# Cognitive Decline:
# A Window of Opportunity for Reducing the Risk of Dementia?

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A thesis submitted for the degree of Doctor of Philosophy of
The Australian National University

October 2021

“Be ambitious about prevention”
-Lancet Commission 2020 Report on Dementia Prevention, Intervention and Care

# Declaration

This thesis details the work undertaken and outcomes of the Doctor of Philosophy between March 2016 and October 2021 at The Centre for Research on Aging, Health and Wellbeing, College of Health and Medicine, The Australian National University, Canberra. I declare that the work contained in the thesis is the result of original research and has not been submitted to any other University of Institution.

This thesis by compilation is comprised of the following publications:

1. McMaster, M., Kim S., Clare, L., Torres, S. J., D'Este, C., Anstey, K. J. (2018). Body, Brain, Life for Cognitive Decline (BBL-CD): Protocol for a multidomain dementia risk reduction randomised controlled trial for subjective cognitive decline. *Clinical Interventions in Aging*, *13*, 2397-2406. doi:10.2147/CIA.S182046

2. McMaster, M., Kim S., Clare, L., Torres, S. J., Cherbuin, N., D'Este, C., & Anstey, K. J. (2020). Lifestyle risk factors and cognitive outcomes from the multidomain dementia risk reduction randomised controlled trial, Body Brain Life for Cognitive Decline (BBL-CD). *Journal of the American Geriatrics Society*, *68*, 11, 2629-2637. doi:10.1111/jgs.16762

And the following manuscripts submitted for review:

3. McMaster, M., Kim S., Clare, L., Torres, S. J., Cherbuin, N., & Anstey, K. J. The Feasibility of a Multidomain Dementia Risk Reduction Randomised Controlled Trail for People Experiencing Cognitive Decline: The Body, Brain, Life for Cognitive Decline (BBL-CD). *The Gerontologist*. Manuscript submitted for review.

4. McMaster, M., Kim S., Clare, L., Torres, S. J., Cherbuin, N., McRae, I. S., & Anstey, K. J. Body Brain Life for Cognitive Decline (BBL-CD) multidomain intervention: Health related quality of life outcomes. *International Journal of Geriatric Psychiatry*. Manuscript submitted for review.

# Contributions

The details of my contribution to project as a whole are as follows:

1. In conjunction with Prof. Anstey, I developed a project proposal and was successful in obtaining competitive funding from the (then named) Alzheimer's Australia Dementia Research Foundation.

2. In conjunction with the research team, I adapted the previously successful Body, Brain, Life (BBL) series of interventions to the Body, Brain, Life for Cognitive Decline (BBL-CD). The prior BBL interventions were primary risk reduction interventions, focussed on various high-risk groups, whereas BBL-CD had a secondary risk reduction focus, on people experiencing cognitive decline. BBL-CD used a similar format to previous BBL interventions, and I modified the educational modules for use with an older, cognitive decline population. Novel intervention components, designed in conjunction with the research team were a Mediterranean diet intervention, a physical activity intervention, and online brain training.

3. In conjunction with the research team, I developed the methodology which drew on some aspects of previous BBL projects, such as one of the primary outcomes of ANU-ADRI, to measure lifestyle risk and the inclusion of online educational modules. BBL-CD also incorporated some new novel methodological

components, such as a Mediterranean diet intervention and the inclusion of a full battery of neuropsychological tests, more fitting with the adapted focus.

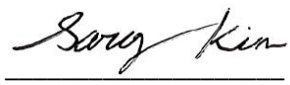
4. I project managed the intervention and data collection. I interviewed the research assistants with Dr. Kim and personally trained these staff to administer the neuropsychological tests and supervised their day-to-day activities. I liaised with the dietitian and exercise physiologist to arrange availability and bookings and was the main point of contact for participants for all aspects of the trial.

5. I undertook introductory training in longitudinal modelling and self-directed learning to conduct linear mixed models in R. I independently completed all statistical analyses in R and the analysis scripts and outputs were then verified by the statistical advisor, Prof. D'Este.

6. I drafted the manuscripts for all papers and co-authors provided critical feedback for revisions as per the authorship of each paper. I managed the submission process including responding to reviewer feedback.

# Collaborating Authors

I agree that Mitchell McMaster completed the work as detailed above as part of a Doctor of Philosophy at the Australian National University.



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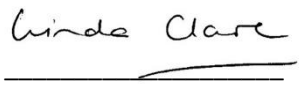

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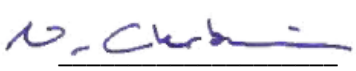

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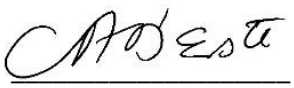

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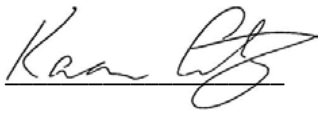

Prof. Kaarin Anstey

Primary PhD Supervisor

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# Conference Presentations

McMaster M., Kim, S., D'Este, C., Cherbuin, N., Torres, S., Clare., L., & Anstey, K. J. Outcomes for a Dementia Risk Reduction Randomised Controlled Trail (BBL-CD) (November 2019). Oral presentation at the Australian Association of Gerontology Conference, Sydney.

McMaster, M., Kim, S., Torres, S., D'Este, C., & Anstey, K. J. (July 2017). A Protocol for a Randomised Controlled Trial of Multidomain Dementia Risk Reduction for Mild Cognitive Impairment - Body, Brain, Life for Mild Cognitive Impairment (BBL-MCI). Poster presented at Alzheimer's Association International Conference, London, UK.
Alzheimer's & Dementia, 13(7), P1201. http://dx.doi.org/10.1016/j.jalz.2017.06.1797

McMaster, M., Kim, S., Clare, L., & Anstey, K. (November 2016). Ageing Well Through the Prevention of Dementia: A Protocol for a Multidomain MCI Intervention. Paper presented at 15th National Emerging Researchers in Ageing Conference, Canberra.

# Community Engagement

Royal Commonwealth Society (March 2017)
A brief overview of the research as an acceptance speech of the Phyllis Montgomery Award.

NHMRC Centre for Research Excellence in Cognitive Health (October 2017)
A presentation on the intervention protocol to the CRE which contributed funding to the research.

National Science Week Shirty Science (August 2018)
An Australian National Science Week funded initiative which pairs a scientist with an artist and together they design an artistic representation of the scientist's research to be printed on a shirt. The launch event included a brief presentation about the research and the artwork.

NHMRC Centre for Research Excellence in Cognitive Health (November 2018)
A presentation on the primary outcomes to the CRE which contributed funding to the research.

Seminar for all BBL-CD participants and (April 2019)
I gave a seminar with Q+A session on the research outcomes to all BBL-CD participants and their guests.

Media Coverage of Primary Outcomes Paper (September 2020)
The journal publisher, Wiley requested to undertake promotional media after acceptance of the paper. ANU Media also distributed a media release which resulted in six radio interviews, three newspaper articles, and a live TV news interview. ANU Media estimated the Australian audience was greater 2.5 million people. The Altmetrics score for the paper is 334 (99.7$^{th}$ percentile of all outputs ever tracked).

# Competitive Awards & Funding

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|---|---|
| 2016-2019 Alzheimer's Australia Dementia Research Foundation scholarship | $104,453 |
| 2017 Royal Commonwealth Society Phyllis Montgomery Award | $5,000 |
| 2018 Helen & Emanuel Poteris Award for Dementia Research | $2,500 |
| 2018 National Science Week Shirty Science: Launch Event (1$^{st}$ place) Overall (2$^{nd}$ place) | N/A |
| 2020 Top Articles of the American Geriatric Society (5$^{th}$) | N/A |

# Acknowledgements

A PhD is no small undertaking. It is long, at times it is stressful, at times it is almost all consuming, but it is also immensely rewarding. There is no way I could have done this alone so I owe a debt of gratitude to many people in different ways and part of this doctorate will belong to each of them.

The largest intellectual thank you must go to Kaarin. When I approached Kaarin to be my supervisor I didn't have the best marks, I didn't have a project in mind, and I didn't have any experience working on an RCT. I did have a passionate interest in dementia prevention, and I had the drive to take on an ambitious project. I'd like to think this is why she said yes to being my supervisor and I hope the quality of the project and it's outcomes repaid that belief- even if it was possibly the longest PhD she has supervised. To my other supervisors and coauthors thank you for your guidance and patience. Each of you brought different knowledge and expertise which greatly added to the project, and it definitely would not have been nearly as successful without your input- thank you.

I would like to thank the pilot participants who generously gave their time to review and give feedback on the intervention. A very large thank you all the participants who gave their time and will power towards changing their own behaviour and confronting their own memory and cognitive problems which for some was a little distressing. I hope ALL of them found some benefit in taking part.

I would also like to thank everyone who contributed financially to my PhD. Dementia Australia Research Foundation and Annette Moxie who awarded my PhD scholarship in conjunction with ANU, Kaarin who contributed research funding, the Royal Commonwealth Society which awarded me the Phyllis Montgomery Award, and Peter and Theona Combos through the Helen and Emanuel Poteris Award.

Thank you all.

# Abstract

The number of people living with dementia is expected to almost double in the next 10 years and more than triple in the next 30 years. Lifestyle risk factors such as obesity, physical inactivity and social isolation are estimated to cause more than 35% of dementia cases worldwide. One of the highest risk groups for developing dementia are those experiencing cognitive decline, such as subjective cognitive decline and mild cognitive impairment. Hence, there is a pressing need to develop interventions to reduce risk, especially for these high risk groups.

In the short- to medium-term, a significant proportion of people with cognitive decline can experience a spontaneous improvement in cognition. There is also preliminary evidence that interventions can be beneficial for this group, though this strategy has not been robustly tested. It has been hypothesised that during the cognitive decline period preceding dementia, the brain retains sufficient neuroplasticity that it is possible to modify the trajectory of decline. The thesis explores the outcomes from a multidomain dementia risk reduction intervention for people experiencing cognitive decline, the Body, Brain, Life, for Cognitive Decline (BBL-CD) intervention. The intervention is a proof-of-concept trial that adapts a previously successful primary risk reduction trial to a secondary risk reduction intervention.

The thesis is comprised of four publications:
First, a protocol paper sets out the rationale, methods and analyses that were conducted. This publication details the evidence for choosing the domains of Mediterranean diet, physical activity, and cognitive engagement. It explains the educational modules the control and intervention groups complete, and the additional activities only undertaken by the intervention group.

Second, the primary outcome measures of this thesis were lifestyle risk for Alzheimer's disease and cognition. This paper demonstrated that the intervention group were able to significantly improve overall lifestyle risk and cognition relative to the control group, which showed little change in either outcome measure.

Third, the feasibility of the intervention in this participant group was tested using three elements of the Bowen Feasibility Framework: Acceptability, implementation, and efficacy to change lifestyle behaviours. The intervention was found to be highly acceptable, was mostly implemented successfully, and mostly demonstrated efficacy to change lifestyle behaviours. While the intervention was found to be feasible, some major learnings and improvements were identified for future interventions.

Finally, a fourth paper examined the potential health-related quality of life outcomes of the intervention. The intervention did not show a significant group x timepoint interaction, required to demonstrate efficacy. However, the presence of several significant between- and within-group differences and the magnitude of these differences (>3 points on SF-36) are reported as potential outcomes of interest in larger, more adequately powered studies in this participant group in the future.

Together, these publications combine to form a thesis that lends support to the notion that secondary dementia risk reduction interventions are both feasible and show efficacy. The results support the conduct of larger, longer study to characterise any improvements in lifestyle and cognition more accurately and determine whether these improvements are sustainable long term. This thesis provides proof-of-concept that the cognitive decline period represents a window of opportunity to reduce lifestyle dementia risk and warrants further long-term investigation.

# Contents

# Chapter 1

## 1.1 Introduction

In 2015 there were 47 million people living with dementia worldwide, by 2030 it is projected that the figure will increase to 82 million and by 2050 to 152 million [1, 2]. The number of people living with dementia has a huge financial impact internationally. In 2018, it was estimated that the global cost of dementia had exceeded $1 trillion USD, a figure larger than the costs of all cancers and cardiovascular diseases combined [3, 4]. In the absence of a cure or even a disease modifying treatment, the World Health Organisation (WHO) has declared that "dementia poses one of the greatest societal challenges for the 21st century" [5].

Dementia is a neurological syndrome characterised by impairments across multiple cognitive domains [6]. Dementia can be caused by more than 100 diseases and disorders. The most common causes of dementia are: Alzheimer's disease (AD) (approximately 70% of cases), vascular dementia (approximately 10%), frontotemporal dementia (approximately 10%), and Lewy body dementia (approximately 5%), however it is common for a person with dementia to show elements of more than one form of dementia [7]. A seminal paper in this area, published by Barnes and Yaffe [8] calculated that globally 50.7% of all cases of Alzheimer's disease (AD) were attributable to seven modifiable lifestyle factors (cognitive inactivity, smoking, physical inactivity, depression, hypertension, diabetes and obesity). This work was later replicated for the Australian population (with some methodological refinements) and came to a similar figure of 48.4% of cases attributable to those same risk factors [9]. More recent work has estimated that the top 12 modifiable dementia risk factors account for around 40% of cases worldwide [10].

Given these estimates, there is a clear need to develop interventions to reduce lifestyle risk for AD and dementia. There are two main approaches to lifestyle risk reduction: primary and secondary prevention. Primary prevention aims to reduce the levels of risk factors in the broader, general population so that fewer people will go on to develop dementia, whereas secondary prevention is a more targeted approach, focusing on people who are beginning to experience symptoms of cognitive decline,

which precedes dementia [11]. Several authors have identified secondary prevention of cognitive decline and dementia as an under researched area that holds much promise [1, 12-19].

## 1.2 Cognitive Decline

Prior to the onset of dementia there is a period of low level cognitive decline. Initially, this may start as deficits which cannot be detected with neuropsychological testing, but individuals are aware of their declines, hence this period is termed subjective cognitive decline (SCD) [20]. Over time, this decline may worsen and individuals develop deficits relative to those of the same age and education, which are detectable through neuropsychological testing, but which do not meet the criteria for a diagnosis of dementia, this condition is called mild cognitive impairment (MCI) [20]. If further decline takes place, people may go on to receive a diagnosis of dementia.

### 1.2.1 Subjective Cognitive Decline

The term "SCD" was coined in 2014, when a conceptual framework was proposed by the SCD Initiative (SCD-I) [21]. While there are no diagnostic criteria for SCD, the SCD-I has proposed two criteria to standardise research in this area: "A self-experienced persistent decline in cognitive capacity, compared with a previously normal cognitive status, which is unrelated to an acute event" and "normal performance on standardised cognitive tests used to classify MCI, adjusted for age, sex, and education"[20]. Further to this, the SCD-I has developed the SCD plus criteria which are indicative of a greater likelihood of future decline. The SCD plus criteria are: Subjective decline in memory; onset within the past five years; onset at ≥60 years; concern associated with decline; confirmation of decline by an informant; persistence over time; and seeking of medical help for the decline [21]. The final two points were not included in the initial criteria but added subsequently. Despite the research criteria for SCD becoming standardised only recently and the absence of any formal diagnostic criteria, research is beginning to characterise the condition in some detail.

The prevalence of SCD varies widely across settings and with sample characteristics. An international study combining data from more than 39,000 participants from 15 countries yielded prevalence estimates between 23.8% and 25.6% of individuals over the age of 60 years [22]. Much like AD and dementia, the prevalence of SCD increases with age; in those older than 85 years the prevalence

increases to 88% [16]. In addition to age, a number of other risk factors for developing SCD have been identified: being male, having lower education, low levels of physical activity, poor diet, obesity, diabetes, hypertension, depression, greater number of chronic medical conditions, having Asian or African ancestry (compared to European American ancestry), and being from a low or middle income country [22-24].

SCD has been shown to be associated with levels of amyloid plaques and tau proteins, two key pathological hallmarks of AD [25]. Recent research is showing that higher levels of amyloid in the SCD group is related to negative outcomes, such as greater subjective cognitive complaints[26], lower global cognition [27] and longitudinally faster declines in memory, attention, executive function, language and subjective cognition [26, 27]. Higher levels of amyloid are also linked to increased likelihood of progression to MCI and AD [28, 29]. The accumulation of tau has also been found to be associated with SCD [30], but is largely confined to the entorhinal cortex, which is one of the first areas to show pathological change in early AD [31].

In addition to amyloidopathy and tauopathy, SCD is associated with atrophy in the medial temporal lobe [32], in particular the entorhinal cortex [33, 34] and hippocampus [35, 36]. Compared to healthy controls the level of medial temporal lobe atrophy is related to the degree of objective cognitive decline [37]. Functional neuroimaging demonstrates that people experiencing SCD also show levels of microstructural white matter damage [38].

Although SCD is explicitly a condition characterised by cognition within the normal range, people with SCD do show very subtle deficits in memory, executive function, working memory, visuospatial skills and language compared to those without SCD when controlling for age, gender, and education[39, 40]. The magnitude of these subtle cognitive deficits is also linked to increased likelihood for future conversion to MCI and AD [39]. In addition to these subtle cognitive deficits a number of other risk factors have been linked to increased risk of progression to MCI including: age, lower education, lower levels of social interaction, and daily drinking [41].

### 1.2.2 Mild Cognitive Impairment

There are multiple diagnostic criteria in use for MCI. The first criteria proposed were the Peterson criteria in 1999, which included: a subjective memory complaint, preferably confirmed by an

informant; objective impairment in memory; normal general cognitive function; normal activities in daily living; and not meeting criteria for a dementia diagnosis [42, 43]. Over time this definition has broadened to include cognitive domains other than memory. The National Institute on Aging- Alzheimer's Association criteria are: concern over a decline in cognition from an individual, informant or clinician; objective impairment in one or more cognitive domains relative to age and education; independence in activities of daily living; and not meeting the criteria for a diagnosis of dementia [43]. MCI is also classified into subtypes based on the pattern of deficits observed: single or multidomain impairments and amnestic or non-amnestic (including deficits in memory or not) [43]. These classifications give four subtypes of MCI: single domain amnestic MCI, multidomain amnestic MCI, single domain non-amnestic MCI and multidomain non-amnestic MCI. The amnestic forms of MCI are more common than non-amnestic forms of MCI [44].

The neuropathology observed in SCD shows further advancement in line with the emergence of objective cognitive deficits in MCI [25, 34, 35, 45]. For example, compared with healthy controls, individuals with SCD, MCI and AD show reductions in entorhinal cortex volume of 18% (SCD), 26% (MCI) and 44% (AD) and for the hippocampus 6% (SCD), 16% (MCI) and 19% (AD) [33]. Amyloid and tau further accumulate in the brain during the MCI stage of disease progression, but show different patterns of accumulation from each other [46, 47]. Amyloid distribution is found diffusely, slowly building up throughout the cortex [46]. Whereas tau spreads from the entorhinal cortex to nearby areas of the temporal lobe, such as the parahippocampal cortex and amygdala, then areas of the parietal and occipital lobes, prefrontal areas and finally the primary cortical areas (controlling sensation and movement). Interestingly, areas in the medial temporal lobe (where tau first appears) are often not involved in amyloid spread, at least not until the later stages of the disease. However, these are the areas which show some of the greatest reductions in volume. Given the similarities in the distribution of tau and atrophy, image-based tau staging correlates with overall cognitive status [46]. In addition to continued deposition of amyloid and tau, other AD and dementia-related features of the brain continue to progress in the MCI stage. Multiple white matter tracts within the medial temporal lobe, parahippocampal cortex, parietal and occipital regions begin to become disrupted [38, 48]. Abnormal neural activation patterns

during cognition and resting state [49, 50]. There is hypoperfusion (low blood flow) and hypometabolism (low glucose usage) both markers of neurodegeneration, cognitive decline and AD [51].

There are a number of factors which increase the likelihood of conversion from MCI to dementia. Amnestic and multidomain subtypes of MCI (especially multidomain amnestic MCI) are at a greater likelihood of converting to dementia [44]. More advanced neuropathology such as greater hippocampal atrophy, cerebral vessel disease and infarcts are also associated with a greater risk of progressing to dementia [52].

Research has also identified factors that are associated with greater likelihood of reversion from MCI to normal cognition and/or lower likelihood of progressing to dementia or AD. Some of these are: younger age, less advanced cognitive decline, a more cognitively engaged lifestyle, greater physical activity, and lower blood pressure [52, 53]. The combination of cognitive and brain reserve, neuropathology and aging all play a role in the clinical expression of MCI and conversion to AD and dementia [52].

Taken together, the emerging pathological profiles of people experiencing SCD and MCI are consistent with preclinical AD and dementia and these individuals are at a much higher risk of progressing to these conditions. A meta-analysis of 28 longitudinal studies calculated that per year about 7% of people with SCD develop MCI and 2% develop dementia, and over 4 years 27% progressed onto MCI and 14% developed dementia [54]. A seven-year follow-up of a group of 2,043 people experiencing SCD showed that 18% had gone on to developed dementia (MCI was not tracked in this study) [55]. For MCI the rates of conversion to AD are 7% at 1 year, 24% at 3 years to 59% at 6 years [56, 57] However, research shows that people experiencing SCD and MCI don't decline in a linear fashion, a significant proportion of these individuals will remit from SCD and MCI back to normal cognition [16, 20, 57, 58]. Given that individuals with these conditions can spontaneously remit to normal cognition with no intervention, may be an indication that at this point in the disease process the brain may retain sufficient neuroplasticity that modification of the trajectory of decline is possible. This period may represent a "window of opportunity" to reduce the risk of future dementia.

## 1.3 Dementia Risk Reduction

One group of interventions for reducing the risk of dementia are non-pharmacological interventions (NPI). NPIs are any interventions that do not involve medications, they include lifestyle, behavioural, social and psychological interventions. These are commonly used in dementia risk reduction interventions to modify lifestyle risk factors for dementia. Three of the most readily modifiable risk factors for which there is good supporting evidence are: diet, physical activity, and cognitive engagement.

### 1.3.1 Mediterranean Diet

Diet is regarded as an important risk factor for dementia and cognitive decline [10, 59, 60]. Except in the case of deficiencies, overall dietary pattern is more important than specific dietary nutrients, such as B vitamins or omega-3 fatty acids for maintaining cognitive status [10, 59]. One of the most extensively researched dietary patterns is the Mediterranean Diet (MeDi) [61]. The MeDi is predominantly a plant-based dietary pattern, including high intake of vegetables, fruits, nuts and legumes, moderately high intake of fish and seafood, low red meat, extra virgin olive oil as the main source of fat and wine with a meal [62].

There is good epidemiological evidence linking higher adherence to MeDi to lower incidence of cardiovascular disease, cancer, stroke, heart attack, type 2 diabetes, weight gain, metabolic syndrome, depression, cardiovascular mortality, and all-cause mortality [63-65]. Importantly, the MeDi has also been linked to lower rates of AD and cognitive decline as well as progression from cognitive decline to dementia [64-68]. One study, [69] found a difference in effects between middle aged people and a group over 70 years, concluding that MeDi may not show positive effects until the onset of age related cognitive decline. The observed benefits of the MeDi are often seen in a dose-dependent manner i.e., greater adherence, results in greater benefits [63, 65, 68, 70].

Compared to the epidemiological evidence base, less RCT evidence is available for MeDi [71]. However, one of the most well-known studies involving MeDi is the Prevención con Dieta Mediterránea (PREDIMED) study [72]which recruited more than 1,000 participants for a three-arm, 6-year intervention. The intervention groups were: MeDi supplemented with additional extra virgin olive oil; MeDi supplemented with mixed nuts; and a control group who received advice to reduce fat intake. At the

conclusion of the study benefits were seen in MMSE and clock drawing test, relative to controls and the MeDi supplemented with olive oil group had a lower risk of developing MCI (all relative to controls) [72, 73].

### 1.3.2 Physical Activity

A substantial amount of literature supports an association between physical activity and lower risk of AD, dementia and cognitive decline [74]. A meta-analysis including 15 prospective studies of people over the age of 65 years, including almost 34,000 people found individuals with a lifestyle with high levels of physical activity had a 38% lower chance of cognitive decline, with 35% lower chance for low to moderate levels of activity compared to sedentary individuals [75]. Another larger (45 studies, 117,000 people), more recent meta-analysis found high levels of physical activity were related to lower risk for AD (OR=0.62), cognitive decline (OR=0.67), all-cause dementia (OR=0.79), but non-significant for vascular dementia [76].

With regard to types of physical exercise, research indicates that for people over the age of 50, aerobic exercise (SMD=0.24), resistance exercise (SMD=0.29), multicomponent training (i.e. aerobic and resistance) (SMD=0.33), and taichi (SMD=0.52) were all associated with cognitive benefits, while yoga was not [77]. Significant effects were found for attention (SMD=0.27), executive function (SMD=0.34), memory (SMD=0.36) and working memory (SMD=0.29), but global cognition showed non-significant outcome. Recommendations from this study were that exercise sessions should be 45-60 minutes, of at least moderate intensity, and include aerobic and resistance training to achieve cognitive outcomes. Exercise was shown to benefit people over 50 years, regardless of cognitive status [77].

Similar effects have been found in systematic reviews of exercise interventions for people with MCI [78-80]. While all studies agree on the efficacy of exercise interventions to improve global cognition for people with MCI, there are some discrepancies in the other domains which show improvements. Null [78] and positive outcomes are reported for immediate (SMD=0.26) and delayed recall (SMD=0.25) for aerobic exercise [79] and null [78] and positive outcomes for executive function for resistance exercise (SMD=0.39) [80].

### 1.3.3 Cognitive Engagement

There is increasing evidence that cognitive engagement is an important variable for cognitive decline and dementia [1, 10]. In a meta-analysis by Yates and colleagues [81], four of five separate analyses showed a beneficial effect of a cognitively engaged lifestyle in reducing the risk of cognitive decline (OR=0.69) and dementia (HR=0.58, RR=0.61, and OR=0.78). Cross sectionally, people with a more cognitively active lifestyle showed higher levels of cognition in late life (β=0.11), better memory (β=0.20), processing speed (β=0.37), and executive function (β=0.23). Longitudinally, those with higher cognitive engagement showed less decline in overall cognition (β=-0.23), language (β=-0.11) and executive function (β=-0.13).

Cognitive engagement interventions are generally classified into three categories: cognitive stimulation which involves engaging in a variety of real world activities aimed at enhancing the level of function; cognitive rehabilitation covers approaches which develop strategies personalised to the individual's deficits to improve real-word function; and cognitive training which is standardised training on tasks linked to cognitive domains aiming to improve or retain the current level of cognitive function [82].

One form of cognitive training which has attracted significant research interest is computer based cognitive training [83]. A key study in the area was the Advanced Cognitive Training in Vital Elderly (ACTIVE) trial [84-86]. The ACTIVE trial was a four-arm RCT, including more than 2,800 cognitively normal people 65 years or older; it included three comparison intervention arms (memory, reasoning, or speed of processing training) and a passive control group, each completing 10 sessions over a 6 week period. The memory training involved strategies to improve verbal episodic memory, reasoning training focused on strategies for solving problems and serial patterns, and the speed of processing group completed computer based training designed to increase the amount and complexity of information processed quickly.

At two years post-intervention, all comparison intervention groups showed improvements in the cognitive domains targeted [87]. However, the 10 year post-intervention follow-up showed a different

pattern of outcomes. Participants in the processing speed group showed a 29% reduction in rates of dementia (8.5%, HR=0.71, p=.049), relative to the control group (10.8%), and neither of the other two comparison groups showed significant reductions in rates of dementia (9.1%, HR=0.79, p=.163 and 9.0%, HR=0.79, p=.177) [85].

Interventions aiming to modify lifestyle risk factors show great potential to improve cognition and potentially reduce risk of AD and dementia for people experiencing cognitive decline[1, 10, 12, 13, 17, 86, 88-90]. In guidelines that the WHO published for risk reduction for cognitive decline and dementia, for people with MCI MeDi, physical activity and cognitive interventions were all reviewed and recommended "conditionally" (i.e. possibly beneficial but may not be appropriate for everyone) [2]. However, these guidelines do rate the quality of evidence for these domains as moderate quality for MeDi, low quality for PA and low to very low quality for cognitive interventions. The SCD-I propose that individuals with SCD be advised on the reduction of modifiable lifestyle risk factors including MeDi, physical activity and cognitive engagement, among others [20].

## 1.4 Multidomain Interventions for Cognitive Decline

Several authors have stated that as dementia is a condition with a multiple risk factor etiology, it is logical that to be most effective, interventions must use a multidomain approach [15, 91].

### 1.4.1 Systematic Review Evidence for SCD Interventions

There is emerging evidence to support the efficacy of NPIs in the SCD population. Systematic reviews of multidomain interventions in the SCD group are generally supportive of a positive effect. A systematic review by Smart et al. [13], which focused on non-pharmacological interventions for SCD found nine RCTs, including physical and cognitive activity interventions and varying in length from 4 to 24 weeks. Two meta-analyses were conducted to examine the effect of interventions on objective cognition; when all studies were combined there was found to be an effect size of d=0.22, and for cognitive interventions alone had an effect size of d=0.37. The authors of this review concluded that findings for NPIs for the SCD population are encouraging and further research is warranted for two reasons: it may prevent or at least delay those who will progress to MCI and dementia; and for those who will not

progress, the interventions may offset some normal age related declines to enhance productive aging and quality of life.

A later systematic review on NPI for SCD by Bhome et al. [88] used a broader search strategy locating 20 RCTs for inclusion. These studies can be classified as: psychological interventions (n=5); cognitive training (n=11); lifestyle (n=2); and supplement interventions (n=4) (some interventions were included in more than one category) and encompassed interventions with from 4 to 24 weeks. Meta-analyses showed significant effects for psychological interventions for wellbeing (g=0.40) and for cognitive interventions for the outcomes of wellbeing (g=0.25) and objective cognition (g=0.13). Neither psychological nor cognitive interventions had an effect on subjective cognition. Insufficient studies and/or data prevented further meta-analyses.

In the most recent of the systematic reviews, Sheng and colleagues [15] evaluated the potential of 18 NPI interventions for secondary prevention of AD for people experiencing SCD. One particular strength of this review over previous reviews is the inclusion of multidomain interventions, rather than focusing on single domain interventions. The RCTs found fell into the categories of: psychological interventions (n=1); mindfulness training (n=1); lifestyle interventions (n=5); cognitive training (n=9); and multidomain interventions (n=2). Meta-analyses showed significant benefits from psychological interventions for objective memory (g=0.53) and cognitive training showed benefits for subjective memory (g=0.49), objective memory (g=0.19), and psychological wellbeing (g=0.27). Due to the low number of interventions in other categories, further meta-analyses were not possible. The authors concluded that “multidomain interventions appear to be an effective prevention strategy for individuals with SCD”, in terms of secondary prevention of AD and that larger rigorous studies are warranted.

### 1.4.2 Randomised Controlled Trial Evidence for SCD Interventions

An RCT conducted by Barnes et al. [92] the Mental Activity and eXercise (MAX) Trial included cognitive activity (intervention: brain training; control: educational DVDs) and physical activity (intervention: aerobic and strength training with stretching and relaxation; control: strength training with stretching and relaxation) interventions for 126 participants with SCD, three days/week for 12 weeks.

Participants were randomised to groups in a 2 x 2 factorial design: cognitive control/physical control; cognitive control/physical intervention; cognitive intervention/physical control; and cognitive intervention/physical intervention. While the greatest level of improvement in global cognition was seen for the cognitive intervention/physical intervention group, three of the four groups did show significant improvements (the cognitive control/physical intervention group did not) and the difference between groups was not significant. One key limitation not noted by the authors was that the study was powered to detect a change of 0.45 SDs between groups and the greatest improvement seen was 0.25 SDs from baseline levels and 0.14 SDs greater than the lowest performing group, hence it was underpowered to detect the magnitude of changes seen.

Small and colleagues [93] conducted a 14-day lifestyle RCT with 17 participants with SCD. The intervention group included: healthy diet, physical conditioning, memory training and relaxation techniques, while the control group continued with their normal lifestyle. At the conclusion of the study the intervention group had significantly higher verbal fluency, relative to the control group. PET scans showed that the intervention group showed reduced cerebral metabolism in the left dorsolateral prefrontal cortex, involved in language production. Lower cerebral metabolism is generally a marker of increased efficiency. Limitations of this study are the small sample size could have led to outcomes which may not be representative of the true effects of the intervention.

### 1.4.3 Systematic Review Evidence for MCI Interventions

More research has been done on the effects of multidomain interventions for the MCI population, than for SCD. A systematic review conducted by Huckans et al. [17] on cognitive rehabilitation therapies for MCI included 14 RCTs comprised of: lifestyle interventions (e.g. physical activity, diet, and cognition) (n=7); multidomain cognitive training (n=3); and single domain cognitive interventions (n=4). Each of the seven lifestyle interventions and three multimodal interventions showed significant improvements in at least one cognitive domain; improvements were seen across the domains of global cognition, memory, executive function, and activities of daily living. On this basis the authors concluded that of the categories reviewed, lifestyle and multimodal interventions show the greatest promise for future research.

Wang et al. [94] conducted a meta-analysis on the effects of cognitive (n=11) and physical activity interventions (n=7) for people with MCI. For cognitive interventions significant effects were found on global cognition (z=2.41), TMT-B (z=2.22), and delayed memory (z=1.99). For interventions focused on physical activity significant outcomes were found for global cognition (z=2.99). The authors noted that higher intensity exercise or the combination of aerobic and resistance exercise may be more likely to have positive effects and that future research in the MCI group should seek to confirm this.

Another meta-analysis by Sherman [95] for NPI interventions for MCI found 32 RCTs that met the inclusion criteria. Combining the effects of all included studies showed that interventions in this group have a moderate effect on cognitive outcomes (g=0.51) and a large effect for memory specifically (g=0.75). Significant effects were found for restorative training (g=0.66), compensatory interventions (g=0.55) and multicomponent and lifestyle interventions (g=0.42). Subgroup analyses on the different MCI subtypes found no significant differences in outcomes. One limitation of this study was that lifestyle interventions were grouped with all other multicomponent interventions (e.g., interventions comprising exercise, social and leisure activity combined with cognitive training interventions focused on multiple domains of cognition). This group of interventions comprised 17 RCTs (53% of included studies) indicating that further division of this classification may have been possible and been more informative.

Another meta-analysis [96] used a Bayesian network analysis of NPIs for people with MCI. Outcomes provided were mean differences (MD) in mini-mental state examination (MMSE) between control and intervention for NPI types, and the network analysis had the added advantage of directly ranking the types of interventions based on percentage likelihood (L) of participants experiencing a benefit. The six types of NPIs included were: cognitive stimulation (n=2); physical activity (n=6); music therapy (n=1); cognitive training (n=7); cognitive rehabilitation (n=2); and multidomain (any combination of the other categories combined) (n=4). Five of the six intervention types showed efficacy to improve cognition, with only cognitive rehabilitation showing non-significant efficacy (MD=0.23, L=18.4%). Cognitive stimulation (MD=1.94, L=78.1%), physical activity (MD=1.76, L=73.9%), multidomain (MD=1.66 L=68.9%), music therapy (MD=1.50, L=60.7%), and cognitive training (MD=1.07, L=42.9%) interventions all showed significant benefits relative to control participants. A clear limitation of this study however was

that the only cognitive outcome of interest was the MMSE. Including only this single outcome, which is generally not considered to be strong tool for assessment of MCI deficits [97, 98], may have limited the available studies and obscured the full potential for cognitive improvements, thereby biasing the results and limiting the generalisability of the conclusions. Including a broader range of outcome measures may have yielded different results, encouragingly though, the results are broadly consistent with other meta-analyses in the area.

### 1.4.4 Randomised Controlled Trial Evidence for MCI Interventions

The Study of Mental and Resistance Training (SMART) study [99] was a 28-week, four-arm RCT for people with MCI. The groups were: a control group with a sham physical and sham cognitive intervention (calisthenics and National Geographic videos); a high intensity progressive resistance training (PRT) group (which included the sham cognitive intervention); a computerised cognitive training (CT) (which included the sham physical intervention); and a combined PRT and CT group. There were significant group x timepoint interactions (i.e., efficacy) for global function, executive function, and category fluency, however contrary to the hypothesis the single domain intervention groups outperformed the combined intervention group across all three of these measures. The greatest improvements were seen in the PRT group, and the effects were maintained 12 months after cessation of training.

Bae and colleagues [100] conducted a 24-week multidomain intervention for people with MCI. The intervention group took part in a combination of physical, cognitive, and social activities compared with an active control. The physical interventions included walking, strength training, and Tai Chi; the cognitive interventions were activities such as visiting a library or museum, karaoke, and playing board games; and the social interventions included socialising, and meeting friends for coffee or shopping. Participants in the intervention group completed two, 90-minute sessions weekly for 24 weeks according to a schedule set by the research team. The active control group completed two, 90-minute general health education classes. Outcomes were a battery of cognitive testing, physical function, and levels of physical activity, and social engagement. The only two outcomes to show a group x timepoint interaction were spatial working memory which improved for the intervention group and declined for the control

group, and physical activity which declined in both groups, but to a greater degree in the control group. Based on only a single significant cognitive outcome the authors reasoned that perhaps the physical and cognitive intervention components were not sufficiently intensive to achieve a greater degree of cognitive outcomes.

A four-arm multidomain RCT was conducted by Lam et al. [101] for 12 months. Participants were given a list of potential intervention activities based on their group allocation and were requested to complete an intervention activity for one hour, three times per week. The four intervention arms were: A physical intervention comprising one stretching and toning exercise, one mind body exercise (e.g., Tai Chi), and one-hour aerobic exercise per session; a cognitive intervention (e.g., reading and discussing newspapers, playing board games), a cognitive-physical (CP) intervention comprising one cognitive session and two mind-body exercise sessions; and a social intervention (e.g., having tea with a friend or watching a film). The authors hypothesised that the strongest outcomes would be achieved by the combined intervention, followed by the physical and cognitive interventions and the least benefits from the social intervention. All groups showed significant improvements in ADAS-Cog, delayed recall, subjective cognition, and verbal fluency. However, there was only a significant group x timepoint interaction for verbal fluency with the CP group showing the highest score. For post-hoc subgroup analyses, participants were divided on the basis of single and multidomain MCI and analyses were rerun. In the single domain MCI analyses the CP group showed significant group x time interaction effects for ADAS-Cog, delayed recall, and verbal fluency, whereas for the multidomain MCI participants, the CP group showed a significant interaction for verbal fluency only. The improvements in ADAS-Cog and delayed recall showed a dose-dependent effect, with greater levels of adherence being associated with greater improvements.

### 1.4.5 Further Evidence for Cognitive Decline Interventions

Some research has been less specific about the research group included, combining participants with SCD, MCI and early AD or participants from groups who are considered at-risk of future dementia to draw more general conclusions across the whole cognitive decline spectrum.

A systematic review conducted by Whitty and colleagues [102] looked at NPIs for people aged 50+ or with SCD or MCI. In total the review included 64 RCTs which focused on psychosocial (e.g., social, art, psychological strategies) (n=12), physical activity (n=36), dietary (n=6) and multidomain lifestyle (n=10) interventions. This study is one of the few reviews to include multidomain lifestyle studies, specifically. The interventions in this category included studies with combinations of physical activity, diet, cognitive and social engagement. Of the seven high quality multidomain studies that were reviewed in depth, four showed significant improvements on at least one cognitive outcome. While the evidence included did not broadly support the efficacy of the Mediterranean diet, on the strength of a single, large, robust study (the PREDIMED study) the authors believed that MeDi does warrant further research. The review recommended that an evidence-based approach to improve global cognition, memory and executive function would be a multidomain intervention of greater than four months, comprising aerobic or resistance physical activity with some element of cognitive engagement.

Yao et al. [103] conducted the only known meta-analysis on whether NPIs can prevent cognitive decline. Other outcomes included were ADAS-Cog, MMSE and activities of daily living (ADL). In total the meta-analysis included 22 RCTs: 10 studies examined diet; eight studies on exercise; and four studies on cognitive training. The analysis for the prevention of cognitive decline combined all interventions with MCI or dementia conversion as an outcome, regardless of category, this analysis showed that those in intervention groups were at significantly lower risk, compared to those in control groups (RR=0.73)(i.e., a 27% lower incidence of progression to MCI or dementia). For the cognitive and functional outcomes, there were no significant effects for ADAS-Cog (MD=-0.69), but significant outcomes for MMSE (MD=0.59) and ADLs (MD=0.73). A major caveat of this study was the inclusion of any study with participants “at risk of decline” rather than a standardised condition such as SCD and MCI.

There have also been a number of RCTs which have used a similar approach to the systematic reviews above by focusing on a mixed participant group. Park and colleagues [104] conducted a three-arm, pilot RCT for people aged 60 or over, not experiencing objective cognitive decline and having lifestyle risk factors for dementia. The three intervention groups were: a 4-week intensive intervention (n=9), involving one-on-one personalized health advice on modifying vascular risk factors, diet, cognitive

engagement, social engagement, and a plan for modifying lifestyle habits; the same intervention with a 20-week maintenance program (n=13) of face-to-face monitoring of adherence to lifestyle changes; and an active control group (n=10) of one time personalised advice on lifestyle modification. The only group to show significant group x timepoint interactions for lifestyle risk factors and cognition was the intervention with maintenance program. Lifestyle improvements only took place for lifestyle protective factors (e.g., high cognitive activity and fish intake), but not lifestyle risk factors (e.g., smoking, and low social engagement). The intervention with maintenance group showed significant improvements in executive function and while this group also had the highest global cognition scores these failed to reach significance. The major limitation of this study is the small sample size (baseline n=32, follow-up n=26) which meant the study was underpowered to detect the full spectrum of possible effects.

Another recent RCT, the Brain Health Champion study [105] involved participants with SCD (n=4), MCI (n=21) or mild AD (n=12) and used a health coaching approach to reduce lifestyle risk factors for AD in the domains of MeDi, physical, social and cognitive activity. The intervention group received weekly motivational interviewing and goal setting phone calls compared with a standard care control group. Participants in the intervention group showed significant increases in adherence to the three lifestyle domains and quality of life, importantly the magnitude of lifestyle change predicted the level of improvement in quality of life. Some of the main limitations of this study are the small total sample size, and the mixed etiologies of unbalanced sizes means results are not entirely generalisable for any one group. Additionally, the study did not include any cognitive measures.

The multidomain approach has been shown to work in other participant groups. One high profile study is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial [90], which included 1,260 people of 60-77 years with no or low levels of cognitive impairment. Intervention participants received group and individual sessions on diet, physical activity, cognitive engagement, and vascular risk factor management, while the control group received general health advice. At the two year follow-up the intervention group showed benefits to executive function, processing speed and global cognition and some benefits in health-related quality of life [106].

In summary of this interventional data, SCD and MCI can show improvements in a range of outcomes, as a result of a range of interventions. One key knowledge gap in the literature is that few RCTs and meta-analyses include multidomain lifestyle interventions, this is despite many authors suggesting that this may be the most effective way to reduce risk of cognitive decline and dementia [1, 14, 15, 19, 89, 91, 107-109]. While only preliminary data is presently available on these interventions for SCD and MCI, the occurrence of spontaneous remission from these conditions, and the preventative effects of lifestyle factors based on epidemiological data indicate that such interventions are certainly worthy of further exploration in this population.

## 1.5 The Body, Brain, Life Interventions

The Body, Brain, Life (BBL) studies are a suite of interventions that have used the multidomain approach to reduce lifestyle risk [110-116]. All BBL studies have included the same online risk reduction educational modules, covering dementia literacy, dementia risk factors, physical activity, nutrition, social engagement, cognitive engagement, self-management of chronic health conditions (with a mood module being added from the 2nd BBL study onwards.) The BBL studies also share a common primary outcome, the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) [117, 118]. The ANU-ADRI is a composite measure which provides scores from 11 lifestyle risk factors (age [moderated by sex], low educational attainment, body mass index, type 2 diabetes, depression, cholesterol, traumatic brain injuries, smoking status, low social engagement, and exposure to pesticides), as well as four protective factors (alcohol intake, physical activity, cognitive engagement, and fish intake), and a total score combining both risk and protective factors. The values for risk and protective scores were derived from odds ratios of risk from meta-analyses and large high quality cohort studies [117]. The index has been validated against three large, international longitudinal cohort studies and found to be a valid predictor of future AD [118]. A difference of 2 ANU-ADRI points has been found to be predictive of significantly increased likelihood of developing AD, thus is considered to be a clinically meaningful difference [118].

The first BBL study [110, 111], published in 2015 was a three-armed RCT, an online only BBL group completed the modules via computer, a face-to-face BBL group completed the modules online as well as attended group seminars on risk factor reduction and an active control group were sent links to

health related websites weekly [110]. The study demonstrated that both BBL groups showed a group x timepoint interaction for total ANU-ADRI (i.e., demonstrating efficacy), but the control group showed no significant change. Post-hoc analyses showed that changes were due to increases in protective lifestyle factors, rather than reductions in risk factors. There were no significant differences in levels of change between the two BBL groups [111].

The second BBL study, BBL-FIT [112] was a pilot study which in addition to the educational modules on risk reduction, incorporated active sessions on diet and physical activity for the intervention group. The dietary intervention was offered to participants who had a BMI outside of the healthy range (<20 or >30), had experienced weight loss or gain in the past 3 years or had an unhealthy dietary pattern at baseline. It involved a one hour, individually tailored, face-to-face dietitian session. All participants in the intervention group took part in the physical activity session, which involved a one hour, individually tailored, face-to-face exercise physiology session to co-design an exercise plan to increase physical activity to 150 minutes of moderate activity per week. Being a pilot program, the BBL-FIT outcomes were not formally published, but were used to inform the methodology and implementation of the next BBL study.

BBL for General Practice (BBL-GP) was the third iteration of the BBL interventions run in conjunction with a group of five primary practice clinics in Canberra, Australia [113, 114]. BBL-GP was a three-armed RCT, the BBL group completed the online modules, and active diet and physical activity sessions. The dietary session was offered to participants who had a change in weight of ≥5kg in the past 6 months or scored in the low range in one or more dietary domains at baseline, it involved a one hour session on dietary advice. The physical activity session with the exercise physiologist was to design a personalised walking intervention based on baseline activity and any injuries or other limitations. As with previous interventions the dietitian and exercise physiologist sessions were one-on-one, individually tailored sessions. In addition to the BBL intervention arm there was a lifestyle modification program (LMP) comparison group and a control condition. The LMP was a series of 12 seminars on health issues that were run by the primary practices as a complimentary service to their clients. The active control condition were sent links to health websites, as in previous BBL studies. In addition to ANU-ADRI, the

cognitive measures of Trails A and B [119] and Symbol Digit Modality Test [120] was also included as outcomes [114]. The intervention demonstrated efficacy through a group x timepoint interaction with the BBL-GP group having significantly lower ANU-ADRI scores than the control group at the 18, 36 and 62 week follow-ups. There were no differences in cognition between any groups.

### 1.5.1 Modifications for Body, Brain, Life for Cognitive Decline

The present study, Body, Brain, Life for Cognitive Decline (BBL-CD) [115, 116] includes several important differences from previous BBL studies.

***Primary vs Secondary Prevention Focus***

Whereas all previous BBL studies have had a primary prevention focus, BBL-CD is the first BBL with a secondary prevention focus, recruiting participants with SCD and MCI. As all participants were experiencing some degree of cognitive decline the focus of the intervention was narrowed to three domains of lifestyle: Mediterranean Diet, Physical Activity and Cognitive Engagement. For the educational modules, the number was reduced to four modules and their content simplified. The first two modules from previous BBL studies were combined into a single module covering dementia literacy and lifestyle risk factors, with a module on each of the three lifestyle domains focusing on their importance to dementia risk and evidence for their effectiveness in healthy aging. All the images in the educational modules which included people under 65 years, were replaced with images of people over the age of 65 years, so that participants weren't unconsciously discouraged while completing the modules.

***Active Components***

Rather than using the educational modules solely for the intervention group as in previous BBLs, these were used for both groups, with the intervention group receiving additional lifestyle support. This additional support was through active components, which were adapted from previous BBLs: For the diet rather than focusing on healthy eating, the Mediterranean diet was chosen with a dietitian having an initial hour long, one-on-one session, followed by two, 30 minute follow-up sessions during the course of the intervention to maximise adherence to the diet and assist with overcoming any barriers; The physical

activity session, rather than a walking intervention, participants were aiming to increase physical activity to 150 minutes of moderate intensity activity per week that they enjoy (e.g. cycling, walking, free weights), ideally this would include cardiovascular, resistance and balance exercises. Participants had an initial one hour appointment with an exercise physiologist to create a workout plan based on types of exercise enjoyed and current level of physical activity, whilst being mindful of any injuries or other limitations, this was followed up with two, 30 minute sessions to modify the workout plan, as needed; the third active component for cognitive engagement was two hours of weekly brain training on the Brain HQ platform [121], comprising exercises of executive function and memory.

***Cognition as a Primary Outcome Measure***

Lastly, as all participants were experiencing cognitive decline, more emphasis was placed on this outcome than in previous BBLs. The battery used was the ADAS-Cog Plus [122] which includes the Standard ADAS-Cog 11[123], supplemented with additional measures more sensitive to early stage deficits: Trails B[119], Symbol Digit Modalities Test [120], Pfeffer Functional Activities Questionnaire[124], and Verbal Fluency for Vegetables[125].

In summary BBL-CD adapts a previously successful primary risk reduction intervention to a group over the age of 65 years experiencing SCD and MCI. This thesis by publication will give an overview of the study, its main outcomes with relevance to the current literature and potential future directions in this area of research. It includes four papers; at the time of submission, two of these papers were published and two were under review. These papers are:

1. The study protocol: This paper gives a thorough overview of the study, prior studies that led to BBL-CD and the rationale for adapting to a secondary prevention intervention. It was published in 2018 in *Clinical Interventions in Aging* [115].
2. The primary outcomes: This paper details the successful results achieved in the primary outcome measures of lifestyle risk for AD and cognition. A secondary analysis separated lifestyle risk into risk factors and protective factors and global cognition into its five constituent measures. Finally, an intention

to treat (ITT) analysis was conducted to account for missing data. The primary outcomes paper was published in the *Journal of the American Geriatric Society* in 2020 [116].

3. The feasibility of BBL-CD: In addition to evaluating the efficacy of the two primary outcomes, the third objective of the BBL-CD trial was to examine the feasibility of the project. This was assessed using the Bowen Feasibility Framework by evaluating the acceptability, implementation, and efficacy of changing lifestyle behaviours. At the time of thesis submission this paper is not yet published but is under review by *The Gerontologist*.

4. Health-related quality of life of BBL-CD: A secondary outcome of the study was health-related quality of life (HRQoL) to look at the broader impacts of the study. At the time of thesis submission this paper is not yet published but is under review by *International Journal of Geriatric Psychiatry*.

Following these four papers, a conclusion chapter will summarise and synthesis the main findings and end with some future directions for research in this area.

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# Chapter 2

## 2.1 Body, Brain, Life for Cognitive Decline (BBL-CD): Protocol for a multidomain dementia risk reduction randomised controlled trial for subjective cognitive decline

This chapter consists of a protocol paper published in Clinical Interventions in Aging. The protocol discusses the rationale, methodology and the strengths and limitations of the trial. The paper also details how BBL-CD draws on the interventions of previously successful trials and combines these into a multidomain trial and applies this to a group experiencing cognitive decline. This combination of Mediterranean diet, physical activity, cognitive engagement has not been trialled in this participant group previously. The protocol paper concludes with the role that secondary prevention could play more broadly in combating the rising numbers of people with dementia, but first interventions such as BBL-CD need to demonstrate efficacy and feasibility.

### 2.1.1 Publication:

McMaster, M., Kim S., Clare, L., Torres, S. J., D'Este, C., Anstey, K. J. (2018). Body, Brain, Life for Cognitive Decline (BBL-CD): Protocol for a multidomain dementia risk reduction randomised controlled trial for subjective cognitive decline. *Clinical Interventions in Aging*, *13*, 2397-2406. doi:10.2147/CIA.S182046

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STUDY PROTOCOL

# Body, Brain, Life for Cognitive Decline (BBL-CD): protocol for a multidomain dementia risk reduction randomized controlled trial for subjective cognitive decline and mild cognitive impairment

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**Background:** With no cure for dementia and the number of people living with the condition predicted to rapidly rise, there is an urgent need for dementia risk reduction and prevention interventions. Modifiable lifestyle risk factors have been identified as playing a major role in the development of dementia; hence, interventions addressing these risk factors represent a significant opportunity to reduce the number of people developing dementia. Relatively few interventions have been trialed in older participants with cognitive decline (secondary prevention).

**Objectives:** This study evaluates the efficacy and feasibility of a multidomain lifestyle risk reduction intervention for people with subjective cognitive decline (SCD) and mild cognitive impairment (MCI).

**Methods:** This study is an 8-week, two-arm, single-blind, randomized controlled trial (RCT) of a lifestyle modification program to reduce dementia risk. The active control group receives the following four online educational modules: dementia literacy and lifestyle risk, Mediterranean diet (MeDi), cognitive engagement and physical activity. The intervention group also completes the same educational modules but receives additional practical components including sessions with a dietitian, online brain training and sessions with an exercise physiologist to assist with lifestyle modification.

**Results:** Primary outcome measures are cognition (The Alzheimer's Disease Assessment Scale-Cognitive-Plus [ADAS-Cog-Plus]) and a composite lifestyle risk factor score for Alzheimer's disease (Australian National University – Alzheimer's Disease Risk Index [ANU-ADRI]). Secondary outcome measures are motivation to change lifestyle (Motivation to Change Lifestyle and Health Behaviour for Dementia Risk Reduction [MCLHB-DRR]) and health-related quality of life (36-item Short Form Health Survey [SF-36]). Feasibility will be determined through adherence to diet (Mediterranean Diet Adherence Screener [MEDAS] and Australian Recommended Food Score [ARFS]), cognitive engagement (BrainHQ-derived statistics) and physical activity interventions (physical activity calendars). Outcomes are measured at baseline, immediately post-intervention and at 3- and 6-month follow-up by researchers blind to group allocation.

**Discussion:** If successful and feasible, secondary prevention lifestyle interventions could provide a targeted, cost-effective way to reduce the number of people with cognitive decline going on to develop Alzheimer's disease (AD) and other dementias.

**Keywords:** dementia prevention, dementia risk reduction, secondary prevention, Alzheimer's disease, subjective cognitive decline, mild cognitive impairment, multidomain lifestyle intervention

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## Introduction

The number of people with dementia is projected to rise to almost 75 million worldwide by 2030, and in the absence of a cure, there is an urgent need for strategies to reduce the number of people developing dementia.[1] It has been estimated that up to half of all Alzheimer's disease (AD) cases worldwide may be attributed to seven modifiable risk factors, the majority of which reflect cardiovascular risks such as physical inactivity, hypertension, obesity, and diabetes.[2]

Primary prevention of dementia aims to reduce risk factors by focusing on improving the lifestyle of middle-aged people prior to or in the very earliest stages of the neuropathological changes which characterize AD and other types of dementia.[3] An alternative strategy is secondary prevention, which aims to minimize any further damage or slow progression once symptoms of a disease begin to emerge. In the case of dementia, it is thought that the very earliest symptoms of disease are characterized by subjective cognitive decline (SCD) and later by mild cognitive impairment (MCI).[3] SCD is a condition in which people report cognitive deficits in day-to-day life, but these are not detectable with cognitive testing.[4] The cognitive deficits of people with MCI are detectable with cognitive testing, but do not reach the threshold to meet the criteria for dementia.[5] Both SCD and MCI are associated with increased risk of progressing to dementia,[5,6] and the earliest stages of brain pathology found in dementia are also present in these conditions.[7–10]

Although dementia is not considered to be a reversible condition, there are some indications that in these prodromal stages the brain may still retain sufficient neuroplasticity that the trajectory of the disease may be modifiable. For instance, in individuals with MCI, conversion rates to AD are 7% at 1 year, 24% at 3 years and 59% at 6 years.[11,12] Annually, approximately 25% of those with MCI revert back to normal cognitive status.[13] There are differing explanations for this pattern of changes in cognitive status such as differing definitions for MCI, differences in testing procedures and test and retest effects that do not adequately represent these participants' true level of cognitive function. One explanation that cannot be discounted is that these low annual conversion rates and a high percentage of people reverting back to cognitively normal status suggest that this period may represent a "window of opportunity" for interventions to modify the disease course.

Three factors that have been identified by systematic reviews as having the potential to decrease lifestyle risk of dementia are diet, cognitive engagement, and physical activity.[14,15]

One dietary pattern that has shown promise in recent research is the Mediterranean diet (MeDi). The MeDi is a dietary pattern which is predominantly plant-based, with a high intake of vegetables, fruits, nuts and legumes, moderately high intake of fish, low intake of red meat, and includes extra virgin olive oil as the main source of fat.[16] The MeDi has been shown to decrease dementia risk indirectly through altering cardiovascular risk factors,[17] as well as directly through lower levels of neuropathology such as amyloid plaques,[18] brain atrophy,[19] and structural connectivity.[20]

One of the most compelling studies in the area of cognitive engagement is the Advanced Cognitive Training in Vital Elderly (ACTIVE) trial.[21] The ACTIVE trial was a computerized cognitive training randomized controlled trial (RCT), comparing memory, reasoning, and speed of processing training conditions to a control condition. The speed of processing training group showed higher cognition and lower incident dementia at 10 years post-intervention, relative to the control group.[21,22] Although the ACTIVE trial was conducted with a cognitively normal sample over the age of 65 years, these effects have yet to be replicated in a group with cognitive decline, such as SCD or MCI.

Similar to diet, physical activity is both indirectly and directly related to dementia risk. Physical activity has repeatedly been shown to be protective against cardiovascular risk factors for dementia[23] and to reduce AD risk directly through a host of neuronal mechanisms, including downregulating pathways that lead to amyloid and tau production.[24] In a review of modifiable risk factors, physical inactivity has the highest attributable risk of the seven dementia risk factors identified (18% of all dementia cases in Australia).[25] Although the bulk of evidence for these factors comes from primary prevention studies (eg, with middle-aged adults), systematic reviews have highlighted the need to explore such approaches as secondary prevention interventions in people experiencing the earliest stages of cognitive decline.[26–28]

Some early studies in the area of secondary prevention have shown encouraging results. A 12-week, single-arm intervention for community-dwelling people with MCI (n=127, average age 70.7 years) involving MeDi, omega-3 supplements, physical activity, cognitive stimulation, neurofeedback, and meditation achieved positive results.[29] At the final follow-up, 84% of the participants showed statistically significant improvements in cognition and 53% of a subsample (n=17) that underwent neuroimaging showed hippocampal growth. Limitations of this study were that there was no control group and participants were not randomized, making it difficult to determine whether the effects were due to the intervention, and the low number of participants in the neuroimaging subsample means that these changes may not be representative of the whole sample. The study concluded

that further multidomain RCTs should be conducted in participants experiencing cognitive decline. One multidomain RCT was conducted in community-dwelling frail and prefrail participants over the age of 65 years, which compared interventions for physical activity, cognitive activity, nutrition, and a combination of the three interventions against a control group.[30] Over 12 months, improvements in different domains of cognition were seen with all groups except the physical activity intervention group, in comparison to declines seen in the control group. As one of the limitations, the study noted that as physical frailty was the primary target of the intervention, only 7% of the sample had a Mini Mental State Examination (MMSE) score less than 26 and the study may have been underpowered to detect all cognitive effects. The study recommended that further multidomain RCTs should be trialed in participants with greater levels of cognitive impairment as greater benefits may be possible with this population.

Although preliminary studies on secondary prevention do report positive outcomes, there is a need for more rigorous, multidomain studies such as RCTs, designed specifically to look at relevant outcomes such as cognition and lifestyle risk factors.

## Objectives

The Body, Brain, Life (BBL) interventions are a suite of multidomain, primary dementia risk reduction interventions.[31–33] The original intervention included educational modules only and more recently face-to-face physical activity and dietary components have been added.[32] The present study, Body, Brain, Life for Cognitive Decline (BBL-CD), draws from the earlier interventions but introduces some new components and adaptations so that it is suitable for participants with cognitive impairment. This study evaluates the feasibility and efficacy of adapting this program for a cognitively impaired population.

The specific aims of the study are to

1. evaluate the efficacy of BBL-CD in the prevention of further cognitive decline;
2. evaluate the efficacy of BBL-CD to reduce overall lifestyle risk of AD and other dementias and
3. evaluate the feasibility of BBL-CD through tracking intervention adherence.

## Methods

### Study design

The study is an 8-week, two-arm, parallel group RCT. The intervention focuses on the following three domains of lifestyle: diet, cognitive engagement, and physical activity. The active control group will undertake four online educational modules and the intervention group will undertake the same online modules complemented by practical and face-to-face sessions with interventionists. The study is expected to complete data collection in late 2018. This study is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12617000792325) and ethical approval for conducting this study was granted by the Australian National University Human Research Ethics Committee (Protocol: 2016/360). The study has been planned and conducted in accordance with the revised Declaration of Helsinki,[34] and all participants provided written informed consent to participate in this study. This protocol was written to conform with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.[35]

### Participants

Participants are community-dwelling individuals with MCI or SCD recruited through advertisements in community newsletters, local print media, and radio. The inclusion criteria are as follows: living in the Australian Capital Territory or Queanbeyan, New South Wales; aged 65 years or over; owning a computer with Internet access; having sufficient English language skills; being prepared to make lifestyle changes to improve health; and having a medical diagnosis of MCI or meeting the Jessen criteria[4] for SCD (clinically normal on objective assessment, self/informant-reported cognitive decline, decline not better accounted for by major medical and neurological or psychiatric diagnosis). The criteria for MCI are met if the participant has previously received a diagnosis of MCI from a suitably qualified medical professional such as a neuropsychologist or geriatrician (no exact criteria for MCI diagnosis are specified). The criteria for SCD are met if the participant expresses the view that they have experienced a decline in any domains of cognitive function in the past 5 years.

Exclusion criteria are as follows: currently participating in any lifestyle change interventions; have a diagnosis of AD or another form of dementia and have major psychiatric, neurological, or physical problems which would prevent them from taking part in a lifestyle change program.

All inclusion and exclusion criteria are assessed via an initial phone call to the research team when potential participants express interest in participating in the study. Participants meeting the criteria are sent an information sheet about the study and a consent form to sign and return.

If at any of the testing points cognitive testing is indicative of potential AD (The Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog] >12), participants are

referred to their general practitioner (GP) for cognitive testing. If found to have probable AD, the participant is withdrawn and no further data are collected; these participants are still allowed to continue participating in the practical components of the intervention, if they choose to (ie, participants will not be penalized or disadvantaged by a dementia diagnosis).

### Randomization and stratification

After completing baseline data collection, participants are randomized in a 1:1 ratio, within strata defined by gender, baseline ADAS-Cog-Plus (above or below the median value of 7.0) and baseline ANU-ADRI (above or below the median value of 10.0), to intervention or control groups in permuted blocks of eight. The randomization sequence is generated from www.sealedenvelope.com by an independent researcher (RB).

## Interventions

### Active control

The active control group undertakes an 8-week, four-module, online educational course on dementia risk reduction and effective goal setting. The four modules are as follows:

1. Dementia literacy and lifestyle risk for AD (week 1): this module describes SCD, MCI, AD, and dementia, modifiable and non-modifiable risk factors and effective goal setting and rewards.
2. Diet (week 2): the diet module explains the importance of a healthy diet in maintaining a healthy brain. It explains the general principles of the MeDi and the scientific evidence that supports MeDi as a diet associated with lower levels of chronic disease and dementia.
3. Cognitive engagement (week 4): this module reviews the evidence for a cognitively engaged lifestyle being related to lower levels of dementia, different forms of cognitive engagement and how to increase cognitive engagement in everyday life.
4. Physical activity (week 6): this module discusses the evidence for an adequate level of physical activity in risk reduction of chronic disease and dementia. It also covers the importance of engaging in a combination of aerobic, strength, balance, and flexibility exercises and the Australian Department of Health's Physical Activity and Sedentary Behaviour Guidelines for people ≥65 years.[36]

The modules are interactive, including some questions to check participants' understanding of the content, and give the opportunity to provide information about aspects of their lifestyle and ways in which they might be able to modify their behavior. Each module provides examples of how to set specific, measurable, achievable, relevant, and timed (SMART) goals for the particular domain. Each module takes approximately 1–2 hours to complete and can be completed across multiple sittings, if desired.

### Intervention

The intervention group receives the same educational modules as the active control group, but each module is complemented by practical components to assist with the implementation of changes into the lifestyle in a sustainable way. The practical components are as follows:

1. Diet: to reinforce the content of the diet module, the participants have three face-to-face sessions with a dietitian, including an initial 1-hour session (week 3) and two further 30-minute follow-up sessions (weeks 10 and 21). In these sessions, the dietitian reviews the participant's previous diet assessment results, discusses any barriers to adherence they are experiencing and ways in which the participant could achieve greater adherence to the MeDi. The MeDi intervention is adapted from the study by Estruch et al.[37] Recommendations are as follows: 1) ≥5 servings of vegetables/day, including two servings of raw vegetables; 2) ≥3 servings of fruit/day; 3) ≥3 serves of fish or seafood/week, including one serving of fatty fish; 4) ≥3 servings of legumes/week; 5) ≥3 servings of nuts/week; 6) preferentially consume white meat, instead of red meat; 7) <1 serving of red meat/day; 8) using olive oil as the main oil for cooking and dressing; 9) ≥4 servings of olive oil/day; 10) <1 serving of butter, margarine, or cream/day; 11) ≥7 servings of wine/week; 12) ≥2 servings of sofrito sauce/week (tomato, garlic, onion, and olive oil); 13) <1 serving of sweet or carbonated beverages/day; and 14) <3 servings of commercial sweets or pastries/week.
2. Cognitive engagement: to enable the participants to live a more cognitively engaged lifestyle, they are provided with a BrainHQ[38] account (week 5) and asked to participate in two executive functions and two memory tasks for 30 minutes each (total 2 hours) per week. The four tasks are as follows: Double Decision (divided and selective attention, speed of processing, dual task, and useful field of view); Freeze Frame (visual phasic and tonic attention, inhibitory control and motor response inhibition); Syllable Stacks (auditory working memory); and Memory Grid (auditory spatial memory). The exercises are psychophysically adaptive and the parameters within each stimulus set are adjusted for an individual participant to maintain ~80% criterion accuracy by increasing or

decreasing task difficulty systematically with correct/incorrect responses.

3. Physical activity: participants attend an initial 45-minute session (week 7) and two 30-minute follow-up sessions with an exercise physiologist (weeks 10 and 21). Based on the participant's medical conditions, current level of exercise and physical activity preferences, a weekly exercise regime is developed with the eventual aim to increase physical activity level to 150 minutes of moderate exercise per week. If participants are already undertaking this level of exercise or greater, the goal is maintenance and combining different forms of exercises (eg, aerobic, strength, balance, and flexibility exercises). In the follow-up sessions, the exercise physiologist discusses progress, any barriers that the participant is experiencing and any modifications to the exercise regime, and (if suitable) increases toward 150 minutes total exercise duration. To be involved in these sessions, participants must have a medical clearance form signed by a GP, detailing any medical conditions or medications which may impact the participant's ability to undertake exercise and approving the participant to undertake moderate physical exercise.

A week-by-week summary of the intervention is shown in Figure 1.

## Modifications made to previous BBL interventions

The BBL intervention has been modified each time it has been conducted, based on participant feedback on the previous version.[31–33] Further modifications were made for this study to increase the suitability for an older population experiencing cognitive decline. The overall size and amount of information that participants are required to learn and remember in the online modules were decreased based on feedback from middle-aged participants that there was too much information to read and remember. Previous versions of BBL contained seven or eight informational modules on different dementia risk factors, followed by 4 weeks of revision. To enable a population experiencing cognitive deficits to effectively learn and modify their behavior without being overwhelmed, the content was reduced to three risk factors that could be most easily targeted to bring about effective risk reductions. Previous BBL studies involved one module on a new risk factor per week for the first 8 weeks. In BBL-CD, after a module on a risk factor is introduced, a week without a module is allotted for participants to implement these changes into their lifestyle. In BBL-CD, in week 8 at the conclusion of all the modules the participants have a week for revision and are sent a one-page summary of each module to convey the key messages of the intervention. Each module summary also provides an example of a SMART goal for that specific risk factor, so that participants can continue to modify their behavior beyond the initial 8-week intervention period. Specific modifications to the modules included the following: the diet module and practical intervention were modified from the previous BBL focusing on a healthy balanced diet to the MeDi in consultation with study dietitians; the brain training is a novel inclusion due to a change in the participant group to one experiencing cognitive decline; and the physical activity program is now focused on moderate physical activity, rather than a structured walking program based on feedback from participants who felt that the walking program was too restrictive. These modified modules and practical components were piloted with a small group of individuals (n=7) who volunteered to be participants but failed to meet a small number of the selection criteria (eg, less than 65 years of age, medical condition preventing dietary modification, etc). Feedback on each module and practical component was collected, and although overall feedback was positive, some modifications were implemented, eg, module wording changes and materials used during practical components.

Due to the high attrition rate in longitudinal intervention studies, several strategies to decrease attrition are being implemented. To make participants feel included and valued in the scientific process, newsletters are periodically sent about the progress of the study; participants are informed about any publications/conference presentations from the research; and participants are thanked after attending data collection and intervention sessions. The intervention group is termed the "Lifestyle Intervention Group" and the control group is termed the "Online Education Group", such that participants in the control group do not feel they are receiving an intervention that is unlikely to have any effect.

## Outcome measures

### Primary outcome measures

#### Cognition

Cognition is measured by the ADAS-Cog-Plus,[39] which contains the standard ADAS-Cog items (word recall, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition, language production, language comprehension, and word finding difficulty)[40] with additional measures for executive function (trail making task,[41] symbol digit modalities test,[42] category fluency task,)[43] and instrumental activities of daily living (Pfeffer Functional Activities Questionnaire items

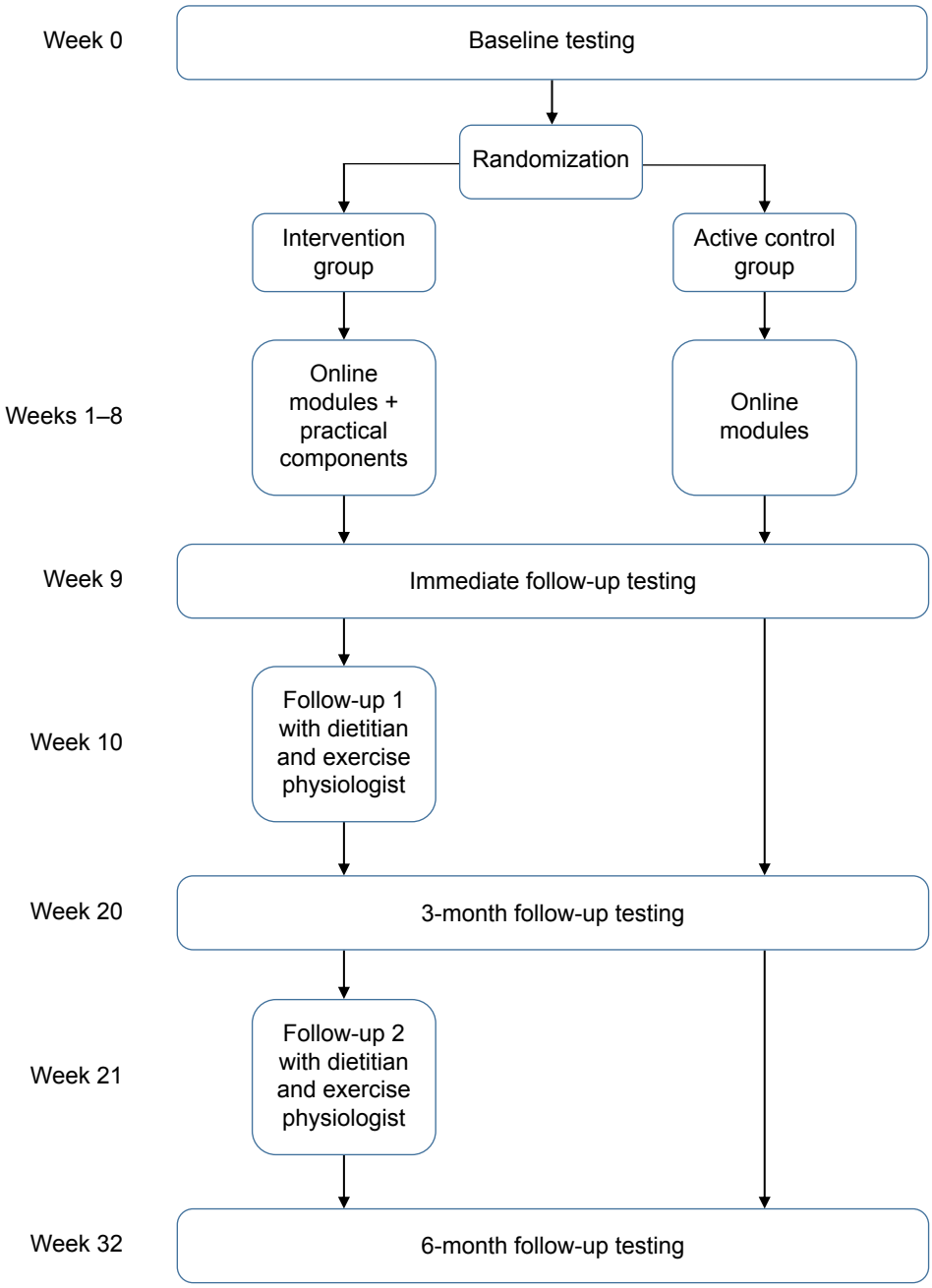


**Figure 1** Timing of intervention components and testing periods.

1, 2, 4, 7 and 9).[44] The inclusion of executive function and instrumental activities of daily living items is designed to maximize sensitivity to early-stage deficits as seen in SCD and MCI. The ADAS-Cog is scored from 0 to 70, with higher scores indicating greater levels of cognitive impairment. ADAS-Cog has good reliability (Cronbach's $\alpha$=0.83, test–retest=0.93)[45] and has been shown to discriminate between individuals with normal cognition, MCI and AD.[40] The inclusion of a full battery of cognitive measures is a new inclusion for the BBL studies, given a population experiencing cognitive decline.

### Lifestyle risk of AD

Lifestyle risk factors for AD are measured by the Australian National University – Alzheimer's Disease Risk Index (ANU-ADRI).[46] The ANU-ADRI covers 11 AD risk factors (eg, age, education and smoking) and four lifestyle factors that are protective against AD (eg, physical activity, fish intake, and cognitive activity). The ANU-ADRI applies an AD risk score for the level of each risk or protective factor, based on ORs derived from systematic reviews.[46] The ANU-ADRI yields a score ranging from −14 (highly protective lifestyle) to 73 (high-risk lifestyle). The ANU-ADRI has

been validated against three large, international longitudinal cohort studies and was shown to be a valid predictor of development of AD.[47]

### Secondary outcome measures

#### Motivation

Motivation to change lifestyle is being assessed by the Motivation to Change Lifestyle and Health Behaviour for Dementia Risk Reduction (MCLHB-DRR).[48] This is a 27-item scale, which was developed based on the principles of the Health Belief Model. It was developed and validated specifically to look at motivation to change lifestyle in health and dementia lifestyle interventions.

#### Health-related quality of life

The 36-item Short Form Health Survey (SF-36)[49] is being used to assess general health-related quality of life. The SF-36 has 36-items which form an eight-scale profile of health-related quality of life which can be summarized into a physical component summary (PCS) and mental component summary (MCS). An overall score of 0–100 can be calculated from the mean values of the eight scales. Higher scores indicate better health-related quality of life. The SF-36 is commonly used in health research, especially in the evaluation of interventions, as it is easily converted to quality of life years (QALYs), which gives a quantitative measure of the benefit of an intervention and can be used in a cost–benefit analysis.[50]

#### Anthropometric measures

Height, weight, waist, and hip circumference are collected. Height to the nearest millimeter is measured using a stadiometer (Seca, Hamburg, Germany), and weight to the nearest 0.1 kg is measured with digital scales (Propert, Sydney, NSW, Australia).[51] Body mass index is calculated as weight (kg) divided by height squared ($m^2$). Waist circumference is measured to the nearest centimeter midway between the lowest rib margin and the iliac crest.[51] Hip circumference is measured to the nearest centimeter at the point yielding the maximum circumference over the buttocks.[51]

### Feasibility and adherence measures

The feasibility of the lifestyle intervention for this participant group is measured through adherence to diet, cognitive engagement, and physical activity. Additional qualitative interviews with a subsample of participants will be undertaken at the conclusion of the study to investigate other factors affecting feasibility and adherence to interventions such as this.

#### Dietary assessment

Dietary adherence to the MeDi is assessed using a validated 14-point Mediterranean Diet Adherence Screener (MEDAS).[52] A score of 0 or 1 is assigned to each item, with a maximum score of 14 indicating greatest adherence to the MeDi. The MEDAS has good convergent validity with a 137-item MeDi food frequency questionnaire and shows significant associations with health indices such as fasting glucose, total:high-density lipoprotein (HDL) cholesterol ratio, triglycerides and coronary artery disease risk.[52]

Dietary quality is assessed with a food-based diet quality index, the Australian Recommended Food Score (ARFS).[53] The ARFS is aligned with Australian Dietary Guidelines[54] and the Australian Guide to Healthy Eating[55] recommendations. The ARFS total ranges from 0 to 73 and includes eight subscales: vegetables (0–21), fruit (0–12), protein (0–7), vegetarian protein alternatives (0–6), grains (0–13), dairy (0–11), water (0–1), and sauces and condiments (0–2). Higher scores indicate greater compliance with the Australian Dietary Guidelines and therefore better diet quality. The ARFS has demonstrated good validity and reproducibility.[53]

#### Cognitive engagement

Duration of engagement with cognitive training and levels completed are tracked automatically via the BrainHQ website for the intervention group.

#### Physical activity

Participants track their daily physical activity on a paper-based physical activity calendar. The activity, intensity (on a 20-point scale),[56] and duration of the physical activity are recorded. Participants are asked to start completing this measure from the day of baseline testing onward and return these to the research team by electronic scan and email or by post at the end of every month.

## Data collection

There are four primary data collection points in the study as follows: baseline (week 0); immediate post-intervention testing (week 9); 3-month testing (week 20); and 6-month testing (week 32). Research staff collecting data are blind to group allocation. Not all outcome measures are administered at each time point, and a summary of this is presented in Table 1.

## Statistical methods

### Sample size calculation

The required sample size was determined to enable detection of a difference between groups at 6 months of 0.70 SDs for the primary outcomes. This equates to approximately

**Table 1** Summary of outcomes measured at data collection points

| | Baseline (week 0) | Immediate post-intervention (week 9) | 3-month follow-up (week 20) | 6-month follow-up (week 32) |
|---|---|---|---|---|
| **Primary outcomes** | | | | |
| Cognition | ✓ | | ✓ | ✓ |
| Lifestyle risk | ✓ | ✓ | ✓ | ✓ |
| **Secondary outcomes** | | | | |
| Motivation | ✓ | ✓ | ✓ | ✓ |
| Health | ✓ | ✓ | ✓ | ✓ |
| Anthropometry | ✓ | | ✓ | ✓ |
| **Feasibility outcomes** | | | | |
| Mediterranean diet | ✓ | ✓ | ✓ | ✓ |
| Dietary quality | ✓ | | ✓ | ✓ |
| Cognitive engagement | Collected daily from week 5 onward for the intervention group | | | |
| Physical activity | Collected daily from baseline (week 0) onward | | | |

**Note:** Data collection at baseline, 3-month and 6-month follow-up is conducted face-to-face, and immediate post-intervention assessments are online questionnaires.

4.2 units for the ADAS-Cog-Plus and 4.0 units on the ANU-ADRI, both of which are clinically significant magnitudes. This requires a minimum of 72 participants (36 participants per arm) at the final follow-up period. Accounting for a potential attrition rate of 10% over four testing periods (60% remaining) yields a target sample size at baseline of 60 participants per group (120 in total).

### Planned analyses

Linear mixed modeling to compare outcomes between intervention and control groups at each follow-up time, adjusted for baseline values of the outcome, will be conducted using complete cases as the primary analysis and full intention-to-treat analysis using multiple imputation to account for missing data as sensitivity analysis.

## Discussion

There is a clear need for dementia prevention and risk reduction studies, given the anticipated rise in the number of people with dementia in the coming years.[1] Several authors have argued that secondary prevention (older populations showing some symptoms of cognitive decline) is an avenue that warrants further exploration.[26–28] Drawing on epidemiological findings and previous trials and applying this to an older, high-risk group is the strategy that has been adopted for this study. Secondary prevention, if feasible and effective, provides a targeted approach to reducing the number of people developing dementia. Such intervention programs could be implemented through primary care providers who identify individuals in the high-risk SCD/MCI groups. Interventions could be run as collaborations between medical and allied health professionals and could be tailored to individuals' specific needs based on their risk factor profile. Targeting a small number of people at very high risk of developing dementia would likely prove to be more cost-effective than targeting a larger number of people at lower risk.

The first step to showing the value of secondary prevention is to conduct randomized controlled studies to demonstrate feasibility and positive effects, such as reductions in risk factors or improvements in cognition in the SCD/MCI group. As a smaller, proof of concept study this research focuses on three of the most important risk factors: diet, cognitive engagement and physical exercise. This study aims to evaluate the efficacy of BBL-CD to prevent further cognitive decline and dementia risk profile and to evaluate the feasibility of the intervention for this participant group. These findings would provide proof of concept for a larger, longer secondary prevention trial with this group in the future.

### Strengths and limitations

A major strength of this project is that all the components of the intervention have previously been used in separate successful interventions,[21,31,32,37] but not with a group experiencing cognitive decline. The efficacy and feasibility of dementia risk reduction interventions in this group have been identified as a major knowledge gap by systematic reviews,[26–28] and the use of multidomain interventions to combat multiple risk factors simultaneously is considered to be the "gold standard" for risk reduction and prevention interventions.[28]

The greatest limitation of this research is the short follow-up time. Systematic reviews of RCTs in dementia

risk reduction interventions recommend follow-up times of a year or longer.[27] Due to the paucity of research in the area of secondary prevention, it is important to first establish the feasibility of an adaptation of the BBL intervention to the SCD/MCI group and test the hypotheses that these individuals do appear to retain sufficient neuroplasticity to warrant a larger and longer trial.

## Data sharing statement

Deidentified individual data sets are available indefinitely upon request to the authors following publication of the results of the study.

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## Disclosure

The authors report no conflicts of interest in this work.

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# Chapter 3

# 3.1 Lifestyle risk factors and cognitive outcomes from the multidomain dementia risk reduction randomised controlled trial, Body Brain Life for Cognitive Decline (BBL-CD)

This chapter consists of an article on the primary outcomes of BBL-CD published in the *Journal of the American Geriatrics Society*. This chapter covers research objective 1, to examine the efficacy of BBL-CD to decrease overall lifestyle risk, and objective 2, to examine the efficacy of the trial to improve cognition in participants experiencing cognitive decline. The primary analyses of the paper demonstrated that the BBL-CD intervention decreased lifestyle risk and increased global cognition, which fulfils objectives 1 and 2. A secondary analysis explored the outcomes further, showing that the lifestyle outcomes were related to an increase in protective lifestyle factors and global cognitive outcomes were likely driven by a small, consistent effect across the cognitive measures. An ITT analysis which imputed missing data showed that all findings were robust and were not the results of selective attrition of participants.

The supplementary materials show all lifestyle and cognitive outcomes at all timepoints and an analysis showing no difference between participants who withdrew and those who remained in the study.

## 3.1.1. Publication:

McMaster, M., Kim S., Clare, L., Torres, S. J., Cherbuin, N., D'Este, C., & Anstey, K. J. (2020). Lifestyle risk factors and cognitive outcomes from the multidomain dementia risk reduction randomised controlled trial, Body Brain Life for Cognitive Decline (BBL-CD). *Journal of the American Geriatric Society*, *68*, 11, 2629-2637. doi:10.1111/jgs.16762

# Lifestyle Risk Factors and Cognitive Outcomes from the Multidomain Dementia Risk Reduction Randomized Controlled Trial, Body Brain Life for Cognitive Decline (BBL-CD)

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**BACKGROUND/OBJECTIVES:** To evaluate the efficacy of a multidomain intervention to reduce lifestyle risk factors for Alzheimer's disease (AD) and improve cognition in individuals with subjective cognitive decline (SCD) or mild cognitive impairment (MCI).

**DESIGN:** The study was an 8-week two-arm single-blind proof-of-concept randomized controlled trial.

**SETTING:** Community-dwelling individuals living in Canberra, Australia, and surrounding areas.

**PARTICIPANTS:** Participants were 119 individuals (intervention n = 57; control n = 62) experiencing SCD or MCI.

**INTERVENTION:** The control condition involved four educational modules covering dementia and lifestyle risk factors, Mediterranean diet, physical activity, and cognitive engagement. Participants were instructed to implement this information into their own lifestyle. The intervention condition included the same educational modules and additional active components to assist with the implementation of this information into participants' lifestyles: dietitian sessions, an exercise physiologist session, and online brain training.

**MEASUREMENTS:** Lifestyle risk factors for AD were assessed using the Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI), and cognition was assessed using Alzheimer's Disease Assessment Scale-Cognitive subscale, Pfeffer Functional Activities Questionnaire, Symbol Digit Modalities Test (SDMT), Trail Making Test-B, and Category Fluency.

**RESULTS:** The primary analysis showed that the intervention group had a significantly lower ANU-ADRI score ($\chi^2$ = 10.84; $df$ = 3; $P$ = .013) and a significantly higher cognition score ($\chi^2$ = 7.28; $df$ = 2; $P$ = .026) than the control group. A secondary analysis demonstrated that the changes in lifestyle were driven by increases in protective lifestyle factors ($\chi^2$ = 12.02; $df$ = 3; $P$ = .007), rather than a reduction in risk factors ($\chi^2$ = 2.93; $df$ = 3; $P$ = .403), and cognitive changes were only apparent for the SDMT ($\chi^2$ = 6.46; $df$ = 2; $P$ = .040). Results were robust to intention-to-treat analysis controlling for missing data.

**CONCLUSION:** Results support the hypothesis that improvements in lifestyle risk factors for dementia can lead to improvements in cognition over a short time frame with a population experiencing cognitive decline. Outcomes from this trial support the conduct of a larger and longer trial with this participant group. **J Am Geriatr Soc 68:2629-2637, 2020.**

**Keywords: dementia prevention; lifestyle risk reduction; subjective cognitive decline; mild cognitive impairment; nonpharmacological intervention**

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The number of people with dementia is expected to rise to 82 million by 2030 and to more than 152 million by 2050.[1] Research has shown that together lifestyle risk factors are responsible for between one-third and one-half of all Alzheimer's disease (AD) cases.[2,3] It is imperative that interventions to reduce risk are designed to limit the number of people developing dementia. This can be achieved



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through primary prevention, focusing on lowering the dementia risk for cognitively normal individuals, and secondary prevention aimed at high-risk individuals beginning to experience subjective cognitive decline (SCD) or mild cognitive impairment (MCI).[4] SCD and MCI are considered to be prodromes of dementia, and emerging evidence clearly demonstrates mild forms of neuropathology related to dementia in both conditions.[5]

Although some evidence is available from large lifestyle interventions for the primary prevention of dementia and AD,[6] systematic reviews have noted the need to further investigate secondary prevention.[7-9] A meta-analysis by Bhome et al.[10] specifically noted a lack of research evaluating lifestyle interventions in those with SCD, and previous randomized controlled trials (RCTs) in this population have been underpowered to detect the full spectrum of potential outcomes included.[8] To date, more research has been conducted on individuals with MCI than with SCD. A systematic review[11] of lifestyle-focused RCTs in the MCI population found that all multidomain interventions evaluated were associated with significant improvements in at least one cognitive domain, suggesting that these interventions were more promising than interventions focusing on single domains, such as physical activity or cognitive engagement alone. The review noted heterogeneity in the cognitive domains showing improvements and in intervention and assessment methods, and it recommended further well-designed and adequately powered RCTs.

### Objectives

This proof-of-concept study adapts elements of previously successful trials from other participant groups to the SCD and MCI groups.[12-16] It is hypothesized that given individualized support, people experiencing cognitive decline can make meaningful lifestyle changes, and in this prodromal stage of dementia the brain will still retain sufficient neuroplasticity to modify the trajectory of the disease. The aims of the work were to evaluate the efficacy of the Body Brain Life for Cognitive Decline (BBL-CD) study to reduce the overall lifestyle risk of AD and other dementias and to prevent further cognitive decline. Here we report on the primary outcomes of the BBL-CD study: lifestyle risk of AD and cognition.

## METHODS

### Design

The full protocol of the study was published.[15] The study was an 8-week two-arm single-blind RCT of a lifestyle modification program to reduce dementia risk for people experiencing cognitive decline. It was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement[17] and the CONSORT statement for nonpharmacological interventions.[18] The trial was registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12617000792325), and ethical clearance was provided by the ANU Human Research Ethic Committee (Protocol No. 2016/360). All participants gave written informed consent to take part.

### Participants

Participants were community-dwelling individuals from the Canberra region, Australia, aged older than 65; owning a computer with Internet access; having sufficient English skills; willing to make lifestyle changes to improve health; and having been diagnosed with MCI by a medical professional or reporting experiencing SCD. The Jessen criteria were used for SCD: clinically normal on objective assessment, self/informant-reported cognitive decline, and decline not better accounted for by a major medical, neurological, or psychiatric diagnosis.[15] Although potentially limiting in this age group, a computer with Internet access was essential for certain intervention components; greater than 50% of Australians aged 65 and older have access to the Internet, and this figure has been increasing in recent years.[19,20]

Exclusion criteria were any major neurological or psychiatric disorder, or other chronic condition that would prevent participation in a lifestyle behavior change program; and currently participating in any other lifestyle change interventions. No restrictions were placed on current levels of or adherence to Mediterranean diet, physical activity, or cognitive engagement.

### Interventions

The active control group completed four online informational modules to reduce dementia risk. The modules covered dementia literacy and lifestyle risk, Mediterranean diet, physical activity, and cognitive engagement. Following each module, participants were given a week with no education to allow them to implement the information into their own lifestyle.

The intervention group completed the same online educational modules, but in the weeks between undertaking the modules, the intervention group took part in practical activities including meeting with a dietitian and exercise physiologist and completing brain training. These practical components were designed to assist the participants to implement the information from the modules more effectively into their lifestyle. Participants had an initial 1-hour appointment with a dietitian (week 3) and two follow-up 30-minute appointments (weeks 10 and 21) to assist with adhering to a Mediterranean diet; an initial 1-hour appointment with an exercise physiologist (week 7) to formulate an exercise plan, and two follow-up 30-minute appointments (weeks 10 and 21) to modify as required; and 2 hours weekly of online brain training (beginning week 5) on the Brain HQ platform.[21] Further details of the intervention are provided in the published protocol.[15] However, there was one deviation from this protocol. The exercise physiologist was hospitalized on two occasions during the study, and no suitable replacement could be identified; therefore the two follow-up appointments were not conducted.

### Outcomes

#### *Lifestyle Risk of Alzheimer's Disease*

Lifestyle risk for AD was assessed using the Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI). The ANU-ADRI yields scores for 11 lifestyle risk

factors (age [moderated by sex], low educational attainment, body mass index, diabetes mellitus type II, depression, cholesterol, traumatic brain injuries, smoking status, low social engagement, and exposure to pesticides), four protective factors (alcohol intake, physical activity, cognitive engagement, and fish intake), or an overall score combining both factors.[22] For the ANU-ADRI, lower scores indicate lower lifestyle risk for all three measures. Participants completed the ANU-ADRI via computer at the research team's office at baseline (week 0), immediately following the intervention (week 9), at 3-month follow-up (week 20), and at 6-month follow-up (week 32).

The largest score component of the ANU-ADRI is age (0–41 points). To assess the effect of the intervention adequately, ANU-ADRI scores were calculated at all time points from the participants' age at baseline. This prevented any scores from increasing as a result of participants moving to a higher risk bracket of age, hence obscuring changes due to lifestyle alterations.

## Cognition

The cognitive outcomes for the study were the measures comprising the Alzheimer's Disease Assessment Scale-Cognitive Plus (ADAS-Cog Plus)[23]: the ADAS-Cog 11,[24] Pfeffer Functional Activities Questionnaire (PFAQ),[25] Trail Making Test-B (TMT-B),[26] Symbol Digit Modalities Test (SDMT),[27] and Category Fluency for vegetables.[28] The

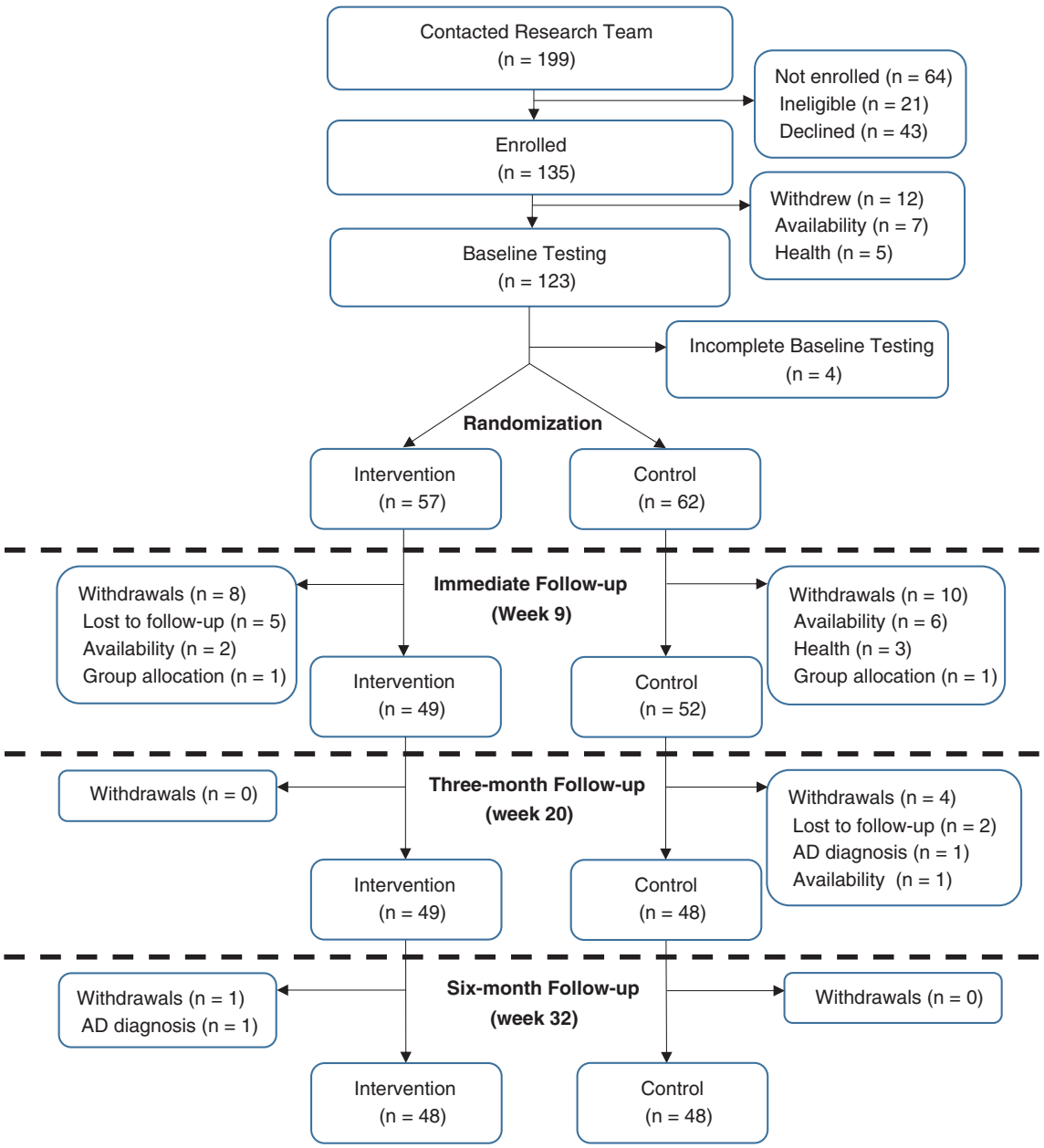


**Figure 1.** Participant flowchart for BBL-CD study. Lost to follow-up: These participants could not be contacted/did not respond. Availability: These participants formally withdrew due to other commitments. Group allocation: These participants formally withdrew due to the group they were randomized to. AD diagnosis: These participants were diagnosed with Alzheimer's disease. [Color figure can be viewed at wileyonlinelibrary.com]

**Table 1. Baseline Characteristics and Primary Outcome Measures of the Two Groups**

| | Intervention (n = 57) | Control (n = 62) |
|---|---|---|
| Age, y | 72.8 (5.3) | 73.3 (5.8) |
| Female (%) | 35 (61.4) | 38 (61.3) |
| Education, y | 12.4 (5.3) | 14.0 (5.9) |
| ANU-ADRI total, score range = −14 to 73 | 8.3 (10.8) | 10.3 (11.6) |
| Protective factors, score range = 0 to −14 | −9.1 (4.2) | −8.9 (4.5) |
| Risk factors, score range = 0 to 73 | 17.4 (9.0) | 19.2 (10.0) |
| Cognitive composite *z* score | .091 (.67) | .095 (.56) |
| ADAS-Cog 11, score range = 0 to 70 | 7.5 (3.6) | 7.0 (3.5) |
| PFAQ, score range = 0 to 15 | .8 (1.6) | .8 (1.5) |
| SDMT, score range = 0 to 110 | 42.1 (9.8) | 41.7 (9.2) |
| TMT-B, s | 97.3 (33.2) | 99.3 (41.7) |
| Category fluency, score range = 0 to ∞ | 14.7 (4.2) | 14.5 (4.4) |

*Note:* Cognitive composite *z* scores were created using baseline means and SDs for all participants, then averaging across these *z* scores to form a composite. Participants with missing data on one or more cognitive measures were not included in the *z* score average.

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ANU-ADRI, Australian National University-Alzheimer's Disease Risk Index; PFAQ, Pfeffer Functional Activities Scale; SDMT, Symbol Digit Modalities Test; TMT-B, Trail Making Task-B.

ADAS-Cog Plus measures were selected because they are sensitive to the deficits seen in early stages of cognitive decline.[23] All cognitive measures were assessed face to face at baseline (week 0), 3-month follow-up (week 20), and 6-month follow-up (week 32). Further details on the outcomes can be found in the protocol article.[15]

These cognitive measures were combined into a single composite score by conversion to *z* scores. These were calculated based on the baseline mean and standard deviation (SD) of each measure. The *z* scores were then averaged across the measures for each participant at each time point. For the ADAS-Cog, PFAQ, and TMT-B, lower scores indicate better cognitive function; for calculating the composite score, these were reversed so that increases indicated better cognitive function for all measures. This composite *z* score as well as the results from the individual cognitive measures are reported.

## Blinding

All testing was carried out by researchers who were blind to group allocation. Due to the nature of the intervention, blinding of the participants was not possible. Participants were asked not to discuss the intervention with any researchers; if they had any questions, they could discuss these with the project manager in private.

## Statistical Methods

At the final follow-up, a minimum sample size of 36 participants per arm was required to detect a difference between groups of .70 SDs in the primary outcome measures. Accounting for potential attrition of 10% per follow-up period gave a baseline target sample size of 120 participants. All participants were randomized to either the intervention or control group in a 1:1 ratio, within strata defined by sex, baseline cognition (above or below median ADAS-Cog 11 score), and baseline lifestyle risk of AD (above or below median ANU-ADRI score) in permuted blocks of eight. The randomization sequence was generated by an independent researcher (R.B.) from www.sealedenvelope.com.

Linear mixed models were used to compare outcomes between groups at each follow-up time. Each model included group, time point, and the group × time point interaction, as well as stratification variables: sex, ANU-ADRI strata, and ADAS-Cog 11 strata. The likelihood ratio test (LRT) was used to assess statistical significance of the

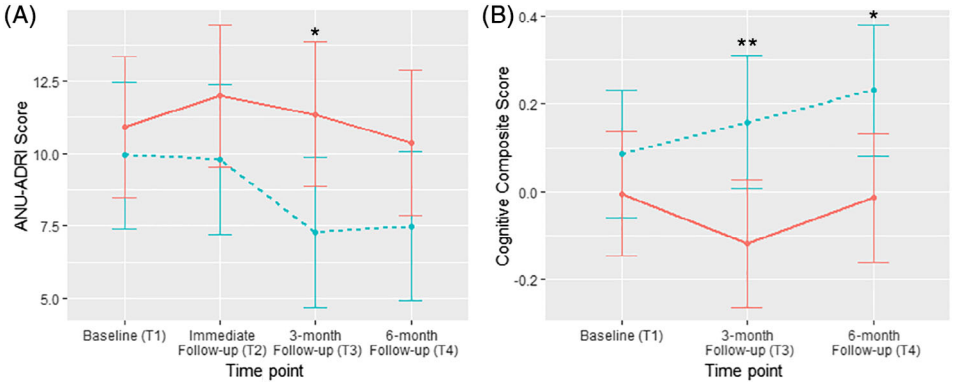


**Figure 2.** Scores for Primary Outcomes: Lifestyle risk and Cognition. Adjusted outcomes for Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI) (A) Group × time interaction: $\chi^2 = 10.84$; $df = 3$; $P = .012$ and a cognitive composite z score (B) group × time interaction: $\chi^2 = 7.28$; $df = 2$; $P = .026$. All data points are least square means generated from regression models after adjusting for strata variables that were not the dependent variable (eg, ANU-ADRI adjusted for sex and cognition strata and vice versa). Lower ANU-ADRI scores indicate lower lifestyle risk. Higher cognitive composite scores indicate better cognitive function. Blue dashed lines represent the intervention group, solid red lines represent the control group, and error bars represent 95% confidence intervals. Between-group significance denoted by $^*P < .05$ and $^{**}P < .01$.

main effects and interaction term.[29] A statistically significant interaction term indicated that the between-group differences changed over time. Difference in least square mean outcomes between intervention groups is reported at each follow-up, with 95% confidence intervals (CIs) and *P* values from between-group *t* tests. A secondary analysis was undertaken to examine the effect of the intervention on the two subcomponents of the ANU-ADRI, risk and protective factors, and each of the five cognitive measures.

The primary analysis was a complete case analysis. Sensitivity analysis was undertaken as a full intention-to-treat (ITT) analysis with missing data accounted for using multivariate imputation by chained equations (MICE).

All preliminary analyses and descriptions of baseline characteristics were carried out with SPSS v.26.0.[30] Linear mixed modeling was undertaken in R v.3.6.0[31] using the lme4,[32] lmerTest,[33] emmeans,[34] and MICE packages,[35] with graphs creating using ggplot2.[36]

## RESULTS

### Participant Characteristics

Recruitment of participants took place between July 2017 and November 2017; 199 individuals were screened, and 135 were recruited into the study. Of these, 119 participants completed baseline testing (January 2018) and were randomized into the intervention (n = 57) or control (n = 62) groups. At the final 6-month follow-up (November 2018), 48 participants remained in each group of the study. The full flowchart of participants can be found in Figure 1.

At baseline, participants had a mean age of 73.0 years (SD = 5.5 years) and had 13.3 years (SD = 5.7 years) of education, and 61% (n = 73) were female. Three (3%) participants had a diagnosis of MCI, and all other participants (n = 116 [97%]) met the criteria for SCD. Baseline characteristics for both groups are shown in Table 1.

Mean differences with 95% CIs and significance levels for between-group differences for all variables, at all follow-up time points, for the primary and secondary analyses can be found in Supplementary Table S1.

Overall, participants were well able to adhere with most of the intervention requirements. All participants from both groups who remained in the intervention until the final follow-up completed the four educational modules. For the intervention group there was mostly strong adherence to the active interventions. All participants who remained in the intervention attended the three dietitian appointments and the exercise physiologist appointment. However, adherence to the brain training component was lower, with 20% adherence (10.8 hours) of the specified 54 total hours (27 weeks × 2 hours/week).

### Primary Analyses

#### *Lifestyle Risk of Alzheimer's Disease (ANU-ADRI)*

The LRT analysis showed a significant group × time point interaction ($\chi^2$ = 10.84; *df* = 3; *P* = .013). The between-group difference was not significant at immediate follow-up (T2 intervention = 9.80; control = 11.98; difference = −2.18; *t* = −1.28; *P* = .204), it was significant at the 3-month follow-up (T3 intervention = 7.27; control = 11.35; difference = −4.08; *t* = −2.36; *P* = .019), and it was no longer significant at the 6-month follow-up (T4 intervention = 7.48; control = 10.37; difference = −2.88; *t* = −1.66; *P* = .098) (Figure 2A). When looking at within-group changes over the course of the intervention, the control group showed only a minor reduction in ANU-ADRI scores (−0.54) compared with the larger reduction seen in the intervention group (−2.46); reductions of 2.0 or more ANU-ADRI points are considered clinically meaningful.

#### *Cognitive Composite z Score*

The LRT analyses found a significant group × time point interaction ($\chi^2$ = 7.28; *df* = 2; *P* = .026). For the between-group differences, the intervention group had significantly higher cognition scores at both follow-up periods (T3 intervention = .159; control = −.117; difference = .276; *t* = 2.62; *P* = .010; T4 intervention = .231; control = −.014; difference = .245; *t* = 2.33; *P* = .021) (Figure 2B).

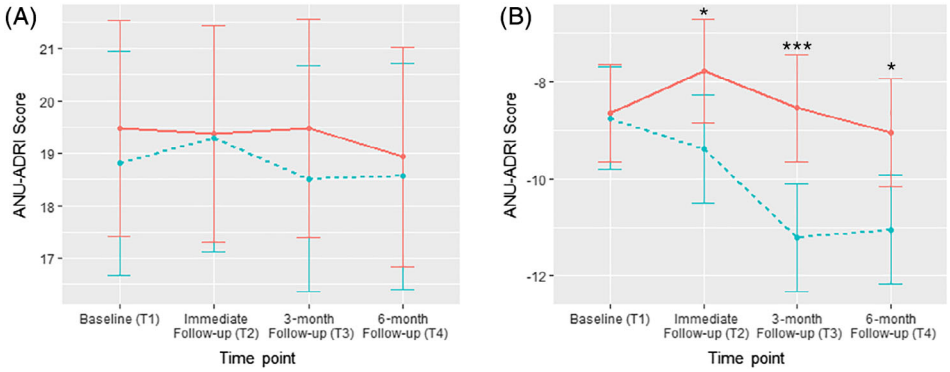


**Figure 3.** Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI) risk and protective factors. Adjusted outcomes for risk factors (A) group × time point interaction: $\chi^2$ = 2.93; *df* = 3; *P* = .403 and protective factors (B) group × time point interaction: $\chi^2$ = 12.02; *df* = 3; *P* = .007. All data points are least square means generated from regression models after adjusting for strata variables (sex and cognition). Lower scores indicate lower lifestyle risk. Blue dashed lines represent the intervention group, solid red lines represent the control group, and error bars represent 95% confidence intervals. Between-group significance is denoted by **P* < .05 and ****P* < .001. [Color figure can be viewed at wileyonlinelibrary.com]

## Secondary Analyses: Drivers of Significant Change

### *Lifestyle Risk and Protective Factor for Alzheimer's Disease (ANU-ADRI)*

The outcomes for the ANU-ADRI risk and protective factors are shown in Figure 3.

### *Lifestyle Risk Factors for Alzheimer's Disease*

The LRT analysis found no significant effects ($\chi^2$ = 2.93; *df* = 3; *P* = .403). Although both groups experienced a within-group reduction of risk factor scores, neither of these was clinically meaningful or statistically significant (T2 intervention = 19.3; control = 19.4; difference = −.092; *t* = .07; *P* = .945; T3 intervention = 18.5; control = 19.5; difference = .962; *t* = .72; *P* = .472; T4 intervention = 18.6; control = 18.9; difference = .339; *t* = .28; *P* = .783).

### *Lifestyle Protective Factors for Alzheimer's Disease*

The LRT analysis showed a statistically significant group × time point interaction ($\chi^2$ = 12.02; *df* = 3; *P* = .007). The intervention group's protective scores were significantly lower than the control scores at all follow-up periods (T2 intervention = −9.38; control = −7.77; difference = −1.62;

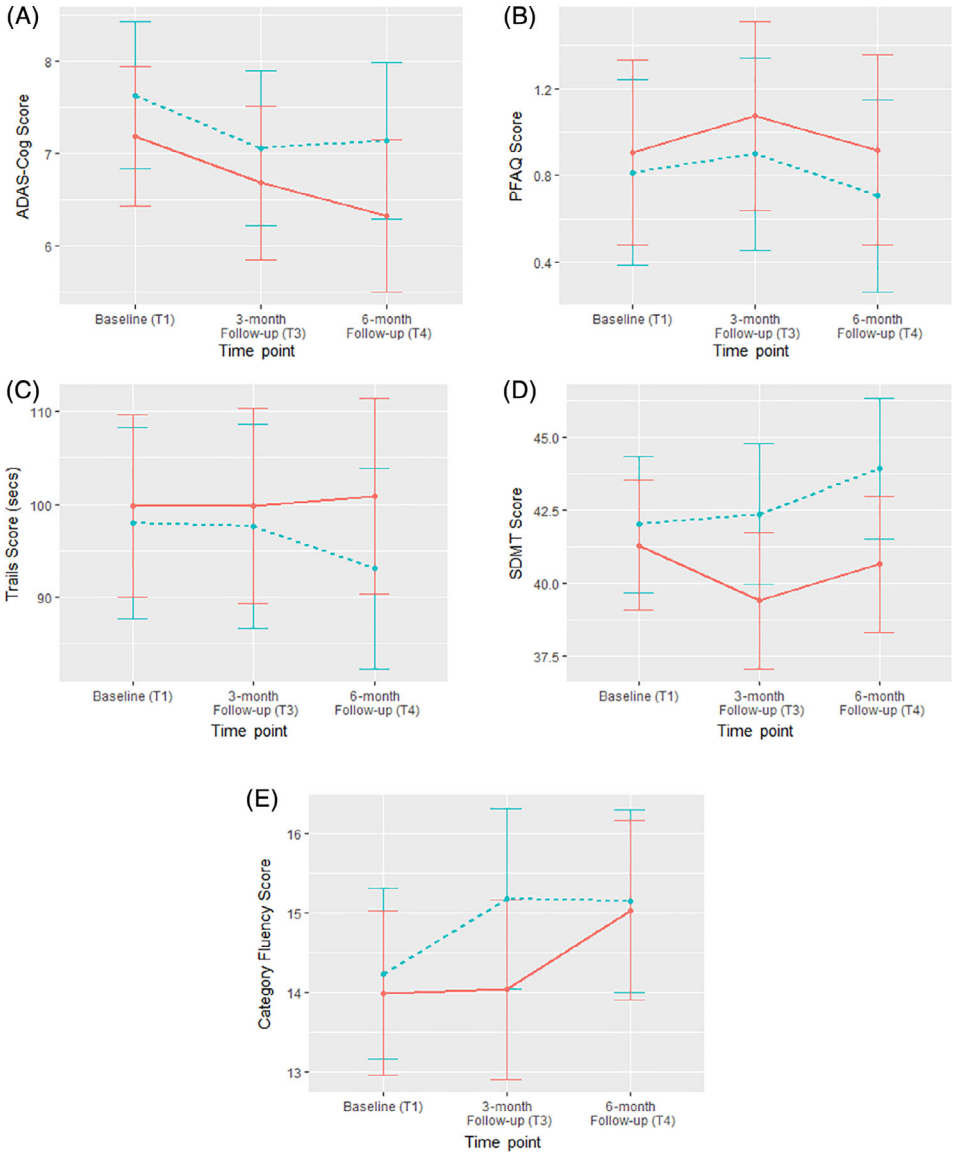


**Figure 4.** Outcomes for Measures of Cognition. Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 11) (A) Group × time point interaction: $\chi^2$ = .73; *df* = 2; *P* = .696; Pfeffer Functional Activities Questionnaire (PFAQ) (B) $\chi^2$ = .44; *df* = 2; *P* = .802; Trail Making Test-B (TMT-B) (C) $\chi^2$ = .94, *df* = 2; *P* = .625; Symbol Digit Modalities Test (SDMT) (D) $\chi^2$ = 6.459; *df* = 2; *P* = .040; Category Fluency (E) $\chi^2$ = 2.04; *df* = 2; *P* = .360. *All data points are least square means generated from regression models after adjusting for strata variables (sex and Australian National University-Alzheimer's Disease Risk Index [ANU-ADRI]). Lower scores for ADAS-Cog 11, PFAQ, and TMT-B and higher scores for SDMT and Category Fluency indicate better cognitive function. Blue dashed lines represent the intervention group, solid red lines represent the control group, and error bars represent 95% confidence intervals.* [Color figure can be viewed at wileyonlinelibrary.com]

$t$ = 2.10; $P$ = .037; T3 intervention = −11.21; control = −8.54; difference = 2.67; $t$ = 3.40; $P$ < .001; T4 intervention = −11.05; control = −9.05; difference = 2.00; $t$ = 2.51; $P$ = .012).

### Cognitive Measures

The outcomes for the individual cognitive measures that made up the cognitive composite $z$ score are shown in Figure 4. The measures were ADAS-Cog (Figure 4A), PFAQ (Figure 4B), TMT-B (Figure 4C), SDMT (Figure 4D), and Category Fluency (Figure 4E).

When all cognitive measures were analyzed separately using the LRT analysis, only SDMT showed a significant group × time point interaction ($\chi^2$ = 6.46; $df$ = 2; $P$ = .040); however, neither of the between-group differences was significant at follow-up (T3 intervention = 42.4; control = 39.4; difference = −2.96; $t$ = −1.77; $P$ = .078; T4 intervention = 43.6; control = 40.6; difference = −3.29; $t$ = −1.96; $P$ = .052).

### Sensitivity Analysis: Intention-to-Treat Analysis

In ITT, which used complete cases following missing data imputation, outcomes were highly consistent with the primary and secondary analyses. All between-group differences at specific time points were retained.

A further analysis was undertaken to examine the impact that attrition may have had on outcomes. Supplementary Table S2 shows that only one variable, protective lifestyle factors, showed a significant difference for those who withdrew and those who remained in the study. Although there was a significant difference, when this variable was further separated by intervention group, it showed the significant difference was only in the control group (withdrew = −6.19; remained = −9.80; difference = 3.62; $t$ = 2.91; $P$ = .005), not the intervention group (withdrew = −8.64; remained = −9.17; difference = .54; $t$ = .38; $P$ = .704).

## DISCUSSION

BBL-CD was a proof-of-concept RCT that adapted a successful primary prevention study[12] to the cognitive decline group and included new components adapted from previously successful interventions conducted in other participant groups.[12-16] The main findings from this study were that a multidomain lifestyle intervention was able to decrease exposure to lifestyle risk factors for AD significantly, and improve cognition in a group experiencing cognitive decline significantly, relative to a control group. The results lend support to the hypothesis that secondary prevention interventions may be able to modify the course of disease progression.

### Adherence

The intervention mostly achieved strong adherence. The lowest levels of adherence were for the brain training component. The lower levels of adherence may have been due to such a large dose of brain training (54 hours) over such a long period (27 weeks). A meta-analysis of brain training in the MCI population showed the average dose across the studies included was 34.2 hours over an average of 14 weeks (according to the study protocols); however, the meta-analysis provided no information on actual adherence to the interventions.[37] The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, which administered 10 to 12.5 hours of speed of processing training over 5 to 6 weeks, resulted in lower rates of dementia in a cognitively normal sample of participants aged 65 and older at 10 years postintervention.[38] This dose was comparable with the actual dose achieved in BBL-CD, albeit over a longer time frame. Unfortunately, in BBL-CD no qualitative data were collected to determine what the barriers to higher levels of adherence may have been.

### Lifestyle Risk of Alzheimer's Disease

By the 3-month follow-up, the intervention group showed a significantly lower ANU-ADRI than the control group, but this difference was not retained at the final follow-up. The decline in overall ANU-ADRI score for the intervention group was 2.7 (T3) and 2.5 (T4) points; a 2-point change in ANU-ADRI is considered to be clinically meaningful.[39] This demonstrates that clinically relevant lifestyle changes are feasible over the short term in participants experiencing cognitive decline. The significant effects in overall ANU-ADRI scores were driven by higher levels of protective factors, rather than lower levels of risk factors. Similar effects were seen in past multidomain lifestyle interventions.[12,40] The reduction in ANU-ADRI score through increased protective factors was 2.5 (T3) and 2.3 (T4). In real terms these changes are similar to the amount of AD risk conferred between low (0 points) and moderate levels (−2 points) of exercise or the presence of diabetes mellitus type II (+3 points).[39] When missing data were controlled for in the ITT, all the between-group differences found in previous analyses were still present, showing that these are robust findings. The only scores that may have been affected by participants withdrawing were protective factors for the control group. Because the control participants who withdrew had higher protective scores (ie, less protective), this may have artificially lowered the control group scores. Given that the only significant effects were for the intervention group, if anything this artificial reduction may have reduced the magnitude of difference between the control and intervention groups. This has minimal impact on the main findings of this study.

### Cognition

At the end of the study, the intervention group had a significantly higher cognitive composite score, and a significant group × time point interaction effect was observed for both follow-up periods. When this was investigated further to determine the specific measures underlying the significant effects, only SDMT showed a significant group × time point interaction; however, there were no between-group differences at specific time points. The most likely explanation for this is a weak but consistent positive effect across measures. Greater statistical power through a larger sample size would be required to assess actual effects on individual cognitive measures. There appeared to be improvements over time for all cognitive measures in the intervention group,

but only the ADAS-Cog and Category Fluency measures showed improvement for the control group.

In the limited number of multidomain SCD interventions that have taken place, significant effects have been found for executive function (color-word Stroop task)[40] and verbal fluency (letter fluency)[41] but not in cognitive composite scores. MCI lifestyle interventions show a very mixed pattern of outcomes with positive and null effects across executive function, memory, and global cognition.[11] Other multidomain lifestyle interventions in different participant groups have found significant differences in cognitive composite scores of a similar magnitude (eg, BBL-CD intervention group, $z$ = .25, vs Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability [FINGER] trial intervention group, $z$ = .20).[6] Importantly, in the present study, the ITT analysis produced results that were highly consistent with the primary and secondary analyses, which is suggestive that significant effects were not statistical artifacts due to participant attrition.

Taken together, the intervention group experienced a statistically significant and clinically meaningful lower lifestyle risk and significantly higher cognition, relative to the control group. No significant differences in lifestyle risk or cognition were found for the control group. These results support the hypothesis that individuals in the early stages of cognitive decline retain sufficient neuroplasticity to achieve cognitive improvements in the short term. The ultimate goal of research in this participant group is to demonstrate long-term improvements in lifestyle risk, cognition, and ultimately slower rates of cognitive decline and lower rates of conversion to dementia. The outcomes achieved in this study warrant the conduct of a larger and longer study to test the longer term sustainability of improvements in lifestyle and cognition.

### Limitations

The main limitation of this study was the limited follow-up time of 6 months. Meta-analyses of nonpharmacological interventions for SCD recommend a minimum follow-up duration of a year or longer.[8] A second limitation was that the study overestimated the magnitude of change that would be observed (.70 SD); hence there may have been insufficient power to detect small differences.[15] Both limitations can be overcome in future studies.

### Implications for Future Research

The pattern of results for lifestyle outcomes illustrate a few potential areas for refinements for this intervention, as well as other studies in this area. First, lifestyle interventions commonly report improvement in protective factors, but significant reductions in risk factors is an area where clear improvements are possible. For this reason, it would be beneficial for future research to look at the outcomes of protective and risk factors separately.

Second, a plateauing of improvement between time points 3 and 4 for ANU-ADRI (a period where no further intervention was being implemented) is suggestive of the need for "booster sessions" to maximize and sustain lifestyle improvements.

In terms of cognition, future interventions in this area do need to account for small effect sizes of cognitive outcomes with adequate sample sizes, so as not to negatively bias evidence in this developing area. Given the heterogeneity of cognitive domains that can be improved through nonpharmacological interventions, future research should choose a battery of cognitive tests to cover all potential domains and also standardize and combine outcomes to detect any subtle but consistent effects across measures. More emphasis on measures of everyday function would also show whether interventions are having an immediate effect on real-world outcomes.

Given there is some heterogeneity in the SCD and MCI groups in terms of stability, progression, and remission of deficits, further characterization of participants through genotyping, neuroimaging, and other biomarkers would be beneficial for any future research.

In conclusion, the present proof-of-concept study adds evidence to the argument that modifying the lifestyle risk of those experiencing cognitive decline can result in improvements in cognition. The results obtained are supportive of a larger, longer trial to investigate the possibilities of sustained improvements in lifestyle and cognition, clearly demonstrate cognitive domains showing improvements, and long-term follow-up with participants to track cognitive decline and development of AD and other forms of dementia for a number of years postintervention.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

**Supplementary Table S1**: Least square differences in means adjusted for strata variables that were not the dependent variable (eg, ANU-ADRI adjusted for sex and cognition strata and vice versa). The *P* values are for *t* tests for between-group differences. Lower scores for ANU-ADRI, protective factors, and risk factors all indicate lower levels of lifestyle risk. Lower scores for ADAS-Cog 11, PFAQ, and TMT-B, and higher scores for SDMT and Category Fluency indicate better cognitive function. Values shown in bold are significant at $P < .05$. ANU-ADRI, Australian National University-Alzheimer's Disease Risk Index; ADAS-Cog, Alzheimer's Disease Assessment Scale- Cognitive Subscale; PFAQ, Pfeffer Functional Assessment Questionnaire; TMT-B, Trail Making Test-B; SDMT, Symbol Digit Modality Test.

**Supplementary Table S2:** The *P* values are for *t* tests for between-group differences. Lower scores for ANU-ADRI, protective factors, and risk factors all indicate lower levels of lifestyle risk. Lower scores for ADAS-Cog 11, PFAQ, and TMT-B, and higher scores for SDMT and Category Fluency indicate better cognitive function. Values shown in bold are significant at $P < .05$. ANU-ADRI, Australian National University-Alzheimer's Disease Risk Index; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; PFAQ, Pfeffer Functional Assessment Questionnaire; TMT-B, Trail Making Test-B; SDMT, Symbol Digit Modalities Test.

Supplementary Table S1: Mean differences for intervention and control groups for all outcome variables at follow-up

| | Immediate Follow-up | | 3 Month Follow-up | | 6 Month Follow-up | |
|---|---|---|---|---|---|---|
| | Mean difference [95% CI] | P value | Mean difference [95% CI] | P value | Mean difference [95% CI] | P value |
| ANU-ADRI Total | -2.18 [-5.54, 1.19] | .204 | **-4.08 [-7.49, -0.68]** | **.019** | -2.88 [-6.31, .54] | .098 |
| Protective Factors | **-1.62 [-3.14, -.10]** | **.037** | **-2.67 [-4.21, -1.13]** | **<.001** | **-2.00 [-3.57, -.44]** | **.012** |
| Risk Factors | -.09 [-2.69, 2.51] | .945 | -.96 [-3.59, 1.67] | .472 | -.37 [-3.00, 2.27] | .783 |
| Cognitive Composite Z-Score | - | - | **.28 [.07, .48]** | **.010** | **.25 [.04, .45]** | **.021** |
| ADAS-Cog 11 | - | - | .38 [-.80, 1.55] | .527 | .81 [-.36, 1.99] | .173 |
| PFAQ | - | - | -.18 [-.79, .44] | .572 | -.21 [-.83, .41] | .502 |
| TMT-B, seconds | - | - | -2.24 [-17.26, 12.79] | .770 | -7.79 [-22.72, 7.15] | .305 |
| SDMT | - | - | 2.97 [-.34, 6.27] | .078 | 3.29 [-.03, 6.60] | .052 |
| Category Fluency | - | - | 1.14 [-.45, 2.74] | .159 | .12 [-1.48, 1.72] | .881 |

Least square differences in means adjusted for strata variables that were not the dependent variable (e.g. ANU-ADRI adjusted for sex and cognition strata and vice versa). P values are for t-tests for between-group differences. Lower scores for ANU-ADRI, protective factors and risk factors all indicate lower levels of lifestyle risk. Lower scores for ADAS-Cog 11, PFAQ and TMT-B and higher scores for SDMT and Category Fluency indicate better cognitive function. Values shown in bold are significant at p<.05. Abbreviations: ANU-ADRI, Australian National University- Alzheimer's Disease Risk Index; ADAS-Cog, Alzheimer's Disease Assessment Scale- Cognitive Subscale; PFAQ, Pfeffer Functional Assessment Questionnaire; TMT-B, Trail Making Test- B; SDMT, Symbol Digit Modality Test.

Supplementary Table S2: Comparison of baseline characteristics of participants who withdrew and remained in the study

| | Remained in Study (n=96) | Withdrew (n=23) | p |
|---|---|---|---|
| Age, years | 72.9 (5.2) | 73.7 (6.9) | .558 |
| Female/Male Ratio, n (%) | 59 (80.8%) / 37 (80.4%) | 14 (19.2%) / 9 (19.6%) | .958 |
| Education, years | 13.5 (5.6) | 12.4 (6.0) | .418 |
| ANU-ADRI Total | 8.5 (11.2) | 12.8 (11.0) | .099 |
| **Protective Factors** | **-9.5 (4.4)** | **-7.2 (3.7)** | **.015** |
| Risk Factors | 18.0 (9.3) | 19.5 (10.7) | .504 |
| Cognitive Composite Z-Score | 0.123 (0.57) | -0.052 (0.82) | .415 |
| ADAS-Cog 11 | 6.7 (2.9) | 7.5 (3.1) | .284 |
| PFAQ | 0.5 (1.1) | 0.9 (0.9) | .221 |
| SDMT | 43.0 (8.6) | 20.6 (10.1) | .277 |
| TMT-B, seconds | 94.9 (32.3) | 103.4 (44.2) | .427 |
| Category Fluency | 14.9 (4.0) | 15.2 (4.1) | .749 |

P values are for t-tests for between-group differences. Lower scores for ANU-ADRI, protective factors and risk factors all indicate lower levels of lifestyle risk. Lower scores for ADAS-Cog 11, PFAQ and TMT-B and higher scores for SDMT and Category Fluency indicate better cognitive function. Values shown in bold are significant at $p<.05$. Abbreviations: ANU-ADRI, Australian National University- Alzheimer's Disease Risk Index; ADAS-Cog, Alzheimer's Disease Assessment Scale- Cognitive Subscale; PFAQ, Pfeffer Functional Assessment Questionnaire; TMT-B, Trail Making Test- B; SDMT, Symbol Digit Modality Test.

# Chapter 4

## 4.1. The Feasibility of a Multidomain Dementia Risk Reduction Randomised Controlled Trial for People Experiencing Cognitive Decline: The Body, Brain, Life for Cognitive Decline (BBL-CD)

This chapter contains the manuscript of a paper examining the feasibility of the BBL-CD intervention, currently submitted for review to *The Gerontologist*. This manuscript achieves objective 3 by demonstrating that the BBL-CD intervention was feasible. The feasibility was evaluated through three of the Bowen Feasibility Framework variables: Acceptability, implementation of the intervention and efficacy to achieve behaviour change. The intervention was found to be acceptable with high levels of participant retention (80.7%). Implementation was mostly good, with all participants completing 100% of online modules, dietitian sessions and the exercise physiology session, however only 20% of cognitive engagement requirements were completed. Efficacy to achieve behaviour change was mostly good with significantly higher levels of adherence for the intervention group relative to the control group in the domains of Mediterranean diet and cognitive engagement, but not in physical activity. Overall, the intervention was found to be feasible. Several recommendations for future BBL trials and other multidomain trials are made.

# The Feasibility of a Multidomain Dementia Risk Reduction Randomised Controlled Trial for People Experiencing Cognitive Decline: The Body, Brain, Life for Cognitive Decline (BBL-CD)

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**Abstract**

**Background and Objectives:** The aim of this study was to evaluate the feasibility of a successful multidomain dementia risk reduction randomised controlled trail, Body, Brain, Life for Cognitive Decline (BBL-CD). The intervention focused on Mediterranean Diet (MeDi), Physical Activity (PA) and Cognitive Engagement (CE). The feasibility is evaluated using the Bowen Feasibility Framework concepts of: Acceptability, Implementation and Efficacy to change behaviour.

**Research Design and Methods:** Acceptability of the intervention was assessed through participant retention. Implementation was evaluated through compliance to requirements set out in the protocol. Efficacy of the intervention was measured through change in adherence to the domains of MeDi, PA and CE using linear mixed models.

**Results:** High acceptability of the intervention was demonstrated through a participant retention rate of 80.7% (Intervention:84.2%; Control:77.4%). Compliance to the protocol was strong with 100% of participants completing all educational modules and all MeDi and PA components, with 20% compliance for CE. Efficacy in behaviour change was established through significant effects of adherence to MeDi ($X^2$=16.75, df=3, p<.001) and CE ($X^2$=9.83, df=3, p=.020), but not in PA ($X^2$=4.48, df=3, p=.211).

**Discussion and Implications:** Overall the intervention was shown to be feasible. Future iterations of this study could include greater PA support and prescribe a lower dose of CE. Recommendations for future trials are: Practical, one-on-one sessions are more effective than passive education at eliciting behaviour change; booster sessions would be required to sustain lifestyle changes; and qualitative data collection should be included to identify barriers to change.

**Keywords: Dementia Prevention, Non-pharmacological Intervention, Subjective Cognitive Decline, Mild Cognitive Impairment, Adherence**

## Background and Objectives

At present there are approximately 50 million people worldwide living with dementia; by 2030 this number is projected to exceed 80 million and by 2050 more than 150 million (World Health Organisation, 2019). It is estimated that together lifestyle risk factors (such as physical inactivity and cognitive inactivity) are responsible for between a third to half of all cases of Alzheimer's disease (AD) (Barnes & Yaffe, 2011; Livingston et al., 2017). Given the expected increase in the number of people developing dementia, there is an urgent need for interventions to reduce dementia risk (World Health Organisation, 2019). Several large-scale trials are planned and underway internationally (Heffernan et al., 2019; Rosenberg et al., 2020).

An important part of maximizing the research effort is investigating the feasibility of these interventions (Rosenberg et al., 2020). The 2016 CONSORT Statement Extension to Randomised Pilot and Feasibility Trials defines feasibility as "whether a trial can be done, should be done, and if so, how" it ought to be done (Eldridge, Chan, et al., 2016). Feasibility studies answer questions such as "Will this protocol work, if not, why not and how should it be changed?" (Eldridge, Lancaster, et al., 2016).

There are theoretical frameworks to guide the conduct of feasibility studies. The Bowen Feasibility Framework (Bowen et al., 2009) proposes eight potential areas of focus for feasibility studies including: acceptability, demand, implementation, practicality, adaptation, integration, expansion, and limited efficacy testing. Depending on the objectives of the particular study, the focus may be on one or some combination of these. While feasibility studies typically occur in preparation for randomised controlled trials (RCT) (Eldridge, Lancaster, et al., 2016), aspects of feasibility can be investigated following a trial to determine the methodological aspects that may be improved upon in future iterations of

studies, or in similar research. Such post-hoc investigations were conducted to assess adherence in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) and Multidomain Alzheimer Preventive Trial (MAPT) studies (Coley et al., 2019). Both interventions were large multidomain dementia risk reduction studies including over 1,000 participants addressing cardiovascular risk factors, nutritional counselling, physical activity, and cognitive activity. Outcomes included identifying participant characteristics that predicted adherence, identifying research questions remaining to be explored, and offering recommendations to maximise adherence in similar trials.

Another example of feasibility research is a lifestyle intervention focused on diet and exercise for participants with metabolic syndrome, conducted by Jeejeebhoy et al. (2017). The study investigated compliance (percentage of intervention visits attended) and adherence (changes in measures of diet and exercise) to research protocols to draw conclusions about the practicality of its implementation and make preliminary recommendation for such studies.

The focus of the present study, Body, Brain, Life for Cognitive Decline (BBL-CD), is a multidomain dementia risk reduction trial for people experiencing subjective cognitive decline (SCD) and mild cognitive impairment (MCI) (McMaster et al., 2018). This RCT demonstrated efficacy in the primary outcomes of lifestyle risk of AD and cognition (McMaster et al., 2020). BBL-CD adapted a previously successful primary prevention intervention, the BBL trial, to a secondary prevention focus which incorporated methodological aspects of other previously successful trials in other participant groups (Anstey et al., 2020; Estruch et al., 2013; Rebok et al., 2014).

The aim of this paper is to examine three areas of feasibility of the BBL-CD intervention: Acceptability, Implementation and Efficacy. In accordance with the Bowen Feasibility Framework, the acceptability of the intervention will be examined through participant

retention and attrition; implementation of the project will be explored through participant compliance with requirements of the protocol; and the efficacy of behaviour change will be examined through an analysis of the participant adherence achieved in the domains of Mediterranean diet (MeDi), cognitive engagement (CE) and physical activity (PA).

## Research Design and Methods

The full trial methodology has been published previously (McMaster et al., 2018). Only methods relevant to this study will be detailed here.

### Design

BBL-CD was an eight-week, two-arm, parallel group RCT of a multidomain dementia risk reduction program for people experiencing cognitive decline. The study aimed to reduce dementia risk by primarily focusing on the lifestyle factors of MeDi, CE and PA. The trial was designed and conducted in accordance with the CONSORT statement (Schulz et al., 2010) and the extension for non-pharmacological interventions (Boutron et al., 2008). This paper was written in accordance with the CONSORT Extension for Randomised Pilot and Feasibility Trials (Eldridge, Chan, et al., 2016). The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12617000792325) and ethical approval was granted by the Australian National University Human Research Ethics Committee (Protocol: 2016/360). All participants provided written informed consent to take part.

### Participants

Participants were 119 community-dwelling individuals, living in the Canberra region of Australia, who responded to media calls for participants from July-September 2017. Participants had a mean age of 73.0 (5.5) years, 61% (n=73) were female. Three (3%) participants had an MCI diagnosis, and all remaining participants were experiencing SCD

(n=116, 97%). Participants were randomised to either intervention (n=57) or active control (n=62) in a 1:1 ratio, stratified by gender, baseline lifestyle risk of AD and cognition.

Inclusion criteria were: 65 years or over; willing to make lifestyle changes to improve their health; owning a computer with internet access; having sufficient English skills; and either a diagnosis of MCI or experiencing SCD, according to the Jessen criteria (clinically normal on objective assessment, self/informant-reported cognitive decline, and decline not better accounted for by major medical, neurological or psychiatric diagnosis). The exclusion criteria were any major neurological, psychiatric, or chronic condition which would prevent participation in a lifestyle behaviour change program; and current participation in any other lifestyle change interventions.

**Interventions**

The active control group undertook an online, four-module educational course on dementia risk reduction. The modules covered: Dementia literacy and lifestyle risk factors for AD (week 1); Mediterranean diet (week 2); cognitive engagement (week 4) and physical activity (week 6). These modules explained forms of cognitive decline and that these conditions were associated with additional risk of AD and dementia and outlined the evidence to support these lifestyle factors in general health and dementia risk reduction. In the week following each of the modules on the three lifestyle factors, participants were given a week with no additional education and instructed to implement the changes they learnt about into their own lifestyle.

The intervention group completed the same online education modules and also completed additional active components. These active components were completed in the weeks in which active control participants were requested to implement the information they had learnt into their lifestyle.

Diet: Participants had an initial one-hour appointment (week 3) and two 30 minute follow-up face-to-face appointments (weeks 10 and 21) with the study dietitian. The session involved the dietitian reviewing the participant's previous diet assessments and discussing ways to increase adherence to the MeDi.

Cognitive Engagement: Participants were provided with a BrainHQ (Posit Sceince) brain training account (week 5). Each week participants were asked to complete two executive function tasks and two memory tasks for 30 minutes each (i.e., a total of two hours). The four tasks were: Double Decision (divided and selective attention, speed of processing, dual task, and useful field of view); Freeze Frame (visual phasic and tonic attention, inhibitory control, and motor response inhibition); Syllable Stacks (auditory working memory); and Memory Grid (auditory spatial memory).

Physical Activity: An exercise physiologist had a one hour appointment with intervention participants to create a PA plan (week 7). This plan took account of the participant's current level of PA, any medical conditions and PA preferences. The eventual aim was to increase PA levels to 150 minutes of moderate exercise per week. The initial design of the protocol also included two, 30 minute follow-up appointments with the exercise physiologist to monitor progress and make alterations to the PA plan, as required. The exercise physiologist was unexpectedly hospitalised during the study and a suitable replacement could not be located. The initial face-to-face appointment was carried out as per the protocol, but no follow-up appointments took place.

**Outcomes**

The outcomes of interest are retention, compliance and adherence, three variables which are identified as important objectives in feasibility research, by the UK's National Institute for Health Research (Eldridge, Lancaster, et al., 2016).

**Retention Outcomes**

Retention was the number and percentage of participants in each group who remained in the intervention until the final follow-up. For those that did not remain in the intervention, the reasons for withdrawal are examined. Participant retention falls under the Bowen Feasibility Framework criterion of Acceptability (Bowen et al., 2009).

**Compliance Outcomes**

To evaluate the feasibility of implementing the intervention, four aspects of compliance were reviewed (Bowen et al., 2009): percentage of participants who completed all four educational modules (both groups); percentage of participants who attended the initial one hour MeDi appointment and two 30 minute follow-up appointments with the dietitian (intervention group only); percentage of participants who completed two hours of online brain training on BrainHQ weekly (intervention group only); and percentage of participants who attended the one hour appointment with the exercise physiologist (intervention group only).

These active components completed by the intervention group were designed such that if participants achieved high levels of compliance to the protocol this would lead to high levels in the measures of adherence.

**Adherence Outcomes**

The efficacy of the intervention to bring about behaviour change was determined by the degree to which participants were able to adhere to the domains of MeDi, CE and PA (Bowen et al., 2009).

**Diet**: Adherence to the MeDi was evaluated via the Mediterranean Diet Adherence Screener (MEDAS) (Schröder et al., 2011). The MEDAS is a 14-point checklist, with one point awarded for each aspect of the diet adhered to. The MEDAS includes intake of vegetables,

fruit, fish, legumes, nuts, white meat, red meat, primary source of dietary fat, olive oil, butter/cream, wine, sofrito, sweet/carbonated beverages, and sweets. The MEDAS was administered by researchers in a discussion format to ensure accuracy of scoring.

CE and PA were both measured as components of the Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI) (Anstey et al., 2013). The ANU-ADRI assesses 11 AD risk and four protective factors to provide an overall risk score. Risk factors are positively scored, and protective factors are negatively scored, determined by the relative risk score of the levels of each factor.

**Cognitive engagement**: Cognitive risk scores in the ANU-ADRI are scored on the basis of frequency of cognitively stimulating activities such as reading books and magazines, writing letters, playing cognitively stimulating games, participating in brain training, visiting museums or libraries and attending concerts, plays or musicals. ANU-ADRI scores are assigned to low (0), medium (-6) and highly (-7) cognitively stimulating lifestyles.

**Physical activity**: In the ANU-ADRI, PA is measured by the International Physical Activity Questionnaire (IPAQ) (Hagströmer et al., 2006). The IPAQ covers frequency and duration of vigorous, moderate, and light activity for work/volunteering, transportation, housework/yardwork, and recreation/leisure. The IPAQ uses an algorithm to combine these data to determine low, medium, and high PA lifestyles. The ANU-ADRI scores for these levels are low= 0, moderate= -2 and high activity= -3.

All outcomes were assessed at baseline (week 0, T1), immediate follow-up (week 9, T2), 3-month follow-up (week 20, T3); and 6 month follow-up (week 32, T4). All researchers involved in data collection were blind to group allocation.

## Statistical Methods

### Sample size calculation

To detect a difference in the primary outcome measures of 0.70 SDs required a minimum of 36 participants per arm (N=72) at the final follow-up period. Accounting for a potential 10% attrition rate per testing period, led to a target sample of 60 participants per arm (N=120) (McMaster et al., 2018).

### Randomisation and Stratification

Participants were randomised 1:1 into intervention and control, in permuted blocks of eight, stratified by gender, baseline cognition (above or below median ADAS-Cog) and baseline lifestyle risk of AD (above or below median ANU-ADRI). An independent researcher generated the permuted block sequence from www.sealedenvelope.com.

### Statistical Analyses

Retention was evaluated by the number and percentages of participants who remained in the study until the final follow-up, formally withdrew or were lost to follow-up. Compliance was expressed as a percentage of participants who completed the intervention as specified in the protocol (McMaster et al., 2018).

Adherence data was analysed using linear mixed models including group, timepoint, group x timepoint and stratification variables (gender, baseline lifestyle risk of AD strata, and baseline cognition strata). Significance of the fixed effects was determined using the likelihood ratio test (LRT) method described by Winter (2013). A statistically significant interaction term indicates that between group differences changed over time showing that the intervention was efficacious. Least square means adjusted for strata variables are reported with between group t-tests performed to determine significant differences at specific timepoints.

Preliminary analyses were conducted in SPSS 26.0 (IBM Corp, Released 2019). Linear mixed modelling and LRT analyses were conducted in R 3.6.0 (R Core Team, 2017) using the lme4, (Bates et al., 2015) lmerTest,(Kuznetsova & Christensen, 2017) and emmeans (Lenth et al., 2017) packages, with graphs constructed using ggplot2 (Wickham, 2016).

## Results

The baseline characteristics and adherence to the lifestyle behaviours of MeDi, PA and CE are shown in Table 1.

[Table 1 approximately here]

### Retention

From the initial sample of 119 (Control:62; Intervention:57) participants randomised at baseline, 101 (Control:52(83.9%); Intervention:49 (86.0%)) participants remained at immediate follow-up data collection (week 9). By the end of the intervention (week 32) the control group had a further four withdrawals for a final sample of 48 (77.4% of initial sample). The intervention group had a further one withdrawal due to an AD diagnosis, which occurred between T3 and T4, following all intervention components for a final sample size of 48 (84.2% of initial sample). The main reasons for loss and withdrawal of participants were unrelated to the study: availability (n=9, 7.6%), loss to follow-up (n=7, 5.9%), and health problems (n=3, 2.5%). The participant flowchart for the study is shown in Figure 1.

[Figure 1 approximately here]

### Compliance

Participants in both groups were able to achieve a high degree of compliance for three of the four components of the prescribed protocol. The compliance rates for both groups can be found in Table 2.

[Table 2 approximately here]

A high level of compliance was achieved by both groups for all four educational modules with 100% completion rates by participants that remained in the study. All scheduled dietitian and exercise physiologist appointments were attended by participants in the intervention group. The only aspect of the protocol where participants did not achieve a high level of compliance was the active component of CE.

**Adherence**

**Mediterranean Diet Adherence**

[Figure 2 approximately here]

The linear mixed models showed that there was a significant group x timepoint interaction for MeDi ($X^2$=16.75, df=3, p<.001). Figure 2 shows that while both groups increased their adherence to the diet over the course of the intervention, the intervention group showed significantly greater adherence than the control group at every follow-up period (T2 intervention:8.45, control:6.64, difference:1.81, t=4.93, p<.001; T3 intervention:9.39, control:7.61, difference:1.79, t=4.81, p<.001; T4 intervention:9.32, control:7.77, difference:1.55, t=4.15, p<.001).

**Cognitive Engagement Adherence**

[Figure 3 approximately here]

Adherence to CE for both groups is shown in Figure 3. There was a significant group x timepoint interaction ($X^2$=9.83, df=3, p=.020). There was no significant difference between groups at the immediate follow-up (T2 intervention:-3.67, control:-3.07, difference:-0.59, t= -0.98, p=.329), but by the 3 month and 6 month follow-ups the intervention group showed significantly greater levels of adherence than the control group (T3 intervention:-4.82,

control:-2.97, difference:-1.85, t=-2.99, p=.003; T4 intervention:-4.75, control:-3.44, difference:-1.31, t=-2.09, p=.038).

### Physical Activity Adherence

[Figure 4 approximately here]

For PA there were significant effects for group ($X^2$=8.26, df=3, p=.004) and timepoint ($X^2$=14.69, df=3, p=.002), but the group x timepoint interaction was not significant ($X^2$=4.48, df=3, p=.211). At the immediate follow-up there was significantly greater adherence for the intervention group, than the control group (T2 intervention:-2.27, control:-1.54, difference:-.73, t=-3.53, p<.001), but this difference was not retained at the final two follow-up periods (T3 intervention:-2.38, control:-1.99, difference:-0.39, t=-1.83, p=.068; T4 intervention:-2.44, control:-2.17, difference:-0.27, t=-1.25, p=.211), as shown in Figure 4.

## Discussion and Implications

Overall, the BBL-CD program was shown to be feasible with high levels of retention, and moderate levels of compliance and adherence.

### Retention

There were high levels of participant retention, with more than 80% of participants remaining in the intervention until the final follow-up. Most participants who withdrew did so during the intervention period (weeks 1-8), citing reasons unrelated to the study. The attrition rates were slightly higher in the control group. The high levels of participant retention demonstrate that the intervention meets the Bowen Feasibility criteria of Acceptability.

### Mediterranean diet

The MeDi aspects of the intervention were very successful in terms of compliance and adherence. All participants completed all prescribed activities. While the adherence to MeDi

increased for both groups, there were significantly higher rates of adherence for the intervention group. This demonstrates that an online MeDi education module is sufficient to increase adherence to MeDi; however significantly greater levels of adherence can be achieved by combining this with individualised dietitian sessions.

Previous studies have acknowledged the challenge of implementing MeDi interventions in non-Mediterranean countries (Hoffman & Gerber, 2013; Martínez-González et al., 2017). One element that is consistently noted as having positive outcomes is one-on-one support with overcoming barriers and maximising adherence (Jeejeebhoy et al., 2017). In a qualitative study, following a MeDi RCT, participants expressed the need for close individualised support (Middleton et al., 2015). Though the FINGER study did not implement a MeDi component, nutritional counselling was found to have the highest rates of compliance among the domains covered by the intervention (Coley et al., 2019). Although nutritional education can improve adherence to certain dietary patterns, the inclusion of an interventionist is usually more effective (de Menezes et al., 2020).

Findings suggest that dietary interventions and more specifically MeDi interventions are feasible in this participant group, and the effects can be enhanced by including an interventionist. In relation to the Bowen Feasibility Framework strong compliance indicates that it was possible to implement the intervention as per the protocol and a significant group x timepoint interaction indicates that the intervention displayed efficacy in changing dietary behaviour.

**Cognitive engagement**

All participants from both groups were able to complete the CE educational module. For the intervention group there was a wide range of compliance for the active component; participants completed an average of only 20% (10.8 hours) of the 54 hours prescribed in the protocol (McMaster et al., 2018). Similar results have been seen with other multidomain

dementia risk reduction studies. In the FINGER trial, the cognitive training component had the lowest compliance with 24.7% of participants completing only two-thirds of the prescribed training. One of the reasons cited was that this component was completed independently by participants with low supervision, similarly to BBL-CD (Coley et al., 2019).

Despite the poor compliance by the intervention group in BBL-CD, there was still a significant increase in adherence to cognitively engaged behaviours relative to the control group, which showed little change over the course of the intervention. Our interpretation of this pattern of results is that passive, online education to increase CE is largely ineffective and that the cognitive training dosage prescribed for the intervention group in the protocol may have exceeded the level required to have an effect; hence low compliance was still sufficient to show increased adherence.

Although there is limited evidence on what level of dosage of cognitive training is required for a positive effect, the amount actually undertaken was similar to the prescribed dose in prior trials. For example, in the ACTIVE trial, 10 hours of computerised speed of processing training resulted in improved levels of instrumental activities of daily living, speed of processing and lower rates of dementia at 10 years post intervention, compared to the comparison conditions (Edwards et al., 2016; Rebok et al., 2014).

A systematic review of brain training in older, cognitively normal participants found that individual home-based training was far less effective than supervised group based training, citing low levels of participant compliance and adherence as potential reasons (Lampit et al., 2014). Some research has indicated that cognitive outcomes from combined physical and cognitive training show a dose dependent effect, so maximising compliance and adherence is of considerable importance and interest (Bamidis et al., 2015).

Viewed through the feasibility framework lens, low compliance is indicative of ineffective implementation for this aspect of the intervention. However, the significant interaction effect indicates that the intervention did display efficacy to change CE behaviour for the intervention group. Drawing on previous literature and these outcomes, a more directly supervised or group intervention for CE may be beneficial.

**Physical activity**

Strong compliance was seen for the educational components for PA for both groups. Participants in the intervention group did comply with the revised protocol. In terms of adherence, for unknown reasons the control group experienced a dramatic reduction in PA at immediate follow-up, before returning to baseline levels. The intervention group showed a small reduction over the same period, but this was much less pronounced. The linear mixed models showed that while there were significant effects of group and timepoint there was not a significant group x timepoint interaction, showing that this aspect of the intervention was ineffective at changing PA behaviours.

The conclusion in light of the other active components is that for PA, neither an online education module nor education combined with a single exercise physiology session were sufficient to achieve increased levels of adherence. Lifestyle interventions with as many as 20 interventionist appointments have been shown to have strong compliance (median compliance >75% of appointments), so additional PA interventionist sessions are likely to be feasible (Jeejeebhoy et al., 2017). Given the adherence achieved in the MeDi component, follow-up interventionist appointments were likely to have led to increased adherence. A meta-analysis by Lemstra and colleagues (2016) looking at PA and dietary interventions found that supervision and support were major determinants of compliance and adherence. A recent RCT which included MeDi, PA, CE and social engagement showed that weekly contact with an interventionist to assess progress, overcome barriers and adjust goals over

time, resulted in significant adherence across all domains relative to controls (H. E. Schwartz et al., 2019). Strong compliance shows the implementation of the PA aspects of this intervention were feasible. Despite this the intervention did not display efficacy to change PA behaviour. From this we can conclude that education with a single exercise physiology appointment is insufficient to change PA behaviours in this participant group.

**Limitations**

One of the primary limitations of this study was that due to the hospitalisation of the exercise physiologist, the original protocol of three PA sessions could not be implemented and was revised to a single session. This may have reduced the adherence to this aspect of the intervention. Additionally, the short follow-up time did not permit the investigation of long-term adherence. No qualitative data to determine reasons for non-compliance and non-adherence were collected. These limitations allow for some improvements to be made to the protocol for any future BBL interventions and also allow for some recommendations to be made for future studies in this area.

**Implications and recommendations:**

These findings on the feasibility of BBL-CD may be helpful in maximising compliance and adherence for other studies. Key recommendations are:

1. Practical, one-on-one sessions are recommended for behaviour change for participants with cognitive decline. Passive education regarding dementia risk factors was less effective than more direct, intensive education.
2. Booster sessions are recommended to maximise and sustain lifestyle change. Further improvements in lifestyle ceased in the absence of further education.
3. Future research should include qualitative data collection to investigate barriers and enablers to compliance and adherence.

These recommendations are further elaborated on below.

Firstly, this trial demonstrates that participants experiencing cognitive decline can complete a set of relatively demanding educational modules. However, depending on the topic, education modules may or may not be effective to elicit significant behaviour change. For example, improved levels of adherence were seen in the control group for the MeDi component, but improvements were quite limited in the control group for CE and PA. Much greater levels of adherence and behaviour change can be elicited through one-on-one sessions with an interventionist, provided there are follow-up sessions to assist with implementation and overcoming any barriers encountered. This is consistent with research across all three of the lifestyle domains included in this study (Lampit et al., 2014; Lemstra et al., 2016; J. Schwartz et al., 2019).

A plateauing of adherence for the intervention group was seen across all three domains between timepoints 3 and 4; this demonstrates that even with the greater adherence of one-on-one sessions, behaviour change only continues to take place in the presence of continuing education. “Booster sessions” after the conclusion of the intervention are most likely required to elicit further change and long-term maintenance (Fleig et al., 2013; Lachman et al., 2018). A useful addition to further studies in the area would be qualitative follow-up to determine specific reasons and barriers to limited compliance and adherence in participants that remained in the study.

## Conclusion

In summary, BBL-CD was a multidomain lifestyle intervention which was successful in its primary aims of reducing lifestyle risk of AD and improving cognition for individuals experiencing SCD and MCI (McMaster et al., 2020). This study builds on these findings by

showing that the intervention protocol was feasible. The intervention was highly acceptable with more than 80% of participants remaining in the study. Both groups were able to achieve 100% compliance with the four educational modules and for the active components, two of the three domains achieved 100% compliance (MeDi and PA), with 20% for the third (CE). For adherence, two of the three domains (MeDi and CE) demonstrated efficacy for behaviour change, while the third did not (PA).

An important finding of this study is that despite undertaking a more demanding program the intervention group achieved similar levels of withdrawals, similar levels of compliance (with the exception of CE) and greater levels of adherence. These results are highly suggestive that in the population of older people with cognitive decline the more intensive approach to lifestyle risk reduction is feasible and has greater efficacy.

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## Tables/Figures

Table 1. Baseline Characteristics and Lifestyle Adherence Behaviours

| | Intervention (n=57) | Control (n=62) |
|---|---|---|
| Age, years | 72.8 (5.3) | 73.3 (5.8) |
| Female | 35 (61.4%) | 38 (61.3%) |
| Education, years | 12.4 (5.3) | 14.0 (5.9) |
| ANU-ADRI Total | 8.3 (10.8) | 10.3 (11.6) |
| ADAS-Cog 11 | 7.5 (3.6) | 7.0 (3.5) |
| Adherence Measures | | |
| MEDAS Score | 6.8 (1.9) | 6.3 (1.9) |
| Cognitive Engagement | -3.4(3.2) | -3.2(3.2) |
| Physical Activity | -2.5(1.1) | -2.1(1.1) |

Note. Adherence measures are least square mean values generated from linear regression models, adjusted for stratification variables. Values in brackets are standard deviations. ANU-ADRI Total score possible range: -14 to 73; ADAS-Cog 11 score possible range: 0 to70; MEDAS score possible range: 0 to 14; cognitive engagement ANU-ADRI score possible range: -7 to 0; and physical activity ANU-ADRI score possible range: -3 to 0.

Table 2. Percentage of Participants completing components of the intervention

| | Educational Components | Active Components | | |
|---|---|---|---|---|
| | All Modules | Mediterranean Diet | Cognitive Engagement | Physical Activity |
| Control n=52 (n=62) | 100% (83.9%) | - | - | - |
| Intervention n=49 (n=57) | 100% (86.0%) | 100% (86.0%) | 20.0% (19.2%) | 100% (86.0%) |

Note. Numbers and percentages without brackets refer to only participants who remained in the study until all intervention components were completed. Numbers and percentages within brackets refer to all participants who were randomised to that group (i.e., including participants who withdrew from the intervention).

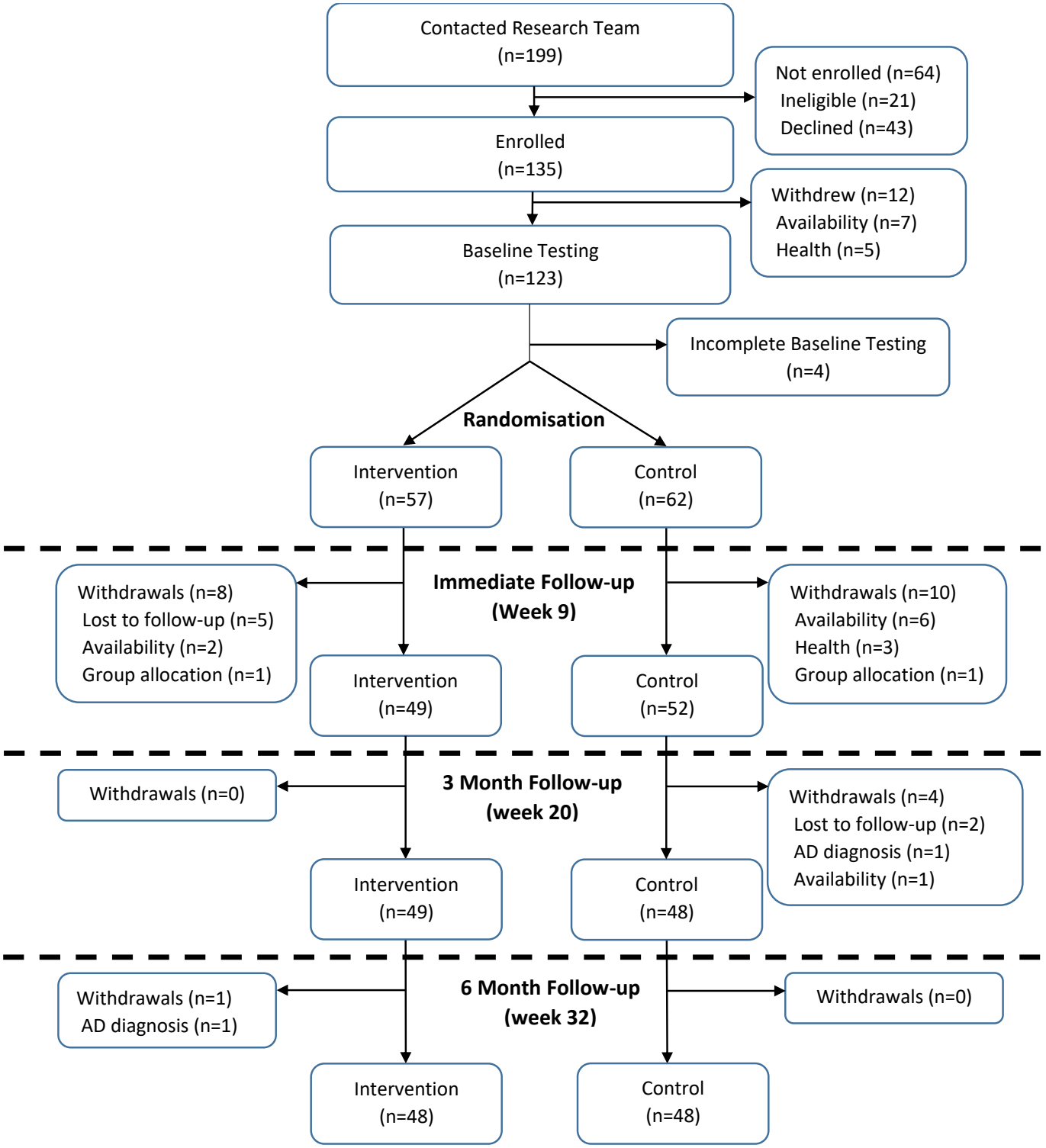


Figure 1. Participant flowchart for BBL-CD study.
Lost to follow-up: These participants could not be contacted/did not respond. Availability: These participants formally withdrew due to other commitments. Group allocation: These participants formally withdrew due to the group they were randomised to. Adapted from "Lifestyle Risk Factors and Cognitive Outcomes from the Multidomain Dementia Risk Reduction Randomized Controlled Trial, Body Brain Life for Cognitive Decline (BBL-CD)" by M. McMaster et al., 2020, *Journal of the American Geriatrics Society*, *68*,(11), 2629-2637.

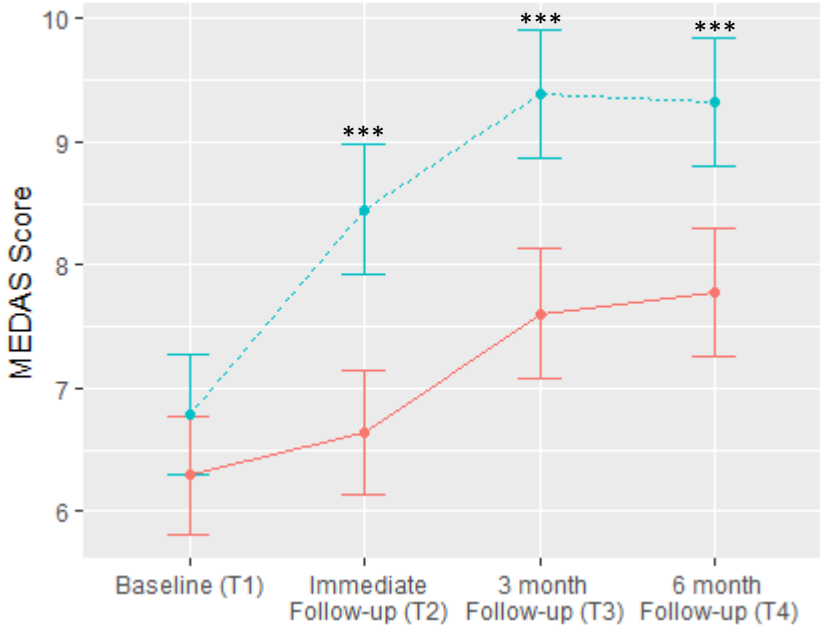


Figure 2. Mediterranean Diet Adherence.
Adherence to MeDi is scored from 0 to 14 with higher scores indicating greater adherence to the diet. The intervention group are represented by the dashed blue line and the control group are represented by the solid red line. Between-group significance denoted by *** p<.001.
Abbreviation: MEDAS, Mediterranean Diet Adherence Screener.

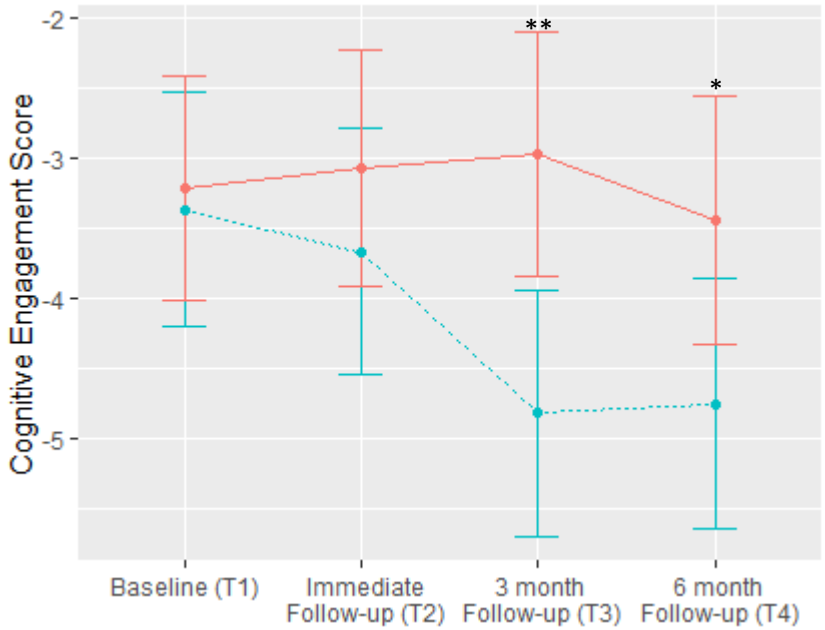


Figure 3. Cognitive Engagement Adherence.

CE is scored between 0 and -7 with lower scores indicating higher adherence to CE requirements (i.e., lower lifestyle risk). The intervention group are represented by the dashed blue line and the control group are represented by the solid red line. Between-group significance denoted by * $p < .05$ and ** $p < .01$

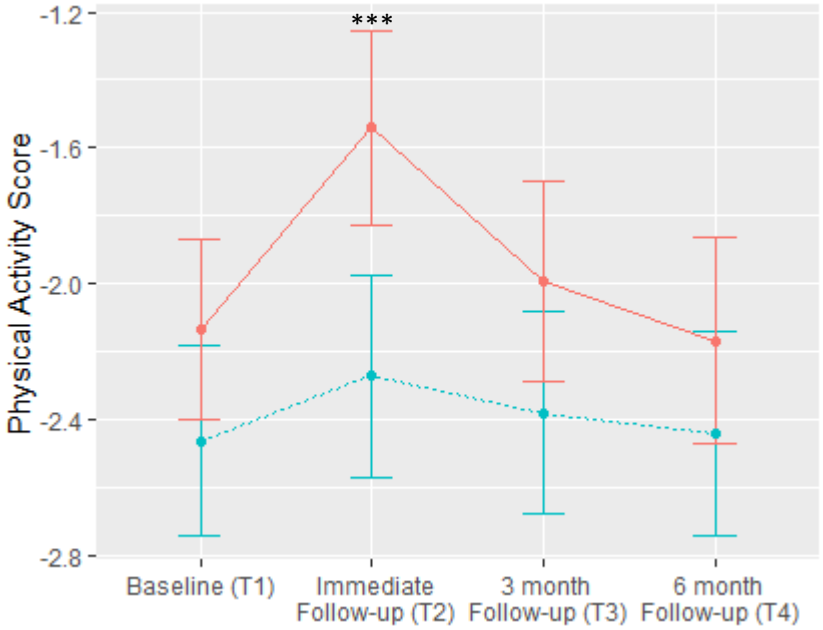


Figure 4. Physical Activity Adherence.

PA adherence is scored between 0 and -3 with lower scores indicating higher adherence (i.e., lower lifestyle risk. The intervention group are represented by the dashed blue line and the control group are represented by the solid red line. Between-group significance denoted by *** indicates $p < .001$

# Chapter 6

## 6.1 Conclusion

The aim of this thesis was to evaluate the efficacy and feasibility of a multidomain dementia risk reduction intervention for people experiencing cognitive decline. As there is limited robust evidence in this area, the study was conducted as a proof-of-concept trial. The approach that was taken to design this study was to adapt a previously successful AD lifestyle risk reduction intervention for cognitively normal individuals, to a participant group experiencing cognitive decline and add additional intervention components from other successful primary and secondary prevention interventions. The primary outcomes of the intervention were lifestyle risk factors for dementia and cognition and the interrelationship between these two variables when lifestyle risk was decreased was of special interest. Another essential consideration in developing interventions is the feasibility of the intervention, with this participant group the acceptability, implementation, and efficacy to change behaviour were examined using the Bowen Feasibility Framework. The last area which was explored were the HRQoL aspects, these relate to how the participants subjectively rated their quality of life based on the health changes that occurred as a result of the intervention. As multidomain lifestyle interventions are an under-explored area, this thesis did lead to a number of important findings which do add to knowledge in this growing area.

## 6.2 Summary of Main Findings

### 6.2.1 Lifestyle risk

Overall, BBL-CD was able to significantly improve the levels of lifestyle risk of AD, successfully meeting research objective 1, as covered in Chapter 3. This finding is consistent with other NPIs in different populations [1-3]. While other NPIs have been run in the SCD group these have not specifically measured the levels of lifestyle risk factors, so this is a novel finding. In BBL-CD, a secondary analysis of reductions in lifestyle risk for AD showed that reductions were due to increases in protective factors, whereas there was no difference between groups in the levels of risk factors, a finding that replicates other similar studies in different populations [1, 3]. An ITT analysis which controlled for missing data was

performed on these outcomes and they were found to be highly robust with all between-group differences found at specific timepoints retained. This suggests that results are demonstrating a true effect and are not related to selective attrition of participants over the course of the trial.

### 6.2.2 Cognition

Research objective 2 was also achieved in Chapter 3 in which cognition also showed improvements, specifically in the domains of global cognition and SDMT. The primary analyses looked at global cognition as a composite of five cognitive tests, which showed a consistent improvement over the two follow-up time points for the intervention group compared to the control group. When the measures which made up the composite were examined individually, only SDMT showed the interaction required to demonstrate efficacy. Making sense of this pattern of results is easier when the nonsignificant cognitive outcomes are also considered. In all five cognitive measures the intervention group improved over the course of the intervention, whereas this only occurred for the control group in two of the five measures (ADAS-Cog 11 and category fluency), showing minor declines in the remaining 3 measures. Hence, combining these measures together provides a clearer single measure of the overall cognitive trajectories of both groups, seen in the significant global cognition outcomes obtained.

### 6.2.3. Combination of Lifestyle Risk and Cognitive Outcome Measures

The most important finding for the BBL-CD project is the link that statistically significant and clinically meaningful reductions in overall lifestyle risk and significant improvements in cognition, namely global cognition, and processing speed. This relationship was only seen for the intervention group, as the control group did not show any meaningful changes in lifestyle risk or cognition. This finding demonstrates success for the primary objectives of demonstrating efficacy of secondary risk reduction interventions to improve lifestyle risk for AD and cognition, at least in the short term. To date the evidence for multidomain lifestyle interventions while generally positive, is quite limited [4-6]. Results support the broader hypothesis that the brain still retains sufficient neuroplasticity that with the right forms of intervention, there can be improvements for people with SCD and MCI. While the ultimate goal of long-term improvements to lifestyle risk, cognition, and a reduction in the rates of dementia is beyond the scope of this study, the findings do warrant the conduct of a longer, larger study.

### 6.2.4. Feasibility

Research objective 3, to examine the feasibility of the intervention, was fulfilled by exploring the feasibility aspects of the BBL-CD intervention in Chapter 4. This paper examined acceptability of the intervention, effectiveness of the implementation, and the efficacy of the intervention to change participant's lifestyle behaviours, three aspects of feasibility recommended by the Bowen Feasibility Framework. In sum, the intervention was shown to be feasible and some possible areas for improvements were highlighted. The intervention was shown to be acceptable through a high participant retention rate of 80.7%. Compliance to the protocol was strong for most aspects with all participants completing the educational components, the MeDi sessions with the dietitian, and PA session with the exercise physiologist, with only 20% compliance for the CE components. In terms of efficacy to change lifestyle behaviours, the domains of diet and CE both showed significant improvements in adherence, whereas very little difference was seen in PA behaviours. Our interpretation of these outcomes is that the dose of CE prescribed in the protocol exceeded the level needed to score as a highly cognitively engaged lifestyle. So even though the compliance was low, there was a significant improvement in behaviour. With PA, there was 100% compliance with the revised protocol, but one session with the exercise physiologist was insufficient to result in significantly improve PA behaviours.

### 6.2.5. Health Related Quality of Life

Chapter 5 met research objective 4 by detailing the HRQoL aspects of the BBL-CD intervention. It is important for all medical and health interventions to report on broader outcomes beyond the primary outcomes; A secondary outcome measure of BBL-CD was HRQoL. No significant group x timepoint interactions were found for any SF-36 domains or SF-6D dimensions, so it is not possible to conclude that there was a significant effect of the intervention on HRQoL. However, examining the outcomes more closely revealed that they were several findings which indicated that there may have been an effect, but this could not be shown to be significant due to insufficient power and too brief a follow-up period for the full effects of the intervention to be demonstrated. This lag in effect has been noted in cognitive outcomes for non-pharmacological interventions [6]. Despite non-significant group x timepoint interactions, at the final follow-up period there were significant between-group differences for one of the

SF-36 domains (Mental Health) and three SF-6D dimensions (Mental Health, Role Limitation and Vitality) albeit contradictory; when examining the change in HRQoL ratings from baseline to the final follow-up there were some statistically significant differences (Vitality and General Health); and other within-group changes while not statistically significant, met the criteria for clinical significance (>3 point change) (Physical Health, Role Limitations due to Emotional Problems, Social Function & Vitality) [7]. Future research which is adequately powered needs to further investigate these potential effects.

The HRQoL trends observed also fit logically with the improvements in lifestyle risk and cognition. The only two SF-36 domains to show significant with-in group improvements from baseline to the final follow-up were Vitality (+4.34, p=.022) and General Health (+4.80, p=.002) for the intervention group; the two domains most likely to be affected by improvements in lifestyle. Overall, there were no significant within-group changes for the control group for any domains, consistent with no significant changes in lifestyle or cognition. One domain which could reasonably be expected to be associated with cognition is mental health. The links between mental health symptoms such as depression and apathy and cognition in older adults are well documented [8]. For the intervention group, the SF-36 showed a significant between group difference at the final follow-up (+7.19, p=.013) in keeping with the improved cognitive outcomes. For the SF-6D, the Mental Health dimension showed a between-group difference due to a decline in the interventions group (-0.19) compared to neutral results seen for the control group (+0.01) over the course of the intervention. While the declines in mental health scores does not full fit with the positive cognitive outcomes observed in BBL-CD, the FINGER trial also showed improvements in cognition coupled with declines in mental health domains of HRQoL for the intervention group [9, 10]. The HRQoL effects of multidomain lifestyle interventions are yet to be fully understood, one possible explanation is that while multidomain lifestyle interventions may result in improvements in lifestyle and objective measures of cognition, they may negative impacts on mental health due to considerable effort required to modify one's behaviour. These paradoxical mental health aspects of HRQoL require further exploration with well-powered studies.

## 6.3. Comparison of BBL-CD Findings with Other Multidomain Trials

The outcomes obtained in BBL-CD are broadly consistent with what has been found in multidomain interventions in the SCD and MCI populations in terms of lifestyle and cognition. While there are some differences between findings from interventions including individuals with SCD, MCI and normal cognition, there are also some consistencies that can be observed. Less evidence has been published on feasibility and HRQoL outcomes in cognitive decline groups, hence the outcomes from BBL-CD add to these areas with preliminary findings, as well as further questions for future exploration. Parallels and differences between the outcomes obtained in BBL-CD and the current literature will now be explored.

### 6.3.1. Lifestyle Risk of Dementia and Alzheimer's Disease

Systematic reviews looking at NPIs for dementia prevention and dementia risk reduction do support the efficacy of these interventions to improve cognition and cognitive decline [11, 12]. One review by Wang et al. [13] used a Bayesian network approach, of the six forms of NPIs included, cognitive stimulation, PA and multidomain interventions were rated as the most likely to have an effect on cognition (diet interventions were not included).

Most studies which take a similar approach to BBL-CD by aiming to reduce lifestyle risk of dementia, fail to adequately report on the effects in risk factors, instead reporting on cognition. While cognition is a very important outcome, failing to report on the direct target of lifestyle risk reduction fails to conclusively link the intervention to the outcomes observed. All interventions within the BBL suite of studies have included the ANU-ADRI as a primary outcome measure, hence are able to accurately demonstrate efficacy to reduce lifestyle risk. The first BBL study was focused on middle aged people with higher lifestyle risk and was able to show a clinically and statistically significant reduction in lifestyle risk (-2.6 points)[14]; The BBL-GP study included adults of any age with chronic health conditions and showed a significant between group reduction of lifestyle risk (-4.6 points)[2]; and BBL-CD achieved significant reductions of a similar magnitude to the first BBL study (-2.7 points)[15]. It is important to note that in the first BBL study, the reductions in overall lifestyle risk scores were primarily due to increases in protective factors, much like in BBL-CD (BBL-GP did not break ANU-ADRI scores down into protective

versus risk factor scores). A similar pattern of significant improvements in only protective factors were seen in a pilot, multidomain dementia risk reduction study conducted by Park et al. [3].

Evidence to date suggests that passive education on lifestyle change is insufficient in the cognitive decline group, whereas passive education (e.g. an online course on diet) supplemented with practical assistance (e.g. a dietitian session) can result in positive outcomes. Some studies aiming to modify lifestyle through multidomain educational interventions have been shown to be effective in cognitively normal participants, such as the original BBL [1] and the Keep Your Brain Fit interventions [16]. Similar interventions fail to achieve significant outcomes with participants experiencing cognitive decline, for example the eMIND intervention [17], which despite demonstrating feasibility and including a slightly larger sample size than BBL-CD, did not achieve improvements in lifestyle or cognition. These results are supported by an absence of effect for lifestyle and cognition for the control group in BBL-CD who received passive education on how to reduce lifestyle risk factors, with no practical assistance to implement this knowledge [15]. The reasons for educational interventions not showing significant effects in individuals experiencing cognitive decline may be related to minor deficits in memory hampering learning of relevant knowledge, or deficits in executive function impairing participants' ability to adequately plan and monitor their behaviour, as cognitively normal participants can. These findings have important implications for future interventional work and public health interventions with this population.

### 6.3.2. Cognition

Systematic review literature in the area is generally supportive of improvements in cognition from these interventions, there is however heterogeneity in the domains reporting these improvements [5, 6, 18]. Improvements in global cognition [18, 19] have been reported for multidomain interventions and while processing speed has not, improvements in processing speed have been shown in single domain NPIs, such as the ACTIVE trial [20]. The speed of processing intervention in the ACTIVE trial was the basis for development of the Double Decision task, employed in the CE intervention in BBL-CD [21, 22].

The largest multidomain RCT in the SCD population was the study conducted by Barnes et al. [23], a four-armed factorial RCT with n=126 participants. While global cognition did improve significantly over time, a significant difference between groups was not able to be demonstrated. A limitation of the design of this study was the inclusion of four intervention arms which reduces the power to show a difference between groups, when compared to a two-armed, intervention versus control comparison. Subsequent research has demonstrated the small effect size of the potential outcomes, for example d=0.22 (averaged effect size of NPIs on objective cognition [6]) similar figures are obtained in other populations, such as z=0.20 for global cognition in the FINGER trial including cognitively normal older participants [9]. Both figures are similar to the effect size obtained in BBL-CD, z=0.25 [15]. Future studies in the area need to account for the small effect size of outcomes with adequate sample sizes.

Some previous research has postulated that multidomain interventions must be sufficiently intensive to result in positive outcomes, the differences in outcomes observed between the control and intervention groups of BBL-CD are in line with this assertion. An example of this is The Multidomain Alzheimer's Preventive Trial (MAPT) [24], evaluating a multidomain intervention comprising group sessions involving 60 minutes of cognitive training, 45 minutes of physical activity demonstrations, and 15 minutes of nutritional advice. These 2-hour sessions were conducted twice weekly for the first month of the study, weekly in the second month, and one-hour sessions monthly for the remainder of the trial. The trial was a four-arm intervention (multidomain intervention + omega 3, multidomain intervention + placebo pill, omega 3 alone and a control condition of placebo pill alone) including 1680 participants, conducted over 3 years. Across 16 outcomes measures, for each of the three intervention groups (i.e., 48 comparisons) the only outcome was significantly less decline in MMSE items related to orientation for the multidomain intervention + omega 3 group, compared to the control condition. The authors noted that one of the limitations of the study was a low initial intensity of intervention which further decreased over the duration of the study. Similar results were obtained by a study by Bae et al. [25] in which participants with MCI were randomised to an intervention group which completed a 90-minute physical (e.g. walking or strength training), social (e.g. socializing or visiting a cafe) or cognitive activity (e.g. visiting a library or playing a game), twice weekly, or a control group which attended two, 90-minuted health education

classes over the course of the 24-week intervention. Outcomes were that the intervention group's MVPA declined significantly less than the control group, and spatial working memory moderately increased compared to the control group's decline. The authors concluded that the interventions prescribed where not sufficiently intense enough to improve any fitness measures and only moderately improve one of the cognitive measures. The same appears to be true for the cognitively normal population, as seen in FINGER [9]. In BBL-CD interventions were initially prescribed at a level appropriate to the participant and were increased as needed to ensure that constant effort was required. This seems to be an important element of successful multidomain interventions.

### 6.3.3. Feasibility

While it is important to be able to demonstrate efficacy to reduce lifestyle risk factors for dementia, it is also important to demonstrate the feasibility of interventions. Few studies look at both outcomes, but both elements were explored in BBL-CD. Some other studies focused on the cognitive decline population have looked at the feasibility of risk reduction interventions in this group. The Brain Health Champion Study [26] was a pilot trial with a mixed participant group comprising SCD (n=4), MCI (n=21) and early AD (n=12). Primary outcomes were adherence to PA, MeDi and social/cognitive engagement interventions, all of which significantly increased for the intervention group. Overall, the results are similar to those obtained for BBL-CD, which also achieved significant increases in adherence to MeDi and CE (with the PA intervention requiring unplanned modifications due to the interventionist being hospitalised). Results are broadly consistent with other participant groups as well, the FINGER trial classified participants as adherent/non-adherent if they attended ≥50% of intervention appointments [27]. Adherence rates were: 90% for nutrition sessions; 60% for PA; and 47% for CE. These results are not directly comparable to BBL-CD compliance rates which used an average percentage of protocol requirements completed but give a similar sense of adherence/compliance: 100% for MeDi sessions; 100% for PA sessions; and 20% for CE sessions. Interestingly, while BBL-CD and FINGER showed the highest increases in adherence for the dietary intervention components, for the Brain Health Champion study the dietary component of the intervention showed the lowest increase in adherence of the three domains. Commonalities between these studies are that practical sessions involving direct interaction

with an interventionist (face-to-face or over the phone) have much greater levels of adherence than self-directed, home-based training.

### 6.3.4. Health-Related Quality of Life

One of the most common ways to evaluate cost-benefits of health interventions is to look at HRQoL. Unfortunately, few studies in the dementia risk reduction area include these outcomes, or if included, fail to report on these [28]. While BBL-CD did include HRQoL outcomes, there were no significant group x timepoint interactions, that are required to show efficacy, so it is not possible to conclude that there were effects on HRQoL. While lifestyle change had plateaued by the 3-month and final, 6-month follow-up timepoint, cognition had still been increasing up to the final follow-up timepoint so it is possible that there may have been positive effects with a longer follow-up period [6]. Despite the absence of significant outcomes using linear mixed models, significant between-group and within-group differences were observed at the final follow-up and the magnitude of differences were suggestive of possible effects. Potential positive effects were noted for the domains of: Role Limitations due to Physical Health, Role Limitations due to Emotional Problems, Mental Health, Social Function, Vitality, General Health and Health Change; positive effects for the SF-6D dimension of Role Limitation and some contradictory results with potentially negative effects of the dimensions of Mental Health and Vitality. A longer trial with greater power may be able to confirm and clarify these effects. The FINGER study evaluated HRQoL using the same HRQoL outcome measure as BBL-CD (SF-36) and found significant improvements in General Health and significantly less decline in Physical Function for the intervention group, relative to the control group [10].

One concerning potential outcome of multidomain lifestyle interventions is a decrease in some HRQoL domains. While this is not confirmed to be a consistent outcome, reductions did occur in both the BBL-CD and FINGER trials. For BBL-CD, a reduction in Mental Health score for the intervention group resulted in a significant difference between groups at the final follow-up. Whereas for FINGER, reductions occurred for all domains, for both groups except General Health which increased for the intervention group. Significant within-group declines were seen for the intervention group for the domain of Physical Function, and for the control group in Physical Function, Role Limitations due to Physical Health, Vitality,

Social Function, and General Health [10]. Future trials should be mindful of potential reductions in HRQoL, it is possible the while lifestyle interventions may benefit overall health, they may have negative impacts in other areas of life. BBL-CD appears to show this association in the short-term (e.g., less than 1 year) and the FINGER trial appears to show this in the medium term (e.g., at 2 years post intervention), but whether these outcomes occur in other similarly intensive multidomain trials or persist in the long-term once lifestyle change is no longer actively occurring is of research interest.

# Strengths and Limitations

## 6.4. Strengths

### 6.4.1 Innovative Design

BBL-CD did have an innovative design as it adapted a pre-existing, successful primary prevention intervention [1] to a secondary prevention purpose by incorporating elements of previously successful NPI interventions: MeDi and it's measurement from the PREDIMED study [29, 30]; computerised speed of processing training, similar to that used in the ACTIVE trial [20, 31]; and passive education on lifestyle risk factors coupled with active interventions for diet and lifestyle similar to the intervention model used in the preceding BBL-GP [2, 32]. While the combination of MeDi, CE and PA have been trialled in other participant groups previously, this combination of factors has never before been implemented with the SCD group. BBL-CD identified a significant knowledge gap in the effects that multidomain lifestyle interventions could have to reduce risk factors and improve cognition, with the ultimate aim of reducing incidence of AD and dementia. Most NPIs for dementia risk reduction focus on a single risk factor in isolation, however AD and dementia are conditions with multiple risk factors. Hence for an intervention to be efficacious necessitates the inclusion of multiple risk factors [33, 34]. While this approach undoubtedly increases the complexity of the intervention, it does broaden the utility and is likely to have greater benefits for overall risk reduction for the community. Many authors have commented that multidomain interventions were the most logical given the multifactorial nature of dementia aetiology [5, 34-41], and that secondary prevention of cognitive decline and dementia are an under researched area holding much promise [5, 6, 18, 38, 41-45].

### 6.4.2. Robust Methodology

One key strength of BBL-CD compared to previous multidomain lifestyle interventions for the SCD population is the robustness of the research design. While some RCTs have been run to look at lifestyle and multidomain NPIs [23, 46] these have been small (n<40 per intervention arm) meaning they are underpowered to detect the full scope of cognitive outcomes. This study ran a power analysis to determine the required sample size at the final follow-up period, based on the effect size of previous research. The power calculation was based on predicted magnitude of change in the primary outcome measures, ANU-ADRI, which showed a significant outcome, and ADAS-Cog which did not show a significant outcome. The power was sufficient to show significant outcomes for other cognitive measures: SDMT and global cognition. A sensitivity analysis was conducted to further explore the primary outcomes found. To account for missing data through attrition of participants, which occurs in all interventions of this type, a full ITT was conducted. Missing data were accounted for using multiple imputation by chained equations (MICE) [47], the results demonstrated that all significant between-group differences were retained for all timepoints across all variables, indicating the outcomes were highly robust. This consistency between the primary and sensitivity analyses strengthens the credibility of the conclusions. A follow-up to the sensitivity analysis was to determine if there were any significant differences between those who withdrew from the intervention and those who remained in the study. It was found that these groups only differed on one of the variables of interest. This variable was protective lifestyle factors which was significantly lower for control participants who remained in the intervention, compared to those who withdrew. Given that the intervention group had a greater reduction in risk, the net effect of this may have been to artificially lower the control group's score to appear to have lower risk, thereby reducing the magnitude of the differences observed between the groups. These differences do not impact the overall conclusions drawn from the study. In addition to the primary outcomes of lifestyle risk of AD and cognition, BBL-CD also evaluated feasibility aspects of the project. This is an important component of proof-of-concept work as it guides any further extensions of the research and also provides useful knowledge for other researchers in the area.

### 6.4.3. Choice of Outcome Measures

An additional key strength of BBL-CD was the choice of outcome variables. The variables chosen were shown to be sensitive to the outcomes in these types of interventions, and in combination made it possible to demonstrate that changes in lifestyle would have benefits for cognition.

For lifestyle risk factors for AD the ANU-ADRI [48] was chosen for several reasons. The ANU-ADRI allowed broad coverage of 11 lifestyle risk factors and four protective factors, covering all the risk factors that were addressed in the educational modules, including PA, CE, and some aspects of MeDi. The ANU-ADRI provides three outcome measures: one comprising lifestyle protective factors for AD; lifestyle risk factors; and a total score combining both protective and risk factors. The weighting of each individual factor is based on odds-ratios derived from the literature and the index has been validated in three, large international cohorts as predictive of incident dementia [49]. The ANU-ADRI was the primary outcomes measure for the previous BBL studies, so this allowed generalisability with previous studies in this broader program of research.

The cognitive measure chosen was the ADAS-Cog Plus, which comprises the standard ADAS-Cog with some additional measures to increase the sensitivity to the deficits seen in SCD and MCI [50]. The ADAS-Cog is one of the most widely used cognitive tests with items covering: word recall and recognition, word finding difficulty, naming everyday objects and fingers, following simple commands, constructional and ideational praxis, orientation, and language production and comprehension [51]. The additional measures added to form the ADAS-Cog Plus are: Pfeffer Functional Activities Questionnaire (PFAQ) to measure IADLs [52]; Symbol Digit Modalities Test (SDMT) as a measure of processing speed and working memory [53]; Trail Making Test-B (TMT-B) which measures executive control, attention and visual scanning [54]; and Category Fluency for vegetables to evaluate executive retrieval and semantic memory [55]. This comprehensive cognitive battery was summarised into a single global cognition score by scoring all measures positively and converting to z-scores.

Few research studies include measures of the effect that the intervention has on the risk factor or factors in question, as well as cognition. For example, the FINGER study demonstrated improvements

in cognition but failed to report on the change in lifestyle variables [9], while the Brain Health Champion Study showed improvements in lifestyle, but did not test any cognitive outcomes [26]. The inclusion of both variables is an important factor, if only one of these outcomes is measured, there is no certainty that the improvements in lifestyle lead to cognitive improvements or that cognitive improvements are the results of improved lifestyle. If both are measured, an improvement in only one outcome shows that the effects are likely not linked, an improvement in both outcomes adds weight to the argument that improvements in lifestyle lead to improvements in cognition. Consistent verification of the association between these two variables is critical for moving this area of research forward. In BBL-CD, showing that the control group did not change their lifestyle risk profile and did not change their cognition was contrasted with the intervention group who were able to significantly improve lifestyle risk and improve cognition. This was a clear strength in BBL-CD.

An important secondary outcome that was also reported on was HRQoL for the study. In the WHO Dementia Risk Reduction Guidelines, [28] HRQoL is listed as an important outcome of interest for all intervention types reviewed, however there was no or low levels of evidence for QoL and HRQoL for most of the factors reviewed, indicating that very few studies are actually measuring or reporting on these variables. QoL and HRQoL outcomes are important as they are direct measures of whether participants believe interventions have improved (or worsened) different aspects of their lives, which has strong implications for whether interventions are considered to be working and whether participants will adhere to these interventions long-term.

## 6.5. Limitations

### 6.5.1. Proof of Concept Study

The primary limitation of BBL-CD was that due to the paucity of research in the area it was a proof of concept trial. Hence by design, it was not a large or a long trial which must be considered when evaluating the outcomes achieved. A power analysis was conducted to determine the sample size, but this was for the ANU-ADRI and ADAS-Cog. As a result, the trial was not powered to evaluate the outcomes of all five cognitive measures, nor was their sufficient power to fully evaluate the HRQoL outcomes.

### 6.5.2. Lack of Diversity in Sample

Another important limitation is a lack of racial, social, and cultural diversity in the sample, which may limit the generalisability of the findings. This was entirely a product of the demography of Canberra, rather than any specific aspects of the trial or recruitment. The population of Canberra is predominantly European Australians , with high levels of education and high socio-economic status [56]. Encouragingly, meta-analyses comprising more diverse samples are broadly in line with these outcomes, however it is still important to replicate these findings in other racial, social, and cultural groups.

## Directions for Future Work

While the BBL-CD intervention was successful, the study was a proof-of-concept trial, hence the results require further validation. There are a few methodological changes that would be beneficial in a further BBL trial with this participant group. Additionally, the results give rise to some directions for future research in this area more broadly.

## 6.6. Future BBL trial

### 6.6.1. Duration and Sample Size

Two of the primary limitations outlined above were the length and sample size of the trial. BBL-CD was conducted over a total duration of approximately eight months (2 months of intervention and 6 month post-intervention follow-up). Systematic reviews identify two aspects of duration as an important consideration in designing interventions. Firstly, longer intervention periods may lead to greater improvements and these outcomes may be longer lasting [57]. Second, a follow-up period of a year or longer is recommended [6]. This is due to the fact that there may be a lag of months or even years for intervention outcomes to become fully apparent and this may be true for lifestyle, as well as cognitive outcomes. The other important limitation identified was sample size. Despite a power analysis being conducted prior to running BBL-CD, it was found that there was inadequate power to fully explore some of the outcomes. While positive results could be shown for a global cognitive composite, improvements could only be shown on one of the five individual cognitive measures, despite improvements occurring for all measures for the intervention group. Greater power would also help to further explain the effects

on HRQoL; these results were not able to demonstrate efficacy, but significant between- and within-group differences and the magnitude of these differences are possible indications of an effect. These outcomes warrant further exploration with a larger sample to provide greater power. A trial of longer duration will also be associated with greater attrition of participants, so sample size would also need to account for this.

### 6.6.2. Sustainability of Lifestyle Improvements

One issue of note was that there was a plateauing of lifestyle change for the domains of MeDi, PA and CE between the 3- and 6-month follow-ups. It appears that regardless of the level of change that had occurred in each of the domains prior to the 3-month follow-up, there was very little change after this point. This is a curious finding as the amount of intervention received during the 3- to 6-month follow-up period differed between each of the domains. For example, for MeDi there was a final session with the dietitian during this period and despite the strong increases in adherence following the first two sessions, this third session led to very little additional change. While there was little effect on PA, the CE variable showed a similar pattern, after two successive periods of improvement there was a maintenance in the level of adherence, despite no difference in the levels of intervention since the introduction of CE in the 4th week of the study. Other multidomain and exercise interventions show this similar pattern of plateauing followed by reductions in adherence at longer follow-up intervals [58]. One way to combat this would be booster sessions to maximise lifestyle change and sustain these changes long-term [59, 60]. Interventions with booster sessions have been trialled in multidomain NPIs with promising results. For example, in the BBL-GP study [2], which used a similar intervention and primary outcome measure to BBL-CD, analyses on lifestyle risk were able to show that improvements were apparent from immediate follow-up at 12 weeks and these significant differences were maintained until the final follow-up at 62 weeks, relative to controls. BBL-GP did include one motivational phone call at week 52 to promote sustained changes in lifestyle. Motivational phone calls could easily be incorporated into any future BBL-CD study to determine if these calls are sufficient to achieve long-lasting effects. Even more intensive follow-up leads to greater adherence, the Brain Health Champion study [26] was a multidomain lifestyle intervention comprising MeDi, PA and cognitive/social domains and involved weekly motivational

interviewing for people with SCD, MCI or early stage dementia. The intervention achieved very strong improvements in healthy lifestyle behaviours in the three domains (Cohen's d=0.87 (large effect) to d=1.37 (very large effect)). However, this intensive approach would prove costly and if the eventual aim is to design interventions that could be rolled out and scaled up to the community level, an approach such as this may not be feasible.

### 6.6.3. Sustainability of Cognitive Improvements

Much like with lifestyle risk, significant improvements in cognition are an important finding in this research group. However, two important gaps in the research knowledge are the longevity of these improvements and whether improvements lead to lower rates of incident dementia in this participant group.

While the sustainability of changes in lifestyle risk were already discussed, it is possible that cognitive outcomes may react differently. This was already seen in the BBL-CD results, while lifestyle risk improved initially it plateaued between the 3- and 6-month follow-ups, global cognition improved almost linearly, from baseline to the 3-month follow-up and again between the 3- and 6-month follow-ups. A systematic review by Smart et al. [6] does suggest that cognitive improvements may take time to become fully apparent so may continue to take place beyond the end of the intervention period. As yet, no one has followed participants in SCD interventions long term to determine whether cognitive improvements are sustained, decline over time or are dependent on further or sustained lifestyle changes, or whether these changes are linked to incident rates of dementia or AD. The ACTIVE Trial [61] was a CE intervention for cognitively normal people over the age of 65, those that took part in the cognitive processing speed arm of intervention were found to have significantly higher levels of speed of processing, IADLs and lower rates of dementia, compared to the control arm of the intervention at 10 years post-intervention [31, 62]. So sustained levels of cognition and lower rates of dementia have been previously found in NPIs for other groups and do warrant long-term investigation in trials for people experiencing cognitive decline. Any future BBL intervention in this group should aim for a longer follow-up and a larger sample size to fully capture and elucidate the lifestyle and cognitive improvements. The trial should also include

methodological elements to increase the sustainability of the intervention such as longer duration and number of sessions in the initial intervention period and booster sessions in the follow-up period.

## 6.7. Recommendations for Future Risk Reduction Trials

### 6.7.1. Participant Group

The evidence obtained in the BBL-CD study supports the conduct of a trial with a larger sample for a longer duration. Given that the sample obtained in BBL-CD consisted of three people with MCI (3%) and 116 people with SCD (97%), the evidence obtained is far more applicable to the SCD population than the MCI population. Hence, any future expanded version of BBL-CD would make most sense to be conducted within the SCD group. However, a key question arising from this is whether these outcomes are possible in the MCI group as well. With the greater levels of neuropathology and objective deficits seen in MCI, a key research question is whether there is still sufficient neuroplasticity to show some improvements. The MCI population may also show greater levels of attrition and less compliance. Systematic review evidence of the effects of NPI for the MCI population [13, 18, 63, 64] are broadly consistent with the effects seen in the SCD population in this trial [15] and other evidence [4-6], so there is reason to pursue further multidomain research in the MCI group.

### 6.7.3. Alternative outcome measures

***Subjective Cognition***

While significant improvements were achieved in objective measures of cognition for global cognition and SDMT in BBL-CD, subjective cognition was not examined. Subjective cognition is an important marker of brain health [65, 66] and has been shown to be related to quality of life [67, 68], hence it is an important outcome measure to include. Interventions in this participant group do characteristically demonstrate small effect sizes in cognitive outcomes [4, 6, 15]. Subjective cognitive measures however, are a more direct measure of whether participants are experiencing real to-day-to benefits in cognition. Outcomes such as this may be indicative of whether people feel that interventions are beneficial and whether adherence to lifestyle modifications are worthwhile in the longer term.

***Amyloidopathy and Tauopathy***

As detailed in the introduction, SCD and MCI show a range of early neuropathological changes, such as the accumulation of amyloid [69-71], tau [70, 72, 73], atrophy of certain brain regions [74-76] and differences in activation [77, 78]. To date there has been limited investigation on the effects that NPIs have on these markers of disease.

To the authors knowledge no NPI study has yet sought to measure differences in amyloid and tau accumulation as an intervention outcome. This remains a major unexplored gap in the literature. In the SCD stage, amyloid is certainly beginning to accumulate in the brain and to a lesser extent tau. The rates of deposition of these pathological features has been shown to be related to likelihood of progressing to AD [79]. Epidemiologically, evidence of lower levels of lifestyle risk and greater levels of cognitive reserve exhibit lower level of neuropathology. What is unclear and largely unstudied is the effect of reducing lifestyle risk factors and promoting neuroplasticity on these neuropathological features, in populations that are beginning to experience cognitive decline. Future intervention should investigate the interrelationships between lifestyle, cognition, and other neuropathological markers.

***Atrophy and Activation***

Some research has looked at the effects of NPIs with other neuroimaging measures. FINGER conducted a diffusion tensor imaging sub-study to look at the effects of the intervention on the integrity to white matter tracts [80]. The results were somewhat inconsistent with the cognitive improvements seen in the primary outcomes paper [9], as the intervention group in addition to improved cognition also appeared to be showing lower levels of white matter integrity. However, FINGER participants were cognitively normal thus were less likely to be exhibiting higher levels of pathological change associated with AD and dementia that could be remediated, so the changes observed through neuroimaging may have been subclinical.

Some PA and CE interventions have demonstrated positive effects on underlying brain structure and function [81, 82]. In one study[83], 100 participants with MCI were randomised into an intervention group which completed two, 90 minute PA sessions per week for 6 months, or an active control group who attended education classes. PA sessions included aerobic exercise, muscle strength training, balance

training and cognition during exercise task. There were no significant group x timepoint interactions for cognitive or neuroimaging measures. A secondary analysis including only the participants with amnestic MCI (n=50) showed significant group x timepoint interactions for MMSE, memory and a reduction in cortical atrophy compared to the control group. For CE, a group of 23 participants with MCI were randomised into a computerised brain training intervention group or a social interaction control group [84]. The main focus of this study was the functional connectivity of the default mode network, a connected network of brain areas located in the medial prefrontal, medial and lateral temporal, and medial and lateral parietal cortices, in which connectivity decreases from SCD though to AD [85, 86]. The intervention group showed increased connectivity with a significant group x timepoint interaction in the left parietal default mode network regions. One study, the SMART trial included participants with MCI and used a factorial design to compare the effects of PA and CE on cognition and neuroimaging outcomes [87]. PA was shown to lead to improved global cognition, increases in grey matter and reversal of white matter hyperintensities (a marker of cerebrovascular damage); and CE was shown to attenuate declines in memory and enhance connectivity between the hippocampus and superior frontal cortex. PA and CE have been shown to have clear benefits for the neuroplastic changes underlying increased atrophy and connectivity in the early stages of dementia. A clear knowledge gap in this area is the effect that multidomain NPIs may have on the atrophy and functional brain measures for people experiencing SCD.

***Rates of Incident AD and Dementia***

The ultimate aim of NPIs in this area is to reduce the number of people progressing on to develop AD and dementia. While BBL-CD was shown to be able to reduce lifestyle risk and to improve cognition, it is still unclear whether maintenance of these improvements would lead to lower rates of incident dementia. There are some difficulties in measuring this outcome, for example demonstration of an effect would take at least 10 years or more. This has been done in some studies such as the ACTIVE trial [31], but it necessitates large samples to account for attrition over time. One uncertainty would be the effect size of benefits but given the small effect size of benefits to lifestyle and cognition it is more than likely that the benefits to dementia may be similarly small. If BBL-CD is shown to have an effect on underlying dementia pathology it is not certain whether this would be to prevent certain individuals from

progressing onto dementia permanently or whether the effect would be to slow the rate of decline and hence delay the onset of the disease. Either outcome would be a tremendous step forward given the current absence of any proven treatments for AD and dementia.

## Conclusion

BBL-CD was shown to have efficacy to reduce lifestyle risk of AD, improve cognition, was feasible in the SCD population and may have some benefits to HRQoL. While the study was a short-term proof of concept trial and cannot demonstrate effectiveness to reduce rates of dementia, it does warrant the conduct of a larger, longer study in the SCD population. More broadly, the results are supportive of the view that secondary prevention of dementia is feasible in this population and constitutes a promising "window of opportunity" to reduce the risk of developing dementia.

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