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"Effects of Adherence to a Mediterranean-style Diet and Healthy Lifestyle on Cognitive Functioning in Independently Living Older Individuals"

By

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Abstract

The world's population is moving into an over 65+ age group. (Mathers, 2013). This 65+ age group is the fastest growing segment with an expected 1.2 billion people worldwide being aged 65 years or over by 2025 (Forette, 2012). In Australia it is estimated that 25% of the population will be 65+ by the year 2030.

The cost of supporting an ageing demographic, particularly with their associated medical requirements, is becoming an ever increasing burden that is predicted to rise in the foreseeable future. The progressive decline in an individual's cognitive ability as they age, particularly with respect to the ever increasing incidence of Alzheimer's disease (AD) and other cognitive complications, is, in many respects, one of the foundations of great concern to all nations. It has been estimated that in 2015, 47 million people around the world were living with various forms of dementia, and this is expected to increase to 85 million by 2030 and potentially 135 million by 2050 (Prince et al., 2016).

There is currently 184,000 Australians living in retirement village accommodation which is predicted to increase to approximately 382,000 by 2025 (Thornton, G et al 2014) The aged care sector in Australia is experiencing an increasing demand for permanent residential aged care, with greater than 50% of permanent residential aged care residents living with dementia (Care, 2017)

Brain ageing occurs over a lifetime and is the progressive and gradual accumulation of potential detrimental changes in structure and function. Furthermore, specific brain structures are the targets of later-life neurodegenerative disorders such as Alzheimer's disease. Cognitive ageing is demonstrated by minor changes in some mental functions such as vocabulary, some numerical skills, and general knowledge, however, other mental capabilities decline from middle age onwards, or even earlier.

As there is currently no available medical intervention available to treat cognitive decline, early intervention through the use of modifiable risk factors is imperative in middle age to prevent the onset of cognitive decline and progression of cognitive decline into mild cognitive impairment and AD.

Previous research has focused on how interventions, such as improving nutritional status and modifying risk factors such as obesity, sedentary lifestyle, hypertension, depression, cardiovascular disease, potentially arterial stiffness, oxidative stress and hyperlipidaemia may be modified by diet (Parrott and Greenwood, 2007a; Mathers, 2013; Dauncey, 2014; Kiefte-De Jong et al., 2014; Vandewoude et al., 2016), and also by physical activity such as exercise or a combination of exercise and or diet (Komulainen et al., 2008; Deary et al., 2009; Komulainen et al., 2010; Rolland et al., 2010; May, 2011; Tarumi et al., 2011; Gorelick, 2018). The impact of how diet and exercise may modify age associated cognitive function was the focus of this thesis.

Table of Contents

List of Key Publications

1. **Roy J. Hardman**, Greg Kennedy, Helen Macpherson, Andrew B. Scholey & Andrew Pipingas

'Adherence to a Mediterranean-style diet and effects on cognition in adults: A qualitative evaluation and systematic review of longitudinal and prospective trials'

Frontiers in Nutrition, 3, 22 (2016). doi: 10.3389/fnut.2016.00022 : Accepted 5 July 2016

2. **Roy J. Hardman**, Greg Kennedy, Helen Macpherson, Andrew B. Scholey & Andrew Pipingas

'A randomised controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition in cognitively healthy older people living independently within aged care facilities: The Lifestyle Intervention in Independent Living Aged Care (LIILAC) study protocol' [ACTRN12614001133628]

Nutrition Journal, 14, 53 (2015). doi 10.1186/s12937-015-0042-z

3. **Roy J. Hardman**, Denny Meyer, Greg Kennedy, Helen Macpherson, Andrew B. Scholey & Andrew Pipingas

'The association between adherence to a Mediterranean style diet and cognition in older people: The impact of medication'

Clinical Nutrition, (2018). doi.org/10.1016/j.clnu.2017.10.015 : Clinical Nutrition 37 (2018) 2156-2165

4. **Roy J**. **Hardman**, Denny Meyer, Greg Kennedy, Helen Macpherson, Andrew B. Scholey & Andrew Pipingas (80% contribution)

'Results of a randomised controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition in cognitively healthy older people living independently within aged care facilities: The Lifestyle Intervention in Independent Living Aged Care (LIILAC)].

Outcomes of the LIILAC trial, currently under review with *Frontiers in Ageing Neuroscience*.

Introduction

Over the past 200 years, human life expectancy has increased by almost 50 years. This change has been observed in both high and low-income countries around the world with populations progressively moving into the 65+ age group. (Mathers, 2013). This age group is the fastest-growing segment of the population with an expected 1.2 billion people worldwide being aged 65 years or over by 2025 (Forette, 2012).

Accordingly, in Australia, it is estimated that the growth of the cohort of persons over 65 years of age will increase over the next 10–20 years. The current population in Australia in the 65+ age group represents 5.5 million people (23.5% of the total population) (Australian Government, 2017). This is important as the ageing process is associated with both physical and cognitive functional loss and can contribute to an increased risk of morbidity and mortality.

The processes associated with age-related chronic disease do not occur over a short period; they are considered to emerge earlier in one's life and are then modulated by the consequence and accumulation of experiences and exposures throughout the life course to become evident in later years (Franco et al., 2009).

The incidence of age-related chronic disease may be associated with a number of factors including one's diet and a sedentary existence, which can also lead to a host of issues such as obesity, high blood pressure, high blood triglycerides, high levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) cholesterol, and insulin resistance. These comorbidities in an ageing population have resulted in an increased incidence of coronary artery disease, diabetes, chronic pain syndrome, inflammatory disease, cardiovascular disease, respiratory disease, end organ damage (Mattson et al., 2004b) and cognitive impairment in an ageing brain (Babio et al., 2014).

Neurocognitive decline across the lifespan has been suggested to affect multiple cognitive faculties. For instance, speed of processing and memory steadily decline from the third decade of life (Peters, 2006) and the speed of retrieval of previously learned spatial locations from short-term memory is reduced by around 50% from the third to the eighth decade of life (Pipingas et al., 2010b). While this slowing of memory retrieval is observed in all individuals and is considered normal age-related cognitive decline, there is considerable inter-subject variability in cognitive trajectories across the lifespan particularly in later life (Christensen,

2003). Importantly, in some cases, normal age-related cognitive decline can progress to mild cognitive impairment (MCI) and dementia (Lipnicki et al., 2013). Alzheimer's disease (AD) is considered the most common cause of dementia, accounting for 60–70% of all dementia cases; vascular dementia is the second most frequent (Fratiglioni et al., 2010). It has been estimated that the risk of AD increases 14-fold in persons aged 65–85 years of age and affects as many as 47% of individuals over the age of 85 (Yankner et al., 2008). Further, it is estimated that by 2040, 85 million older adults worldwide will be living with some form of dementia (Ferri et al., 2005). As a result of late-life cognitive decline, the personal and societal effects of dementia, even in its mildest form, can significantly influence levels of functional dependence (Millan-Calenti et al., 2012).

This is demonstrated through the effect on the burgeoning aged care sector in Australia, with >50% of permanent residential aged care residents living with dementia (Australian Government, 2017). Thus, cognitive decline substantially contributes to the increasing cost of supporting an ageing demographic.

It has been suggested that our individual cognitive trajectories relate to our overall health, and, as such, are considered modifiable (Finch, 2003). Because there is currently no available medical intervention to treat cognitive decline, early intervention through the use of modifiable risk factors is imperative in middle age to prevent the onset of cognitive decline and its progression into MCI. Many risk and protective factors have been identified that determine the cognitive trajectory in an individual, as well as their risk of AD. These modifiable risk factors need to be identified and introduced into easy-to-maintain practical interventions that can be adopted by individuals earlier in their life to potentially prevent or reduce cognitive decline.

The Ageing Brain, Cognitive Ageing and Risk Factors

Brain ageing over a lifetime is identified by the progressive and gradual accumulation of potential detrimental changes in structure and function. These changes in the brain do not occur to the same extent in all brain regions (Peters, 2006; Fratiglioni et al., 2010), indicating possible differential cognitive ageing (Grady, 2012); cognitive ageing is not unitary with specific cognitive functions declining more rapidly than others (Christensen, 2001). Further, specific brain structures are the targets of later-life neurodegenerative disorders such as AD. Subtle brain changes that occur earlier in life may indicate an increased risk for brain disease in later

life and this has challenged researchers to better understand the normal ageing brain in order to identify early signs of insidious neurodegenerative processes (Yankner et al., 2008).

From a physical perspective, age-related changes in the brain can be identified by an overall reduction in brain volume and weight (Anderton, 2002). For example, it is predicted that brain volume decreases at a rate of 5% per decade after the age of 40 years and that this accelerates after 70 years of age (Peters, 2006).

At the micro-anatomical level there are age-related changes in neuron number and neuronal re-organisation although these changes cannot be observed easily *in vivo* in the human brain (Park and Reuter-Lorenz, 2009). At a macro level, the result of longer-term neuronal decay manifests as cortical thinning, changes in grey and white matter and changes in neurotransmitters and neuro-metabolites (Park and Reuter-Lorenz, 2009; Huizinga et al., 2018; Scheller et al., 2018). These changes can be observed *in vivo* to some extent using advanced neuroimaging methods (Burke and Barnes, 2006). It has been demonstrated that gradual neuronal loss occurs with age in the neocortex and with hippocampus and disconnection between brain regions, particularly involving the prefrontal cortex (Burke and Barnes, 2006; Yankner et al., 2008).

Brain morphological changes in the ageing brain can be visualised by magnetic resonance imaging (MRI). MRI has revealed that both white and grey matter decrease in volume over time (Scahill et al., 2003). In particular, the prefrontal cortex, striatum, temporal lobe, cerebellar vermis, cerebellar hemisphere and hippocampus are brain regions that have been found to change (Anderton, 2002; Barnes, 2003). There also appear to be gender differences with regard to brain ageing. For instance, in males, the frontal and temporal lobes are most affected whereas in females, the effects are seen in the hippocampus and parietal lobes (Murphy et al., 1996; Compton et al., 2001).

Ageing is a process that reduces the ability of the brain to regenerate, resulting in a decrease of spine densities and reduced neurogenesis, particularly within the hippocampus, and changes in different neurotransmitter systems resulting in general neural dysfunction (Segovia et al., 2006). There are also shifts in neurotransmitter levels, importantly in those generally considered to relate to working memory and ageing, which are dopamine, serotonin and acetylcholine (Froudist-Walsh et al., 2018). For instance, dopamine levels have been found to decrease by at least 10% per decade from early life, which is considered to be associated with a decline in cognitive and motor skills (Friedman, 2003); whereas decreases in serotonin and

brain-derived neurotrophic factors in the ageing brain are associated with deterioration in the regulation of synaptic plasticity and neurogenesis in the adult brain (Mattson et al., 2004b). Further, acetylcholine declines in the hippocampus and prefrontal cortex, which have been demonstrated to be vulnerable to ageing, have been linked to learning memory and cognitive decline (Hof and Morrison, 2004; Segovia et al., 2006). These changes have been largely observed post-mortem; however, with technological advances, it may be possible to quantify and better understand shifts in neurotransmitter levels with age. This is also important as early shifts in these levels, in particular acetylcholine, may be important for understanding the evolution of early brain disease such as AD.

In addition to these intrinsic brain changes, external factors including cardiovascular functioning, arterial stiffness and central blood pressure impinge on the integrity of the brain (Tadic et al., 2016; Iulita et al., 2018). The normal ageing brain is associated with an increase in central (aortic) arterial stiffness. These changes in central arterial stiffness are caused by the changes in arterial structure and function, with arterial stiffness being found to be a predictor of cognitive decline (Redheuil et al., 2010; Pase et al., 2012).

Increased stiffness of the aorta and carotid arteries can result in reduced capacity to buffer the pulsatile flow that is generated by the heart with every contraction, and hence reduce dampening of blood pressure fluctuations over the cardiac cycle. This reduced dampening can result in continuous rather than pulsatile tissue perfusion in downstream smaller vessels, ultimately limiting oxygen delivery to high-flow organs such as the brain (Pase et al., 2012; Iulita et al., 2018). Recent evidence suggests that increases in central arterial stiffness and pulse pressure are associated with increased microvascular resistance and the incidence of subcortical infarcts (Mitchell et al., 2011; Tarumi et al., 2011). It is also important to note that central hypo-fusion and the resultant hypoxia are recognised as contributing to the risks of dementia (Roman et al., 2002; Ruitenberg et al., 2005).

Other mechanisms that can potentially affect the brain across the lifespan include oxidative stress, inflammation and poor glucoregulation. Oxidative stress is considered to be an imbalance between the production of reactive oxygen species (ROS) and the biological antioxidant defences (Betteridge, 2000; Dai et al., 2008). The increase in ROS in the brain leads to apoptotic cell death of neurons and increased oxidative damage to DNA, lipids and apolipoprotein E4 (ApoE4), which can accelerate cognitive ageing (Dai et al., 2008; Hajjar et al., 2018). Neuro-inflammation is a process that occurs within cells of the central nervous

system in the brain such as the glial cells, neurons and leukocytes. The inflammatory process compromises the integrity of the blood–brain barrier, resulting in an increase of irritants entering the brain and a consequent increase in the production of inflammatory cytokines. These inflammatory cytokines impair adult neurogenesis, which is important for learning, memory and cognitive function (O'Callaghan et al., 2008). There is also a peptide hormone produced in the pancreatic ß-cells, referred to as insulin, which is essential for brain function because if its role in the modulation of glucose uptake (Convit, 2005). The plasma levels of glucose in the brain are relatively stable; however, small changes in glucose levels will alter metabolic homeostasis. The change in homeostasis has been linked to insulin resistance to glucose uptake leading to hyperglycaemia and cognitive impairment in older individuals (Meierruge et al., 1994; Owen et al., 2013; Croteau et al., 2018; Hajjar et al., 2018).

At the micro-anatomical level there are age-related changes in neuron numbers and neuronal re-organisation, although these changes cannot be observed easily *in vivo* in the human brain (Park and Reuter-Lorenz, 2009). At a macro level, the result of longer-term neuronal decay manifests as cortical thinning, changes in grey and white matter and changes in neurotransmitters and neuro-metabolites (Park and Reuter-Lorenz, 2009; Huizinga et al., 2018; Scheller et al., 2018). These changes can be observed to some extent *in vivo* using advanced neuroimaging methods (Burke and Barnes, 2006). It has been demonstrated that gradual neuronal loss occurs with age in the neocortex, and hippocampus and disconnection between brain regions, particularly involving the prefrontal cortex (Burke and Barnes, 2006; Yankner et al., 2008).

Research has identified the potential involvement of decay of brain structure in cognitive ageing. There is evidence to suggest that reduced brain volumes, cortical thinning and changes in neuro-metabolite levels to at least some extent are responsible for a commensurate decay in cognition with age (Yankner et al 2008, Park, 2009). As mentioned earlier, cognitive ageing is non-unitary and it appears that differential brain structural changes can relate to differential effects on cognitive processes. There are also more complex considerations that make it difficult to study the relationship between structure and function, including the capacity for the brain to re-organise through compensatory mechanisms such as increased dendritic sprouting and differences between individuals in the capacity to maintain a cognitive reserve. The cognitive reserve of an individual relates to how their brain activity is able to cope with neural damage by utilising pre-existing cognitive processes as a compensatory mechanism (Colombo

et al., 2018). It has been proposed that an individual with a higher cognitive reserve would cope better with neural damage than an individual with a lower cognitive reserve during the ageing process (Colombo et al., 2018; Nilsson and Lovden, 2018).

The mechanisms responsible for cognitive ageing have been a greatly researched area, providing insights into the cognitive processes that decline with age and those that may be early indicators of more insidious disease. Moreover, cognition has provided an important target for interventions—cognitive training, pharmacological, dietary, lifestyle interventions and psychological training, among others (Deary et al., 2009; Lipnicki et al., 2013; Rosenberg et al., 2018).

It is evident from both observational and cross-sectional studies that performance on cognitive tasks requires a range of perceptual and cognitive processes that decline across an adult lifespan (Kramer et al., 2004). It has been observed that knowledge-based crystallised abilities (a term for knowledge and the content of culture) such as verbal knowledge and comprehension tend to be maintained with age, whereas process-based fluid intelligence (such as reasoning, speed of processing and other activities not reliant on experiences) are affected by age-related cognitive decline (Baltes et al., 1999). Specifically, processing speed, reasoning, memory and executive function decline as the brain ages (Deary et al., 2009).

Cognitive changes with age may affect multiple areas of function including memory, executive function and cognitive speed (Christensen, 2001). Cognitive ageing is demonstrated by minor changes in some mental functions such as vocabulary, some numerical skills and general knowledge; however, other mental capabilities decline from middle age onwards, or even earlier. There is a general belief that crystallised abilities (e.g., vocabulary and general knowledge) generally remain stable until very late in life whereas fluid abilities (e.g., attention, executive function and memory) decline from middle adulthood until late old age (Gunstad et al., 2006).

Currently there is no cure to mitigate cognitive impairment in later life to reduce the financial and physical burden associated with the most common forms of dementia, although it has become increasingly apparent that early intervention is critical for the maintenance of brain health across the lifespan (Carter et al., 2007; Tariq and Barber, 2018).

Previous research has focused on how interventions—such as improving nutritional status and modifying risk factors that may impinge directly and/or indirectly on brain functioning—can reduce the risk of neurocognitive impairment (Parrott and Greenwood, 2007b).

The aforementioned risk factors that affect age-associated cognitive impairment—such as obesity, sedentary lifestyle, hypertension, depression, cardiovascular disease, potentially arterial stiffness, oxidative stress and hyperlipoidemia—may be modified by diet (Parrott and Greenwood, 2007a; Mathers, 2013; Dauncey, 2014; Kiefte-De Jong et al., 2014; Vandewoude et al., 2016), physical activity such as exercise, or a combination of both exercise and diet (Komulainen et al., 2008; Deary et al., 2009; Komulainen et al., 2010; Rolland et al., 2010; May, 2011; Tarumi et al., 2011; Gorelick, 2018).

How diet and exercise may modify age-associated cognitive decline is discussed in the following sections.

Nutrition and the Effect on Cognition

Lifestyle with respect to diet and exercise is considered one of the most important contributors to overall health. The effect of one's long-term diet is considered a major influence on brain function as nutrition through one's life has a profound effect on the mechanisms that underpin brain structure and function (Pinilla, 2006). Substantial research indicates that changes to diet can influence cognitive changes (Blundell et al., 2003; Pinilla, 2006; Nash, 2007; Coutre and Schmitt, 2008; Psaltopoulou et al., 2008; Dauncey, 2014). As we age, our cognitive health is a representation of the life-long preferences we have in our diet and our exposure to other health behaviours and environmental factors (Kuczmarski et al., 2014; Wahl et al., 2016).

Over time, there have been substantial changes to the environment, food production, types of food available and food quality. This change in food availability has resulted in food that was traditionally prepared, eaten and shared with the family now being available outside the home. Such food may not be of high nutritional value and is referred to as 'fast food'. The availability of fast food high in fats and the potential for reduced physical activity has continued its upward trend (Singer et al., 2014). In addition to fast food the 'Western diet' is a term commonly used to describe the diet containing large amounts of red meat, refined sugars, grains and high-fat foods that is common in developed countries. The high levels of saturated fat and trans-fatty acids produced and available in the diet have contributed to an obesity epidemic in Western

countries. The Western diet is associated with diseases of chronic inflammation including metabolic syndrome, atherosclerosis, cancer, diabetes, obesity and pulmonary disease (Singh et al., 2014; Gotsis et al., 2015), which can also increase the risk of cognitive decline. For instance, obesity has been linked with impaired cognitive function and an elevated risk of late-onset dementia, such as AD (Fitzpatrick et al., 2009; Smith et al., 2011). A diet that is rich in saturated fats has been demonstrated to decrease learning and memory and to increase metabolic distress (Carter et al., 2007; Gomez-Pinilla, 2008).

The human brain consumes up to 20% of the total energy taken into the body and this energy requirement is supplied by the nutrients needed to maintain a healthy brain. The Western diet is a high-energy, low-nutrient diet that does not supply the brain with the potentially rich micronutrients required for effective brain energy. Combined with a sedentary lifestyle, the Western diet affects general health, including increased rates of obesity, high blood pressure, high blood triglycerides, high levels of LDL and low levels of HDL cholesterol, and insulin resistance (Mattson et al., 2004a; Zobel et al., 2016).

Provision of effective energy for the human brain requires B-complex vitamins including B1-thiamine, B2-riboflavin, B3-niacin, B5-pantothenate, B6-biotoin, B9-folate and B12-cobalamin, which produce neurotransmitter regulators. Epidemiological data suggest that there is a protective effect associated with the B vitamins, particularly B12, B6 and B9, with respect to cognitive function (Ordovas, 2008b; Kennedy, 2016a). Given their role in neurotransmitter function, the B vitamins may influence energy, brain function and modulation of mood (Gesch et al., 2002). For instance, B6 is important as it is a co-factor for the enzymes that synthesise the neurotransmitters serotonin, epinephrine, nor-epinephrine and gamma-aminobutyric acid (GABA) (Gomez-Pinilla, 2008). In addition, B vitamins have been identified as regulators of homocysteine levels, which are considered a risk factor associated with cognitive decline (Ordovas, 2008a; Kennedy, 2016b).

Dietary antioxidants such as vitamin E, beta-carotene and flavonoids that are found in fruit and vegetables may also have a protective effect against oxidative damage to the brain, by enhancing antioxidant defences (Van Dyk and Sano, 2007). Further, it has been suggested that plant polyphenols contained in fruits and vegetables interact with ageing neurons in the brain, increasing their capacity to maintain effective and proper functioning during the ageing process (Gomez-Pinilla, 2008).

Taken together, the evidence relating to the importance of a healthy diet for a healthy brain has led many researchers to suggest that a diet rich in B vitamins, antioxidants and the omega-3 essential fatty acids is required for mental fitness (Van Dyk and Sano, 2007). Therefore, adherence to a nutritious diet may result in an increased quality of life and healthier cognitive ageing (Morley, 2001; Murphy, 2008).

A dietary pattern that includes fruits, vegetables, whole grains, nuts and fatty fish, and is low in milk and low-fat dairy products, has been found to be associated with better cognitive test scores in both elderly men and women, compared with diets with less of these healthier food alternatives (Wengreen et al., 2009). The intake of fruit and vegetables is considered protective against age-related cognitive impairment because of the micronutrients contained within fruit and vegetables (Peneau et al., 2011). The best advice to maintain a healthy ageing brain is to consume a nutritious diet and reduce intake of fat and fatty meat. The consumption of a poor diet has been demonstrated to potentially result in biological and neurological damage leading to the development of some cancers, cardiovascular disease, Parkinson's disease and AD (Morris et al., 2012; Katsiardanis et al., 2013; Dauncey, 2014).

Many dietary patterns have been studied. However, it has been suggested that a plant-based dietary style will potentially supply nutrients for a healthy brain—a diet abundant in plant foods such as leafy greens, fresh fruit and vegetables, cereals, beans, seeds, nuts and legumes. One such dietary pattern is a Mediterranean diet (MedDiet), which is low in dairy, includes minimal red meat and uses olive oil as its major source of fat (Feart et al., 2013).

The Mediterranean Diet and Cognition

A MedDiet refers to the dietary practices of populations from the Mediterranean regions and consists predominantly of fruits, vegetables, nuts, cereals, legumes, fish and olive oil, with a lower intake of alcohol, red meat and poultry. A MedDiet, which is high in the essential micronutrients available in fish, fruit and vegetables—including flavonoids, polyunsaturated omega-3 fatty acids, zinc, copper and vitamins A, B, C, D and E—has the potential to supply the energy requirements to meet the optimal energy demands of the brain, in turn potentially improving cognitive performance (Dauncey, 2014; Loughrey et al., 2017).

The MedDiet dietary pattern has been studied in many countries, both around the Mediterranean and around the world with inherent heterogeneity associated with cultural

differences, food practices and choices leading to differences in definitions. This has resulted in challenges in research around different methodologies and reported outcomes. In essence, there is limited standardisation of assessments with the evaluation based on the cohort of people under investigation.

To assess an individual's dietary pattern, food intake can be assessed by recording all food intake in a food diary, or via a food frequency assessment that analyses the food consumed over a period of time prior to the assessment. The various food groups are then categorised to create a score (Buscemi et al., 2015). This is referred to as the Mediterranean Diet Score (MedDietS). These scores are of course dependent on the food groups that relate to the cohort being investigated that further complicates comparison across studies; a factor that is discussed in Chapter 2.

There is a growing body of evidence demonstrating that adherence to a MedDiet may be protective against many chronic conditions. For instance, adherence to a MedDiet has been linked to lower risk of mortality and vascular events (Klonizakis et al., 2013). More recently, a MedDiet has been purported to support healthy brain ageing (Knoops et al., 2004; Gardener et al., 2012; Vandewoude et al., 2016). In one study, older, dementia-free people following a MedDiet exhibited a slower rate of global cognitive decline over seven years that did those not adhering to a MedDiet (Tangney et al., 2011). Similarly, nutrient components of a MedDiet have been correlated with better performance on individual measures of memory in people aged 55–80 years (Valls-Pedret et al., 2012). However, it is important to note that the majority of these studies are observational and a causal link has not been confirmed (Hardman et al., 2016; Petersson and Philippou, 2016). Nonetheless, cohort studies completed in the Mediterranean region have had more cohesive outcomes with respect to the positive benefits of a MedDiet on cognitive function, demonstrating that a MedDiet may have a major role in maintaining global cognitive health and the risk of AD and dementia (Aridi et al., 2017; Loughrey et al., 2017). Despite this evidence, it is important to note that diet is only one modifiable risk factor; it is also important to consider whether combining dietary change with other lifestyle interventions that may be beneficial for cognitive function, such as exercise, would have an enhanced effect on the reduction of cognitive decline.

Exercise as a Means to Reduce Risk Factors and its Effects on Cognition

Increasing one's exercise as a lifestyle change is potentially an effective, non-pharmacological intervention that may reduce the effects of ageing on the brain and reduce the effect of cognitive decline (Barha et al., 2017).

Exercise has been demonstrated to reduce cardiovascular disease and consequently the risk of cognitive decline; it is proposed that this effect occurs via reducing vascular dysfunction (Picano et al., 2014). This is important because with increasing age there is an increased risk of stiffening of central arteries due to structural changes. For instance, recent studies have identified a relationship between arterial stiffness, cerebral small vessel damage and cognitive performance (Singer et al., 2014; van Sloten et al., 2015).

Many studies have investigated the effect of different modes of exercise on cognitive function and neuroplasticity, with promising findings. In particular, aerobic exercise such as walking and running and resistance exercise such as lifting weights has been found to be potentially beneficial, with aerobic exercise considered a means to attenuate the progression of neurodegenerative processes. This may be related, in part, to exercise-related benefits for cardiovascular health and fitness (Ahlskog et al., 2011). Further, exercise is a means by which risk factors such as obesity associated with cognitive decline may be reduced, and a number of studies have investigated the relationship between exercise and cognition (Colcombe et al., 2004).

The results from the *National Long Term Care Survey* indicate that exercise has a favourable effect on cognition and lowers the risk of dementia (Jedrziewski et al., 2010). It was reported that participants who were involved in at least four physical activities, such as walking, riding a bike, jogging and gymnastics, over a two-week period reduced their risk of dementia relative to those who engaged in one or no activities (Jedrziewski et al., 2010). This study suggests that the exercise session must be at least 20 minutes long and occur at least three times per week. The most common form of exercise was aerobic walking (Miller et al., 2012).

Another key mechanism may be an exercise-induced improvement in vascular function, reduced stress and inflammation, along with improved insulin sensitivity. In animal studies, the mechanisms by which exercise seems to improve cognition include neurogenesis, synaptogenesis and synaptic plasticity (Garcia et al., 2012). For example, brain-derived

neurotrophic factor (BDNF), which is a molecule implicated in learning and memory, is considered to be upregulated by exercise and has an important role in synaptic plasticity, cell genesis, growth and cellular survival, particularly in the hippocampus, dentate gyrus and perirhinal cortex (Rea, 2017). The action of exercise may also have an effect on epigenetic regulation such as DNA methylation of gene expression, which has a central influence on long-term brain function (Fernandes et al., 2017). However, further longitudinal studies need to be conducted to substantiate this (Bherer et al., 2006; van Praag, 2009; Kennedy et al., 2017).

Cognitive Effect of Medications in an Ageing Population

With an ageing population in Australia, and other westernised countries, maintaining health status is critical. The use of prescription medications is key in the armamentarium of the medical practitioner to maintain and normalise health status for an ageing individual. It is not uncommon for ageing persons to be prescribed a variety of different medications to maintain their current life. For instance, blood pressure medications, cholesterol-lowering medications, blood thinners, pain medications and antidepressant medications are commonly prescribed in older individuals. This is generally referred to as poly-pharmacy (Rosenblat et al., 2016).

Many types of medications are prescribed to manage comorbidities and risk factors already associated with potential cognitive decline. Medications prescribed may have an effect on cognitive maintenance over the lifetime by either enhancing or stabilising cognitive processes in the brain (Kovshoff et al., 2016).

Blood pressure medications are one example of medications that are used to reduce the incidence of high blood pressure (hypertension). High blood pressure results in vascular restriction in the brain, which has been linked to the onset of vascular dementia. However, the level of medication to potentially prevent dementia and the class of antihypertensive that may achieve this requires further randomised controlled clinical trials to confirm (Majeski et al., 2004; Hajjar et al., 2005; Yasar et al., 2008).

Similarly, there is a substantial literature investigating the relationship between cognitive function and statin medication used for lowering cholesterol, but no studies have shown a significant cognitive benefit of statin medication in the elderly. Further studies need to be conducted to provide evidence of their benefit for the treatment of cognitive decline and dementia (McGuinness et al., 2013; Steenland et al., 2013; Gauthier and Massicotte, 2015; Ott

et al., 2015; Power et al., 2015). Moreover, in assessing the effects of lifestyle on cognitive health in older cohorts in which there is an inherently high prevalence of prescription medication usage, it is important to consider the potential confounding effects of these medications on these relationships. In essence, it is not clear that prescribed medications will enhance, protect or compromise cognitive performance. Research to date appears to support, for some classes of medications, a positive effect with respect to cognitive outcomes, while others may be potentially detrimental to cognitive performance (Johnson, 2013; Obermann et al., 2013). Despite these mixed findings, it is important to consider the effect of medications that is prevalent in cognitively healthy older populations.

The Key Rationale

The key rationale for conducting this research was that few studies have investigated the effect of diet and exercise on cognitive function within a non-clinical ageing population. This may, in part, be due to the perceived complications of conducting a randomised controlled trial in such an age group with a high prevalence of comorbidities and prescription medication usage. Specifically, very few trials have assessed the effect of a MedDiet and exercise on cognition, in a randomly controlled setting. The participants in this research represented a typical group of ageing individuals between the ages of 60 and 90 years. The participants were screened and deemed cognitively healthy at the beginning of the trial and were not excluded as a result of the medications they were taking.

The focus of the study presented in this research was the effects of lifestyle changes such as taking up a MedDiet and improving exercise on cognitive performance in older adults who are living independently in aged care facilities. It was hypothesised that measures of cognitive performance would be improved with dietary interventions, relative to the controls, and that the combination of diet and exercise would be the most effective intervention over that of a control group.

A secondary aim of this research was to investigate the relationships between cognitive function, blood biomarkers and cardiovascular function, which have been proposed as mechanisms that may influence the rate of cognitive decline in an ageing population. The effects on mood, quality of life, cardiovascular function and overall perceived wellness in these cohorts were also investigated as potential mechanisms by which exercise and dietary change may have an influence on cognition.

By investigating these variables, the study aimed to identify and target modifiable risk factors, as well as identifying objective biological indicators of the efficacy of interventions that are aimed at ameliorating the rate of cognitive ageing.

Aims and Hypothesis

The primary aim of the study was to examine the 6-month effects of change to a MedDiet, increased exercise through walking, and a combination of both on cognitive performance in an older population living independently in aged care facilities. It was hypothesised that measures of cognitive performance would improve in both the exercise and dietary intervention groups relative to the controls and that the combined diet and exercise intervention would show the greatest improvement of all groups.

As a secondary aim, this study also investigated the associations between cognitive function, blood-based biomarkers and cardiovascular function, which have been proposed as mechanisms, or indicators of mechanisms, that may influence the rate of cognitive ageing. By investigating these variables, the current study aimed to identify and target modifiable risk factors, as well as identifying objective biological indicators of the efficacy of interventions that are aimed at ameliorating the rate of cognitive ageing.

Discussion

This research seeks to understand the effects of a 6-month evidence-based diet and exercise intervention on cognitive abilities, mood, general health and perceived wellness in cognitively healthy elderly persons 60–90 years of age, living independently in aged care facilities in and around Melbourne.

This is followed by a critical assessment of findings, strengths of the research, contribution to the literature and study limitations. Finally, implications of the research and recommendations for future directions are discussed and the thesis is concluded.

Summary of Findings

Effects of Mediterranean Diet on Cognition

The first published article 'Adherence to a Mediterranean-style Diet (MedDiet) and effects on Cognition in Adults: A Qualitative evaluation and Systematic Review of Longitudinal and Prospective Trials' aimed to evaluate longitudinal and prospective trials to gain an understanding of how a MedDiet may affect cognitive processes over time. The included studies were published between 2000 and 2015 and included assessments of dietary status using either a FFQ or a food diary assessment. Eighteen articles meeting the inclusion criteria were subjected to systematic review. The review revealed that higher adherence to a MedDiet is associated with slower rates of cognitive decline, reduced conversion to AD and improvements in cognitive function. The specific cognitive domains that were found to benefit, with improved MedDietS, were memory (delayed recognition, and long-term and working memory), executive function and visual constructs.

Irrespective of the study design, the studies that demonstrated improved cognitive outcomes examined a broad range of cognitive domains of attention, memory and language. The studies that focused on the cognitive domains of motor or action did not report favourable outcomes in relation to MedDiet adherence. This may be because of the insensitive nature of the cognitive assessments used. The more specific cognitive domains that improved with a MedDietS were memory, delayed recognition, executive function, long-term working memory and visual constructs. It appeared that more positive relationships between a MedDiet and cognitive

improvement were reported for studies that utilised a computer-based sensitive cognitive assessment.

With few studies available to assess the benefits of a MedDiet intervention in a healthy older population, it was recommended that further randomised controlled trials be conducted. Trials that focus on the assessment of a MedDiet need to include a standard food frequency/dietary assessment. It was also recommended that future randomised controlled studies utilise validated computer-based cognitive tests that are sensitive to cognitive faculties, which are potentially compromised with age.

Mediterranean Diet Adherence and its Effect on Cognition in a Cognitively Healthy Ageing Population

Previous studies investigating the effects of medications on cognition have suggested that medications act to normalise health and potentially stabilise cognitive function. Conversely, other areas of research have suggested that medications may impair cognitive function. However, it appears that no previous studies have taken medication use into account when considering the association between adherence to a MedDiet and cognitive performance.

Thus, the third published article 'The association between adherence to a Mediterranean style diet and cognition in older people: The impact of medication' aimed to investigate the association between adherence to a Mediterranean-style diet, cognition and medication usage in cognitively healthy older individuals.

In this study, the relationship between two cognitive speed clusters and four medication clusters was investigated by categorising the 93 participants with respect to their cognitive measures and medications taken. The clustering allowed assignment of participants to groups with similar data patterns for the variables considered.

The findings suggested that when medications are taken into account, a higher MedDietS is associated with a faster response in cognitive function tests. It was concluded that larger cross-sectional and longitudinal studies are needed to properly evaluate this proposition.

Six-month Adherence to a Mediterranean Diet and Aerobic Exercise on Cognition in an Ageing Population

The fourth article presented, 'Findings of a randomised controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition in cognitively healthy older people living independently within aged care facilities: The Lifestyle Intervention in Independent Living Aged Care (LIILAC) study' (currently under review), aimed to investigate the effects of 6-month MedDiet and exercise interventions on cognition, mood, general health and perceived wellness in older persons living independently in aged care communities. It was hypothesised that measures of cognitive performance would be improved in both the exercise and dietary interventions relative to the control, and that the combined diet and exercise intervention group would show the greatest improvement of all groups with respect to cognitive outcomes.

This study used a 2 × 2 factorial design of 102 participants (age 60–90 years) from 15 independent living aged care villages that were allocated to one of four intervention groups: exercise (an unsupervised walking program), a diet intervention (adherence to a MedDiet), a diet and exercise group (combined diet and exercise group) and a no intervention group (control). The primary outcome was a composite memory measure to assess cognitive performance using the SUCCAB. The secondary outcomes included other SUCCAB measures, mood, wellness, peripheral and central blood pressure, and systemic markers of inflammation, glucoregulation and nutrient status.

The findings regarding the composite memory measure did not include any significant differences between any of the intervention groups and the control group. However, when the other cognitive measures were considered, a combination of exercise and diet was associated with a significant improvement over the control group in performance for spatial working memory. The exercise alone, and exercise and diet groups demonstrated significantly lower scores on the total DASS compared with the control group. However, no significant differences were found between the intervention groups and the control group when comparing cardiovascular outcomes. There were a number of mixed findings for blood biomarkers between the groups.

The summary of this 6-month clinical trial research supports the proposition that by changing diet (to a Mediterranean style) and exercise (aerobic walking) there is potential to improve cognitive and mood outcomes in a cognitively healthy ageing population.

A Critical Assessment of Study Findings

The Assessment of an Older Cohort—The Effect of Medications

The participants in the study were all screened as being cognitively healthy and were all aged between 60 and 90 years. However, unlike in the majority of previous trials assessing the effects of diet on cognition, individuals taking medications were not excluded. Rather than exclude individuals that take medications, Hardman et al 2018 recorded their medication use (which may have been cognitively enhancing or compromising) and took this into account in statistical analyses.

There was a high prevalence of medication use in the demographic investigated in the study: 91% of all participants in the study were taking some form of medication and 30% were considered 'cardio compromised' with 96.4% of this cluster taking cholesterol-lowing medications and 89.3% taking blood pressure medications. This group seems to have been representative of the broader population in that there was a high prevalence of medication use in the general community, with 87% of women and 83% of men over the age of 60 taking at least one medication (Elliott, 2006). Previous studies investigating diet and cognition interactions in healthy participants have excluded participants taking medications; the results of those studies are thus not generalisable to the demographic being investigated.

The analysis outlined suggested that cognitive status may depend on medication use and that this is an important factor to take into account when considering the relationship between dietary status and cognitive outcomes.

The 6-month analysis did not control for medication use as this remained constant for each individual. Participants maintained their medication regimen over the 6-month intervention period. Moreover, the 6-month analysis controlled for numerous variables including age, gender, level of education completed and homocysteine. Given the sample size it was not statistically feasible to also control for medication clusters. However, it is acknowledged that medication use measured at baseline may have had some bearing on cognition outcomes at 6 months across the four groups; this is a limitation of the current study. Future studies involving

more participants, and thus with the ability to control for more variables, should also consider controlling for medication use when analysing the interaction of interventions over time.

At baseline, the results showed that there was an important relationship between medication and cognition. Broad medication classes such as antihypertensive drugs, cholesterol-lowering drugs, anti-depressants, blood thinning drugs and pain medications were measured. Future studies should consider specific medications as there may be differential effects of these medications and their actions on cognition and interactions when considering the relationship between diet and cognition. Further, dose and duration of medication use may have some bearing on diet–cognition relationships and should be considered.

Cognitive Findings and Sensitivity of Cognitive Testing

The systematic review identified that the majority of studies evaluated cognitive changes using a global assessment tool, the MMSE. This paper-based assessment tool is open to interpretation. The MMSE is primarily used for clinical assessment and to screen for cognitive impairment; it is not intended for use in cognitively healthy individuals. This may be why numerous studies examined in the review did not identify a relationship between a MedDiet and the intervention of a MedDiet.

The outcome of the systematic review included identifying that greater adherence to a MedDiet demonstrated improved cognitive outcomes when specific cognitive domains in addition to the MMSE were used and/or the participants in the trial were cognitively assessed via a computer-based cognitive assessment battery. The review identified that the specific cognitive domains found to benefit with improved MedDietS were memory (delayed recognition, and long-term and working memory), executive function and visual constructs. Previous research utilising the SUCCAB battery of tests with an elderly population also found that the sensitivity of a series of computerised cognitive tasks demonstrated improvement in memory-based cognitive assessments (Pipingas et al., 2010b). The Pipingas et al. study emphasised the importance of memory-based tasks such as spatial working memory and contextual memory. It was reported in the paper that the sensitivity of a computer-based cognitive assessment of older people may offer the capacity to detect the subtle changes that occur in response to pharmaceutical or other interventions (Pase et al., 2010; Pipingas et al., 2010a; Macpherson et al., 2012).

Based on the literature showing significant changes in cognition as a result of age-specific cognitive domains and the use of computer-based assessments, combined with knowledge

provided by previous research utilising the SUCCAB, it was expected that changes would be observed to be associated with memory-based cognitive assessment such as spatial working memory and contextual memory.

In both the baseline assessment outlined in the published article and the 6-month assessment, the SUCCAB battery was utilised. The baseline study data analysis demonstrated that when medications are considered, a higher MedDietS is associated with a faster response on cognitive function tests.

In the 6-month trial outlined, although the primary outcome—which was a composite measure of reaction time did not demonstrate any significant differences between the intervention groups and control, it was discovered that a higher adherence to a MedDiet combined with exercise resulted in a significant improvement in performance in the SUCCAB spatial working memory task compared with the control group. The other cognitive domains tested did not demonstrate any significant improvement over the 6 months of the intervention compared with the controls. Consistent with these results, previous studies utilising the SUCCAB have identified similar sensitivity with spatial working memory (SWM).

Other studies utilising computerised cognitive tasks have demonstrated sensitivity using measures of both speed and accuracy (McMillan et al., 2011; Lee et al., 2015). Computer-based testing provides millisecond sensitivity that has enabled the detection of subtler changes that may occur early in the course of cognitive decline or in response to a therapy or intervention (Macpherson et al., 2012; Pase et al., 2010; Pipingas et al., 2010). It is suggested that this ability to measure subtle cognitive changes is central to the observation of the outcomes in this thesis.

It is of value to understand why only significant changes were found in SWM. SWM is an important component of working memory, and has an essential role in high-level cognitive abilities. SWM is involved in the temporary maintenance, updating and integration of visuospatial information and is essential for the accurate localisation and tracking of external stimuli during the performance of a cognitive task (Baddeley, 2002). SWM declines with age as it is a test of fluid intelligence (Yankner et al., 2008). Using various neuroimaging task-based studies it has been shown that regional activation of brain areas such as the lateral prefrontal and parietal cortices are associated with SWM capacity, suggesting that widely distributed brain regions underlie individual SWM processing and this may be affected with age (Nash, 2007; Liu et al., 2017).

The possible reasons for not observing changes in other cognitive domains include that these domains are less sensitive to the interventional change, and the small number of participants included in the analysis may have provided insufficient statistical power to observe such changes. Moreover, it was difficult to actively encourage better adherence with the dietary and exercise interventions because of limited resources; this may have led to a stronger effect of the interventions and consequently the observation of additional cognitive benefits in other domains. With larger interventional changes there may be greater cognitive change and more specific cognitive change in other domains.

To investigate potential mechanisms for cognitive improvement, various blood biomarkers and measures of cardiovascular function were assessed as secondary measures in the trial. These measures represent potential modifiable risk factors worthy of investigation that may be responsible for cognitive changes in response to the interventions. These biomarkers were chosen to assess mechanisms represented in the literature that appear to change with age and that are potentially amenable to interventions such as diet and exercise.

Numerous studies have investigated the effect of diet and/or exercise on cognition and a limited number of trials has also explored potential mechanisms of action through the measurement of blood biomarkers. The current study included measures of inflammation, glucoregulation, lipids, cardiovascular risk, specific nutrient levels and BDNF to complement cognitive outcomes. However, with the exception of vitamins B6 and B12, none of these measures showed any significant change in association with any of the interventions. There are a number of potential reasons for this. Again, sample size may have been inadequate and adherence may not have been high enough to produce changes in biomarker measures. An alternative explanation is that the changes in cognition may have been more directly influenced by the interventions effecting change in neurotransmitter levels that in turn affected cognition and mood. Interestingly, BDNF, a marker of brain plasticity, did not change with interventions. Previous studies have suggested that BDNF increases with exercise whereas diet is not as prominent in its effect on BDNF (Maass et al., 2016).

Vitamins B6 and B12 showed changes that were significantly related to exercise, and exercise and diet, interventions respectively. The level of B6 was significantly lower in the exercise group than in the control group after 6 months. The reason for this is unclear but one possible explanation is that B6 is important for aerobic exercise—being principally required for amino acid metabolism and glycogen breakdown—and is a co-factor for the enzymes involved in

protein transamination and deamination reactions (Woolf and Manore, 2006). Protein synthesis is also required to produce the synaptic modification needed for long-term memory storage (Hernandez and Abel, 2008) and is a co-factor for the production of serotonin. Vitamin B6 has been shown to be an important nutrient for cognition (Pipingas et al., 2008), hence the inclusion of this biomarker in the current study. As B6 is indeed required for healthy cognitive function and decreased in the exercise group, potentially as a result of increased metabolic processes, this may have limited the cognitive benefit in this group. This underscores the importance of a lifestyle approach through optimal dietary nutrient intake complemented by exercise.

It was identified that within the exercise and diet group, there was an increase in B12 levels that was greater than that of the control group. Vitamin B12 is a coenzyme that assists in DNA synthesis and is necessary for the formation of red blood cells and for brain health, being one of the coenzymes for protein synthesis (Manore et al., 2000). B vitamins act as coenzymes within enzymatic processes responsible for all cellular physiological functions and are a rate-limiting co-factor in the synthesis of neurotransmitters such as dopamine, serotonin, noradrenalin and GABA (Kennedy, 2016a). The synthesis of neurotransmitters is sanative to B vitamin levels and potential effects on cognition (Pipingas et al., 2014; Kennedy, 2016a). Thus, the improvement in SWM observed in the exercise and diet group may be related in part to increased amounts of B12 brought about by dietary change. Although this is speculative, one previous study reported that when B12 was increased through supplementation, there was a significant (9.63%) improvement in global cognitive scores in older individuals (Chauhan and Agarwal, 2016).

The shared risk factors in cardiovascular and cognitive health have been previously noted. Hardman et al. (in review) predicted that lifestyle changes of diet and exercise would also influence aspects of cardiovascular health, particularly peripheral and central blood pressure and arterial stiffness. After controlling for age, gender and education, there were no significant differences in these cardiovascular indices between any of the intervention groups and the control group. As there appears to be a moderate improvement in SWM the lack of change in cardiovascular function suggests that the improvement may be due to non-vascular mechanisms. Significant changes may not have been observed because of the lack of power to detect the predicted cardiovascular changes over the 6 months in these relatively small intervention groups. Another potential reason is that cardiovascular function was already largely normalised through medications that participants had been taking, providing limited

scope for further change. Medication use certainly needs to be taken into consideration in larger longitudinal trials to potentially gain further understanding of the effect of normalising an ageing population with medications that may be masking underlying pathology.

As part of the suite of secondary measures in the 6-month LIILAC trial significant changes in mood were recorded. This improvement may indicate shared neural pathways with cognition and implicate the involvement of neurotransmitter systems such as serotonin and dopamine in these processes (Qiu et al., 2018; Weger and Sandi, 2018). Although this is speculative, the lack of change in blood biomarkers and the observation of both cognitive and mood change may indicate that exercise and diet interventions have more direct effects on neural function through neurotransmitters. With the exception of BDNF, which was measured in the current study, there were no other biomarkers that help to elucidate these neural underpinnings. Future studies utilising neuroimaging methods such as magnetic resonance spectroscopy (MRS), a technique used to assess brain chemistry *in vivo*, may help to shed light on potential neurochemical changes in response to these lifestyle interventions.

Mood and Mental Health

Mood and perceived wellness were self-reported assessments conducted at baseline and 6 months. One of the assessments utilised the overall score of the DASS scale, a validated tool that was used to measure changes in mood over the 6-month intervention period. As reported, the exercise group and the exercise and diet group demonstrated a significantly lower score on the DASS, indicating improved mood after 6 months, compared with the control group. Further, there were a number of mixed findings between the groups for biomarkers. This finding is also consistent with other previously reported outcomes. It is thought that this stress reduction occurs through the activation of the noradrenaline, serotonin and GABA neurotransmitter systems (Kennedy et al., 2017).

Although the results indicate that the participants in the exercise, and diet and exercise groups demonstrated less depression, anxiety and stress, there is a dichotomy of findings, in that the Perceived Wellness Assessment was lower at 6 months in the exercise and diet group compared with the control group. This contrasted with our hypothesis that perceived wellness would improve in this intervention group. However, as the participants in this study over 6 months have become more aware of their health and our interventions they may have perceived they

are not as well as they think, and thus were able to complete a more comprehensive self-assessment about their wellbeing. Further studies in this age group are required.

Strengths of the Research and the Quality and Effect of the Resulting Publications

There are a number of key positive outcomes with regard to the current research that are worthy of reflection and may provide useful knowledge to guide future research. The trial was challenging as it was conducted with limited financial support and resources: unlike previous trials conducted in the laboratories at the Centre for Human Psychopharmacology (CHP) at Swinburne University of Technology, the current trial was conducted in independently living aged care facilities, requiring substantial daily travel by the researchers. However, this did provide an opportunity to test participants in their natural environment, negating the need for them to make their own way to the university facilities, which potentially affects their mental state because of the associated logistical and mental challenges. This on-site testing resulted in efficiency in testing and allowed for a consistent location, time and pattern of behaviour to be established, giving consistency to testing processes. The more usual approach would have also limited overall compliance, with a greater attrition rate predicted due to the inconvenience and challenges associated with travel.

The trial benefited from the cooperation of facility managers in all 15 facilities, which provided private rooms for testing. This resulted in the standardisation of testing by day and time, which was essential for consistency in evaluation of the participants.

A key to the recruitment success was the facilitation by staff to speak with all residents in an open forum to inform them about the trial, the requirements and what was expected. Harmonising with facilities to conduct such meetings was essential and helped to negate any concerns of the participants; it also demonstrated support from facility management. Moreover, with respect to participants who required the confidence and comfort of their own facility to participate there was a more positive outcome in terms of recruitment and ongoing compliance.

Notwithstanding the limited resources—lack of financial support and staffing—that limited the number of participants tested and the scope for facilitating compliance with interventions, the trial does provide data and a model for future studies greater in depth and breadth. The study combined in a novel way for the first time a factorial design investigating diet and exercise

interventions on cognitive functioning and health in older independently living individuals. This novel preventative approach provided insights into the manipulation of modifiable risk factors in at-risk individuals to improve health and potentially influence cognitive trajectories in the longer term. A number of recent studies have produced similarly encouraging data: a prospective study by Morris et al. (2015) demonstrated a positive influence of dietary style on cognitive decline and the incidence of AD in older Chicago residents; and the FINGER trial (Rosenberg et al., 2018) showed that multimodal lifestyle and cognitive training interventions can modify cognitive trajectories.

The current research has produced encouraging results from the application of a combined approach of a MedDiet adherence and exercise change in independently living individuals capable of modifying their lifestyle. The improvements in both memory and mood over 6 months provide a basis for future research to confirm and extend these findings. Moreover, the research was conducted in individuals representing the general population. There was no restriction of medications that were being taken to normalise health. The published papers, the review, protocol and baseline empirical study have already received favourable acknowledgement and citation.

The first paper is a systematic review: 'Adherence to a Mediterranean-style diet and the effects on cognition in adults: A qualitative evaluation and systematic review of longitudinal and prospective trials'. The review was published in *Frontiers in Nutrition*, which has an impact factor of 3.51 and is one of the most highly cited journals in this area of research. This article has had over 36,000 views (ranking in the top 1% of all Frontiers articles), more than 2,400 downloads (top 2%, Frontiers), over 70 media releases (Altmetric of 544) and 20 citations (top 10%, Frontiers).

The second paper describing the protocol was published in *Nutrition Journal*, a quintile 2 journal in nutrition and dietetics. The paper was submitted to substantiate the quality of the research design and to date has 12 citations in Scopus.

The third paper was published in *Clinical Nutrition*, which has a ranking of quintile 1 in nutrition and dietetics. This is the first published study to consider the effect of medications on the relationship between a MedDiet and cognitive outcomes.

The fourth paper has been submitted to *Frontiers in Ageing Neuroscience*, a quintile 1 journal. This paper is currently under review.

Limitations of This Research

This research has identified a number of limitations that have influenced its outcomes. Understanding these imitations will assist in the design of future studies.

A substantial limitation was the number of participants and the attrition rate between the time of the baseline assessment and following 6 months of intervention.

Initially when the protocols were established, it was understood from previous trials examining the effects of exercise fitness interventions that there was the potential for fitness training to improve cognition in sedentary but otherwise healthy older adults. In one study, fitness training increased cognitive performance by 0.5 standard deviations on average, regardless of the type of cognitive task or the training method (Colcombe and Kramer, 2003). According to Cohen's effect size criteria, this represents a medium effect size (Cohen, 1992). A power analysis was thus conducted in the current study using GPower 3.1.3 to determine the sample size required for a four-armed intervention (exercise change only, diet change only, exercise and diet change, no change) using an analysis of variance (ANOVA) design. This analysis indicated that a total sample of 128 participants would be required to detect a moderate effect size with power of 80% and significance level of 5%. Based on previous trials conducted by the Swinburne University CHP, an allowance for a 15% dropout from the trial was factored in. Therefore, a total recruited sample of 148 participants would have been required for this trial, with 37 individuals randomised to each arm of the study. However, at the 6-month assessment there were only 81 participants remaining from the 102 successfully recruited at baseline: 20 in the exercise group, 18 in the diet group, 18 in the exercise and diet group, and 25 in the control. This represents a 23% attrition rate for the exercise group, 28% for the diet group, 25% for the exercise and diet group, and 7% loss for the control group between the time of initial recruitment and the 6-month assessment. However, there was no significant difference in attrition rates between the groups. Overall the final numbers represent a significantly smaller number of participants than was required to meet the objectives of the power analysis.

Understanding that the recruitment process sought participants between 60 and 90 years of age with an average age of 77 years of age, the reasons participants gave for leaving the trial varied from their inability to maintain the intervention, the incapacity and illness of a partner or loved

one, family commitments and a reduction in their health status. With such a reduction in numbers it is perhaps not surprising that the predicted outcomes of the intervention with respect to cognitive changes were not observed. The research demonstrated a moderate effect size for the change in SWM. SWM is an age-sensitive measure of the effect of interventions, which may be why this change was observed. The attrition rate and small numbers of participants in the intervention groups may be the reason for the lack of effects observed. In essence it would have been necessary to double the number of study sites from 15 to 30 allowing for maintenance of numbers to enable changes from the interventions to be observed and cognitive changes to be effective.

For a research study to be effective, the interventions initiated to potentially bring about change over a 6-month period must be adhered to. Without compliance outcomes for the intervention groups are difficult to substantiate. In this study there were two major interventions. One was the change to a MedDiet and the other was improving aerobic exercise by walking. Within the MedDiet groups every participant was issued with a diet guide publication and a self-assessment chart that was used as a guide to facilitate their own evaluation of how they were maintaining or achieving a conversion to an improved MedDiet. From the initiation of the trial, a daily assessment was made by placing a number on a chart. Each number in the chart represented a compliance percentage, with 1 = < 50%, 2 = 50–75%, 3 = 75–90% and 4 = 90%+. Of participants who completed 6 months on a MedDiet, 13.9% recorded an average of 1, 44.4% an average of 2, 33.4% an average of 3 and 8.3% an average of 4. This represented an average compliance of around 50%.

This medium to low compliance with the MedDiet among participants may have influenced the outcomes observed for these groups, and may have occurred for several reasons. Not only was the study dealing with older people with established dietary habits, it was also attempting to influence participants to try new foods including extra virgin olive oil and reduce their reliance on high-fat and sugar-rich foods. The use of Mediterranean food hampers, regular discussions between a dieticians and the diet groups and regular dietary counselling may have improved compliance and outcomes. As there was only limited time and resources to commit to this, a regular monthly visit may have improved the participants' knowledge of the benefits of a MedDiet and conversion to a MedDiet, and hence improved compliance and effects on cognitive assessment tests.

There were similar difficulties with assessing compliance with the exercise intervention. Every participant allocated to exercise was given a pedometer to record the steps they took and a chart to record their times walked and distance covered. An explanatory booklet was also supplied for them to self-assess and complete. It was almost impossible to assess compliance from the available data because of a lack of consistency in recording, loss of data, loss of pedometers, inconsistencies associated with the steps recorded and problems associated with partners in the same groups swapping pedometers. This resulted records lacking any accuracy. The only way of assessing the improvement in walking was via a 6-minute walk test that demonstrated whether walking ability, some of the vital signs of body mass index and weight had improved. This certainly influenced the outcome of the study: if a way to demonstrate accurate compliance could have been identified, the intervention may have been more successful and hence led to an improved cognitive outcome and potential associated biomarker assessment.

To improve and assess compliance in future studies for an aerobic walking group it may be possible to set walking times for particular days and provide digital body-worn devices that record the distance walked, time taken and number of steps, and digitally feed these data back to the researchers for every participant to ensure accuracy in compliance assessments. In addition, the ability to counsel participants on a monthly basis by including an exercise physiologist on the research team would ensure greater compliance and understanding of the requirements. Improved compliance would enable future studies to more accurately identify the effect of an exercise intervention.

This study, as with any study, relied on particular resources to initiate, implement and maintain the interventions through to the finish. The study was initiated without any allocation of equipment, finances or the ability to utilise testing facilities. As the study was not funded it had available only the internal resources of the CHP; the assistance of supervisors and other personnel; allocated student funds; the initiative to borrow and acquire resources from other departments within the university; in-kind cooperation from industry; and a donation in kind from Cobram Estate of extra virgin olive oil, which made this study possible.

The lack of funding meant that substantial amounts of the candidate's time that may have been allocated to the project was taken up with activities that could have been outsourced with the assistance that funding would have allowed. Despite the very limited overall resources, a substantial study was able to be completed. The limited resources also potentially contributed

to the low numbers eventually assessed within the trial, which affected the overall outcomes as it reduced the power to demonstrate an effect of the interventions on cognitive test results.

The way to overcome this in the future is to use this experience to understand the complexity of such a large trial and the intricate nature of working on site within an aged care facility, and ensure that both equipment and financial support for internal assistance is available within the university so that more time is available for recruitment and testing to ensure a more positive outcome.

This research was conducted at 15 sites around Melbourne with a travel range of up to 80 kilometres. All travel was undertaken by car and a portable laboratory was carried and established at every facility on the day of participant testing. Duplicating the test laboratory facility based at a university is no easy task and requires the duplication of testing devices. On occasion, working around an active aged care facility with fixed regimes of staff at times resulted in delays and/or cancellation by the participants, requiring re-booking. As the sites were a significant distance apart, the time delays were significant as a whole day might be lost to assess one or two participants at an on-site facility. This resulted in limited contact at the respective testing sites and became difficult to manage. The time taken to travel and set up the equipment limited the number of visits that could be undertaken to facilities and in turn limited the number of participants that could be assessed during the study.

The complications associated with the distances travelled resulted in limited numbers or frequent visits required to the same site, which allowed no time to explore the possibility of recruiting more participants at each site. This restriction in exposure to a site may have also contributed to the low numbers eventually recruited to the study and once again reduced the ability to properly explore the intervention and increase numbers of participants in the intervention groups or ameliorate the attrition rate experienced.

In the future, it would be preferable to involve only aged care facilities within 30 minutes of the university so that more frequent visits could be undertaken and reliability of contact could be assured. Utilising large aged care facilities would allow the flexibility of having more participants at one site and enable several consecutive days of testing at one site rather than having to move equipment to a different site every day. A greater focus on numbers per site would enable greater cooperation, reduce travel times and improve communication within

facilities to increase group numbers, potentially reduce attrition and improve overall interventional outcomes with cognitive testing.

Implications and Future Directions

In Australia, as in the rest of the Western world, the progressive ageing of the population has resulted in an increase in the number of people living with age-related neurological disorders, such as AD, characterised by cognitive deficits (Australian Government, 2017; Rakesh et al., 2017). It was estimated that in 2015, 47 million people around the world were living with various forms of dementia, and this is expected to increase to million by 2030 and potentially 135 million by 2050 (Prince et al., 2016). Currently there are no effective medical treatments to alleviate the accelerated cognitive decline leading to AD. The increased incidence of AD has placed substantial financial demands on health and other related services. The aged care sector in Australia is experiencing an increasing demand for permanent residential aged care, with greater than 50% of such residents living with dementia (Care, 2017).

This research initially asked the following question: What are the effects of greater adherence to a MedDiet, increased exercise through walking, and a combination of both, over a 6-month period on cognitive performance in an elderly population living independently in aged care facilities?

The significance of this research and the positive implications it has a pilot study, together with the understanding of its limitations and how they might be overcome, provides the basis for a larger longitudinal study. The health and economic burden associated with the potential avalanche of expected dementia in our ageing population now needs to be addressed. If we do not initiate and focus now on lifestyle intervention such as a MedDiet or similar, along with an increase in exercise, then the expected dementia burden will be a reality and not a prediction. This study has indicated that even with small numbers of participants there can be a change in memory improvement such as SWM. There is also the possibility that cognitive decline can be minimised and the incidence of MCI and possible conversion to AD reduced. If we can implement and encourage lifestyle change programs much earlier prior to the age of 60 years we will potentially see positive cognitive outcomes.

This research not only forms the basis of further, larger studies; it also has demonstrated that with dedication and the implementation of simple lifestyle interventions, everyone can maintain cognitive health throughout their life.

Conclusions

In summary, this research has supported the proposition that by changing diet and exercise, there is the potential to improve cognitive and mood outcomes in an ageing population. Further larger randomised controlled trials are required to substantiate the benefits of the introduction of diet and exercise programs into independent living facilities to target cognitive health. The data demonstrated that when combining aerobic exercise with a MedDiet there was a significant improvement performance in SWM. This study has demonstrated that the use of a MedDiet pattern with the addition of aerobic exercise can be of benefit with respect to cognition together with improvement in blood biomarkers.

With the growth in the age sector in Australia and the concomitant use of medications, it is important that further work considers how diet and medications may affect both the mind and body of ageing Australians. It is imperative that the future cost burden of sickness and cognitive decline be reduced within our population and that people can live a healthier longer life, both physically and mentally.

The studies evaluated have suggested that when assessing an ageing population, it is important for evaluation to record and consider the medications that are being prescribed. Another important finding from this research is the considerable need for more preventative programs for people in their mid-40s to consider a Mediterranean style of diet with weekly moderate exercise activity to potentially reduce the onset of the potential dementia epidemic that is facing the world. In addition to this, a program within aged care facilities to maintain a cognitively healthy ageing population could involve the introduction of tuition in a healthy diet and a moderate exercise program.

The focus of this research was to understand the effects of a 6-month evidence-based diet and exercise program on cognitive abilities, mood, general health and perceived wellness in cognitively healthy elderly persons 60–90 years of age, living independently in aged care facilities in and around Melbourne, Victoria, Australia. The outcomes have demonstrated that through adherence to a Mediterranean style of diet combined with improvements in exercise

through walking, not only can one's memory be improved, but mood and overall health can also be improved. This is potentially the way to ensure a cognitively healthy ageing population.

Further longitudinal diet and aerobic exercise programs need to be considered to substantiate this proposition.

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