AHPs and rolled out in partnership with DYHS and SWAMS, with participants in the intervention group receiving a range of additional services and support from our AHPs, nurses, dietitians, exercise physiologists, and psychologists. We will provide this added support and follow the intervention group for a period of 12 months, and then compare its impact with a group of participants who received standard healthcare.

Urgent action is required to develop and implement interventions to reduce dementia and cognitive decline among older Indigenous Australians. More evidence is required to establish the feasibility, acceptability, and effectiveness of interventions to reduce dementia and cognitive decline. These interventions must be informed by state-of-the-art knowledge about what works to prevent dementia and cognitive decline in other populations and what works best for implementation in the Indigenous community. Cognitive decline is of particular importance, as it is an established precursor to dementia, supporting early intervention with the potential to preserve functionality.

4. AIMS & HYPOTHESES

Our primary aim is to examine the efficacy of a lifestyle modification program to improve cardio-metabolic disease risk and prevent or delay the development of dementia in Aboriginal and Torres Strait Islander people with elevated risk for cardiovascular disease onset or complications.

We hypothesize that the intervention group will have a reduction in blood pressure and cardio-metabolic risk factors compared to the usual care (control) group after a 12 month follow-up. Further, we anticipate that compared to the usual care group, the intervention group will experience greater improvements in cognitive symptoms of dementia and significantly increase healthy diet and lifestyle behaviours.

5. DEFINITION OF OUTCOMES

5.1 PRIMARY OUTCOMES

The primary outcomes are change in systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) from baseline to 12-months follow-up.

5.2 OTHER SECONDARY OUTCOMES

(1) Elevated blood pressure (either systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg) at 6- and 12-months follow-up.

(2) Change in other cardio-metabolic risk markers (absolute cardiovascular risk score, waist circumference, HDL-C and HbA_1C) at 6- and 12 months follow-up.

(3) Change in cognitive function at 6- and 12 months follow-up.

(4) Change in the proportion of participants meeting the recommended Australian dietary and physical activity guidelines at 6- and 12 months follow-up.

6. STUDY DESIGN

6.1 OVERALL DESIGN

This is a 1:1 individually randomised controlled, parallel group trial in which participants will be randomised into either the usual care group or the intervention group that will receive an AHP-led 1-year program to reduce their cardiovascular risk factors. Data will be collected at baseline, 6 months and 12 months.

6.2 PARTICIPATION CRITERIA

We will recruit participants aged 35 to 60 years of age from Perth and Bunbury in Western Australia. Participants will be recruited through DYHS and SWAMS. The estimated population of Aboriginal people aged 35 years and above in the south-west region of Western Australia is approximately 5,000. Participants will be eligible if they have ANY of the following:

1) Prior likely atherosclerotic CVD (patient self-report) – stroke, coronary artery disease (myocardial infarction, angina, previous revascularisation intervention), peripheral vascular disease, heart failure. People with atrial fibrillation (only) and valve disease (only) will not be eligible just based on this criterion alone. Eligibility will also depend on whether the participant is well enough to participate in the intervention.

2) Current regular smokers (self-reported smoking status). Only tobacco smoking will be included and those that smoke at least daily.

3) Any two of the following risk factors (from previous health records ≤3 months ago):

Risk factor	Criteria
Elevated BP	≥140/90 mmHg
Elevated waist circumference	Men: >104 cm Women: >88 cm
Reduced HDL-C	≤1.0 mmol/L
Elevated LDL-C	>2.0 mmol/L
Elevated HbA_{1C}	>5.7% or >39 mmol/L

Participants who do not have eligibility criteria 1 or 2 and are unsure if they have eligibility criteria 3, will be asked to come in for a screening risk profiling visit to assess criteria 3. Participants will only be excluded if they are assessed as not being able to participate in the proposed interventions, they have a prior diagnosis of dementia and/or cognitive impairment or they are enrolled in another clinical trial with similar interventions. Female participants who are currently pregnant or planning a pregnancy will also be excluded. Once participants are confirmed eligible and have provided consent, they will be randomised into either the usual care (control) or intervention group. An overview of the study procedures is shown in Figure 1.

6.3 Participant recruitment strategy

A broad recruitment strategy will be used to disseminate information about the study through yarning circles, Noongar radio and other information sharing activities conducted in partnership with DYHS and SWAMS. Flyers and advertisements will also be placed in the SWAMS and DYHS clinics. Aboriginal Health Professionals/nurses who are in daily contact with Aboriginal patients will also identify potential eligible participants and inform them of the study.

Informed consent procedure

Interested participants will be provided a verbal explanation of the study by the Aboriginal Health Professionals/nurse in Plain Language Statements targeted at Year 8 reading level. Eligibility for the study will be determined by the AHP/nurse in person during a face-to-face visit. Once confirmed to be eligible, a baseline visit will be organised for the baseline assessments. Informed consent procedures will occur at the baseline visit. Participants will be informed of what procedures will occur in both the 'usual care' and 'intervention' groups.

6.4 Randomisation

All eligible participants who consent to participate in the trial will be randomised to either the intervention or usual care group in equal numbers. The randomisation list will be computer-generated by an independent statistician and carried out centrally to ensure concealment. Stratified block permuted randomisation will be used with the study site (Perth and Bunbury) and age group (35-44 years, 45-60 years) as stratification factors to ensure balance in treatment allocation within each centre. The 2 sites can access the randomisation schedule using the REDCap database. The patient assigned intervention will be registered and maintained throughout the trial. All other participants who: (1) decline to participate in the trial; or (2) complete risk profiling, but do not meet the inclusion criteria, will be provided with a written summary of their risk profile and given a letter to their General Practitioner (GP) for any follow-up tests.

7. PARTICIPANT MANAGEMENT PROTOCOLS

7.1 SCREENING & BASELINE VISIT

Figure 1 below shows how participants will be selected to be involved in the study and the screening and baseline procedures to be undertaken.

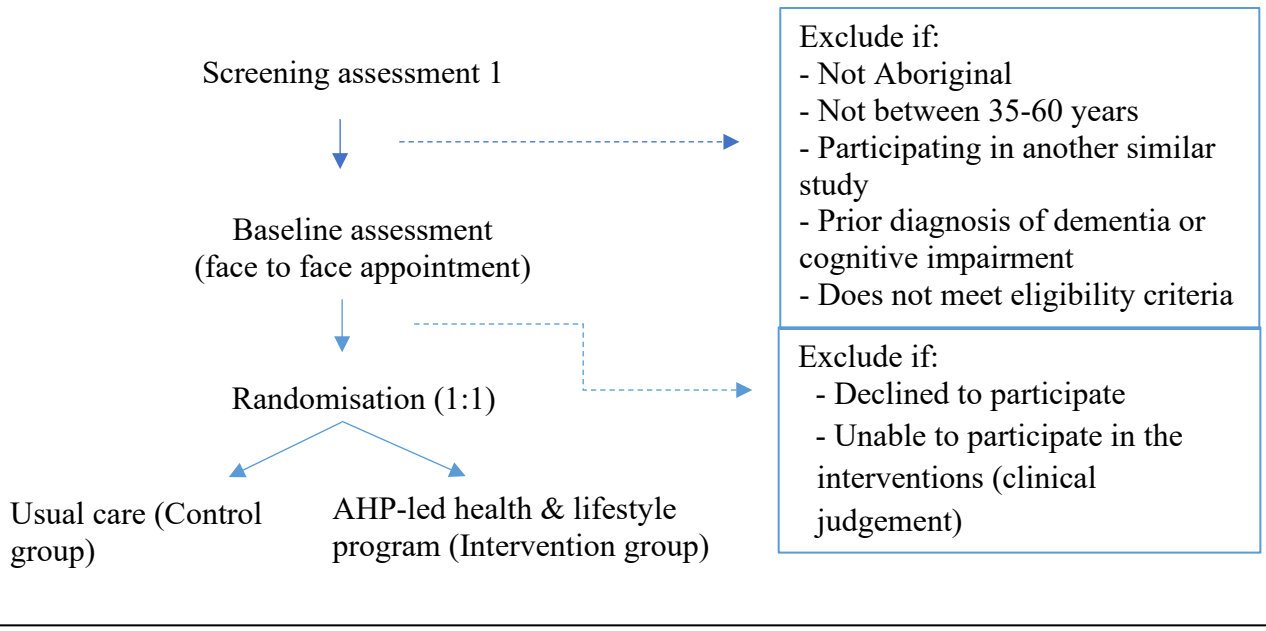


Figure 1. Flow chart showing screening and baseline procedures

7.2 SCHEDULE OF FOLLOW-UP VISITS FOR OUTCOME MEASUREMENTS

Follow-up visits for outcome measurements will be scheduled at 6 months and 12 months after the baseline visit. Table 2 below shows the study visits and the study procedures to be undertaken during each visit.

Table 2. Study procedures and visits.

STUDY PROCEDURES	Screening*	Baseline	6 months	12 months
Anthropometry	X*	X	X	X
Blood samples taken from venepuncture examined for: lipids, HbA_1c,	X*	X	X	X
Systolic and Diastolic blood pressure	X*	X	X	X
General Health Questionnaire (REDCap)		X	X	X

Patient Health Questionnaire-9 (aPHQ-9)		X	X	X
Assessment of Quality of Life (AQoL 4D) (REDCap)		X	X	X
I-ACE food frequency questionnaire		X	X	X
Cognitive Function Assessment (Mixture of pen and paper and Laptop)		X		X

7.3 Intervention Schedule & Summary

The intervention represents a collaboration between the participant and the healthcare team at DYHS and SWAMS, whereby an AHP or nurse will actively deliver tailored strategies, which include: individualised risk factor targets; a sustainable physical activity program; nutritional advice, as well as adherence to medications and participant / family education in the management and control of risk factors using educational resources and motivational interviewing techniques. The aim of the intervention is to deliver coaching whilst integrating management with the DYHS and SWAMS clinics to support individuals to achieve improved risk and risk factor management. The key components of the intervention are summarised in Tables 3 & 4. All advice regarding nutrition, exercise will be tailored to local cultural values of men and women and family contexts. Dietitians and exercise therapists will test all study procedures with local DYHS and SWAMS staff and refine the content to fit with local language and values. All changes to the intervention protocol will be discussed as a group and documented in the study protocol. Written material will be culturally relevant, addressing themes such as shopping and cooking for large family groups, how to balance personal needs, and familial and social expectations.

Table 3. Summary of intervention procedures

Procedures	Details
1. Cardio-metabolic risk factor management	AHPs will work with the participants and primary care providers to coordinate care (including review and prescription of medication) with the clinics to overcome barriers to the achievement of ideal levels based on recommended guidelines (with consideration for the circumstances of individuals).
2. Nutritional program	The nutrition program will utilise an Interactive Lifestyle Assessment, Counselling and Education (I-ACE) program, which will be adapted for use with Aboriginal people in this study. The I-ACE software will be used to conduct nutrition and physical activity assessments that will be the basis for tailored individual lifestyle counselling. Dietitians will undergo training to utilise this program and conduct the counselling sessions. Individuals assigned to the intervention will participate in monthly individual counselling sessions and a monthly group session with a dietitian for 12 months. Written educational materials on diet (and physical activity) written in plain English and tailored to local Noongar cultural values will be given to participants to supplement face-to-face advice sessions.
3. Physical activity	A qualified exercise therapist will develop a physical activity program tailored for the age range, targeted at reducing cardiovascular risk factors and tailored to the specific needs of the participants. The exercise therapist will then train the Aboriginal Health Professional / nurse to deliver the program to participants. Participants will be invited to attend two group sessions per month. The instructor will complete sessions built around muscle strengthening, aerobic exercise and will provide participants with instructions for home exercises. The sessions will guide exercises that can be conducted outdoors (including walking) and at home (simple muscle strengthening activities). Participants will also be encouraged to the national guidelines of 150 minutes of physical activity per week.

4. Smoking cessation advice	Current smokers will be assessed on their nicotine dependence and readiness to cease smoking and will be provided appropriate counselling to encourage them to quit. If required, referrals to GPs in the ACCHOS will be facilitated for prescribed smoking cessation medical therapy (e.g. Varenicline, Bupropion) or nicotine replacement therapy.
5. Management of depression	All participants that are diagnosed with depression (PHQ- 9 score >9) will receive a referral and advice to see their GP for treatment. Individuals in the Intervention group will be followed-up at regular one-month intervals and further supported to attend visits with their GP for management of depression by the study AHPs and nurses.

All intervention procedures will be pilot tested before being implemented to determine feasibility and cultural appropriateness. All staff will be appropriately trained with each component.

Usual care (control) Group

Participants randomised to the usual care group will receive their usual care at the health service and a risk profile report; a copy will be sent to their GP / health care provider. These participants will also receive three individual dietary counselling sessions over 12 months, and no guided group or individual physical activity sessions. For other assessments such as the PHQ-9, appropriate referrals will be made if at risk of depression.

Table 4. Summary of the intervention procedures and schedule

	Support Person	Frequency
Cardio-metabolic risk factor management - Anthropometry - Blood pressure - Lipids (blood samples taken from venepuncture) - HbA1C (blood samples taken from venepuncture) - General health - Cognitive assessments (Cogstate and Symbol Digit Modalities Test) - Primary health questionnaire (PHQ-9) - Assessment of Quality of Life (AQoL-4D) Measures of dementia risk, blood samples taken from venepuncture	GP & AHP/nurse	- Clinical tests will be undertaken at baseline, 6 months and 12 months (with the exception of cognitive assessments which will be undertaken at baseline and 12 months only) - Regular review of the care plans will be undertaken monthly
Nutrition	Dietitian & AHP/nurse	Monthly individual & group sessions
Physical activity	Exercise Therapist & AHP/nurse	Fortnightly group sessions for first 6 months; Monthly group sessions from months 7-12

	Support Person	Frequency
Smoking cessation advice	AHP/Nurse	Appropriate referrals will be made for quit smoking resources. AHP/nurse will ask about smoking during the regular visits.
Management of depression	AHP / Nurse / GP	Referral to GP and/or mental health professional will be facilitated for appropriate treatment.

8. PRIMARY AND SECONDARY ENDPOINTS

8.1 PRIMARY ENDPOINT

1) Change in systolic blood pressure (mmHg) from baseline to 12-months follow-up.

2) Change in diastolic blood pressure (mmHg) from baseline to 12-months follow-up.

8.2 SECONDARY ENDPOINTS

1) Change in absolute cardiovascular risk score (Modified Framingham risk score) from baseline to 6- and 12-months follow-up.

2) Change in waist circumference (cm) from baseline to 6- and 12-months follow-up.

3) Change in HDL-C (mmol/L) from baseline to 6- and 12-months follow-up.

4) Change in HbA1C (mmol/L) from baseline to 6- and 12-months follow-up.

5) Change in cognitive function (measured using both the Symbol Digit Modalities Test and CogState Brief Battery) from baseline to 12-months.

6) Meeting the recommended Australian dietary (no/yes) and physical activity (no/yes) guidelines at 6- and 12-months follow-up.

9. DATA PROCESSING

9.1 DATA FORMS

Baseline and follow-up data will be collected via validated and reliable methods comprising of questionnaires and clinical assessment conducted by an AHP/nurse. All assessments will be pilot tested among a small group of community participants to ascertain the time taken to complete the survey and to ensure that the interpretation of the questions was correct. REDCap will be employed as the primary collection method, with hardcopy forms available as a backup. The following information will be collected at baseline, 6 months and 12 months (with the exception of cognitive assessments, which will be collected at baseline and 12 months only):

A) General health and social factors survey (self-reported): This survey will include socio-demographic indicators such as age, sex, marital status, work status, income, education, ethnicity, along with questions about their current health (physical and mental morbidities, medications), sleep and health behaviours (smoking, alcohol and other drug use). These questions will be based on standardised surveys that have already been developed.

B) Data on food frequency and from nutritional assessments in follow-up appointments will be collected using I-ACE (interviewer administered).

C) Cognitive assessments (interviewer administered).

1) The Cogstate Brief Battery (Cogstate) (consists of four computerised tests of psychomotor speed, visual attention, visual learning, and memory and working memory);

2) The Symbol Digit Modalities Test (SDMT) (assesses attention and processing speed). This will be done using a paper-based form. Scores and the form will be uploaded onto REDCap by the AHP/nurse;

D) Clinical assessments: Blood pressure; anthropometry (height, weight, BMI, waist and hip circumference). The blood samples provided at baseline, 6 and 12 months will be tested for:

- HbA1c, total cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (2 vials – 10 ml)

E) Mental Health Assessment: Primary Health Questionnaire-9 [aPHQ-9] (adapted version) (self-administered or interviewer).

F) Assessment of Quality of Life (AQoL) 4D (self-administered or interviewer).

9.2 DATA ENTRY AND MANAGEMENT SYSTEM

All data will be stored securely on the University of Melbourne password protected server with data management based at the University of Melbourne. The majority of the data will be collected and stored on REDCap (on the University of Melbourne server) which is a secure server-based research data capture software accessible only by study researchers. Once data collection is completed, all data will be exported and stored on password protected folders on the University of Melbourne server.

Data collected through the I-ACE software will be stored on an Azure cloud server. The Azure platform includes industry-standard, built-in security and privacy features. The I-ACE software was developed and will be maintained throughout the study by Barillet (Israel) LTD. The built-in data security features of I-ACE include separation of the application, business, and data layers of the program, a sophisticated permission system, and encryption (using SlowStart) of the identifying data of all users.

Cumulative study participant data on dietary intake and physical activity will be downloaded from Azure platform by the Gertner Institute investigators, using only the participants' study ID number, without other identifying data. Files will be prepared for data analysis at the Gertner Institute, and then securely transferred to the University of Melbourne study coordinators and stored securely on university servers.

10. STATISTICAL CONSIDERATIONS

10.1 STUDY POWER

The original sample size calculation at trial commencement was based on a binary primary outcome, as outlined in Section 1.6. A total sample size of 300 (150 intervention subjects and 150 control subjects) will provide 80% power to detect a minimum clinically important difference of 4mmHg in mean change in diastolic blood pressure at 12 months follow-up between the intervention and control arm with two-sided α=0.05 divided between the two primary outcomes. This assumes equal standard deviations of 11mmHg in both groups based on estimates from Carrington et al. (2021) and no correlation between baseline and follow-up diastolic blood pressure (conservative assumption).[2] Accounting for potential loss-to-follow up of 15%, overall the trial would require 177 participants randomized in each group. This sample size provides >95% power to detect a minimum clinically important difference of 8mmHg in the other primary outcome, systolic blood pressure, between the two study arms, assuming a standard deviation of 15mmHg.[2]

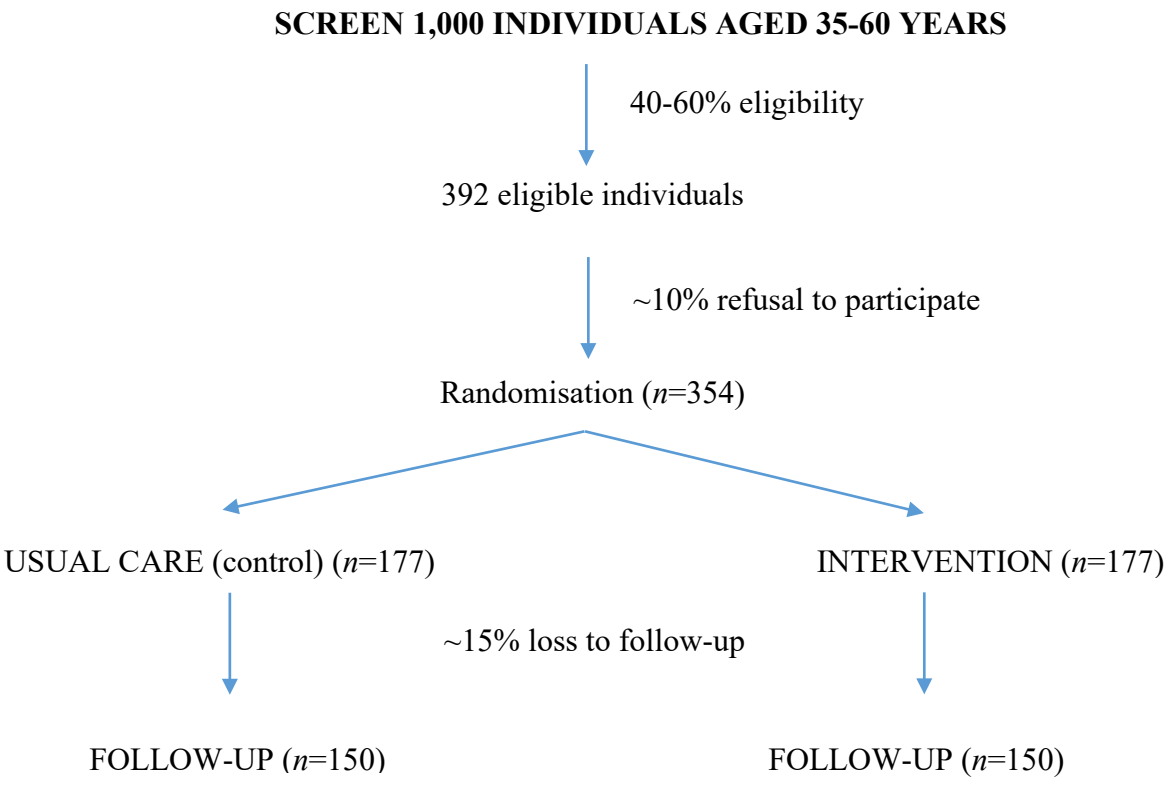


Figure 2. Flow chart

10.2 DATA ANALYSIS

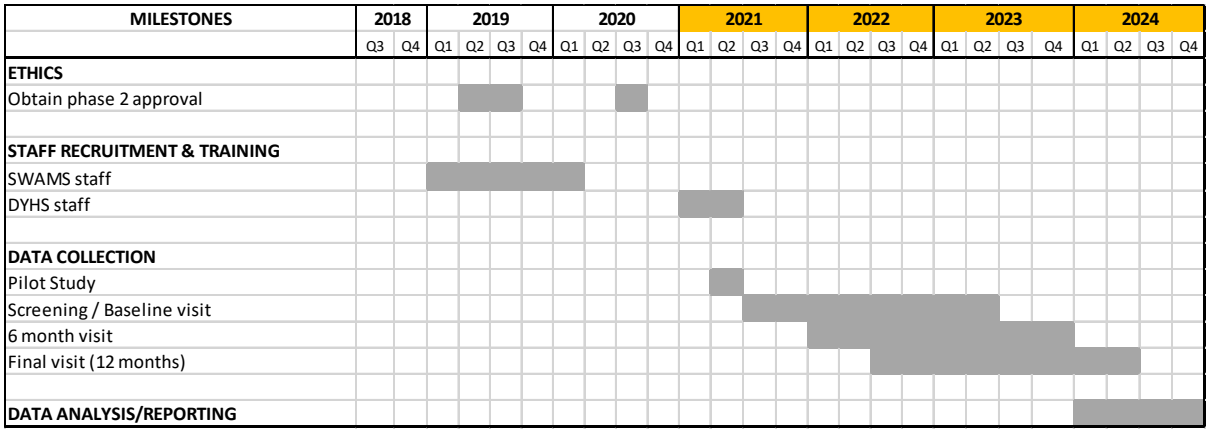
A detailed statistical analysis plan will be finalised before locking the database. The analysis will be undertaken on an intention-to-treat basis by a biostatistician blinded to the group

allocation from the Methods and Implementation Support for Clinical and Health research Hub at the University of Melbourne, with all randomised participants included according to the treatment they were randomised to receive.

Constrained longitudinal data analysis (cLDA) models will be used to examine the change in each of the primary outcomes (systolic and diastolic blood pressure), with the response consisting of all scores (baseline, 6 months, 12 months) and the model including factors representing group (intervention/control), time, intervention by time interaction and the strata (site and age group), with the restriction of a common baseline mean across interventions. This is based on the assumption that at baseline there are no differences in the mean secondary outcomes between the treatment groups; namely, that the randomisation was effective. The mean change in each of systolic and diastolic blood pressure from baseline to each follow-up time point between the two treatment arms will be obtained. The primary research question will be evaluated by obtaining the estimated differences between the two treatment arms in mean change in systolic and diastolic blood pressure from baseline to 12 months follow-up (primary time point), two-sided 97.5% confidence intervals and p-values. A similar approach will be used for continuous secondary outcomes. For binary outcomes, logistic regression models controlling for stratification factors will be fitted using generalised estimating equations to account for clustering of time within participants, with risk differences and 95% confidence intervals calculated.

Statistical oversight will be provided by the biostatistical Chief Investigator on this study, Dr Grace Joshy.

11. STUDY TIMETABLE



12. STUDY ADMINISTRATION

12.1 ORGANISATIONAL UNITS AND STAFF

University of Melbourne (UoM) (Administering Institute), Curtin University (CU), Australian National University (ANU), The Baker Heart and Diabetes Institute, Tel Aviv

University, Edith Cowan University, South West Aboriginal Medical Service (SWAMS), Derbarl Yerrigan Health Service (DYHS).

Chief Investigators: Professor Sandra Eades, Professor Emily Banks, Professor Kaarin Anstey, Associate Professor Melinda Carrington, Associate Professor Daniel McAullay, Dr Ofra Kalter-Leibovici, Dr Grace Joshy, Lesley Nelson, Dr Jason Agostino, Dr Ellie Page.

Associate Investigators: Dr Kathleen Abu-Saad**,** Dr Bridgette McNamara**,** Dr Sophie Andrews**,** Dr Ranmalee Eramudugolla**,** Dr Lina Gubhaju**,** Dr Kyle Turner**,** Ms Francine Eades**,** Ms Kerry Hunt**,** Dr Rona MacNiven, Dr Robyn Williams, Associate Professor Carrington Shepherd, Dr Richelle Douglas.

Study Partners: South West Aboriginal Medical Service (SWAMS) and Derbarl Yerrigan Health Service (DYHS).

SWAMS Staff: Salena Linforth-Milham.

DYHS Staff: Sadia Rind, Dolores Gilbert, Margo Richardson, Sinimol John

Specialist staff: Dietitians and exercise physiologists will be employed in each site to develop the dietary and physical activity interventions.

SWAMS/Bunbury: Fiona Collins (Dietitian).

DYHS/Perth: Melissa Dunham, Kanita Kunaratnam, Claire Kneafsey (Dietitians).

Trial biostatisticians: Associate Professor Karen Lamb (UoM); Dr Digsu Koye (UoM).

12.2 FUNDING MECHANISM/STUDY RESOURCES

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