Physical Activity and Cognition in the Elderly

By

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Abstract

Dementia is a common cause of disability in the elderly and, in the absence of a successful long-term treatment, it is important to investigate possible lifestyle interventions to help reduce an individual's risk of developing the condition. This thesis investigated the relationship between physical activity and dementia risk, finding that not all research supports the link. The literature review presented in this thesis (Chapter 2) highlighted several possible mediating factors, specifically the type of physical activity performed, the cognitive domains being studied and participant characteristics. Women seemed most susceptible to the effect of physical activity and some other forms of midlife interventions, possible mechanisms for which were discussed in another review (Appendix A). The cognitive test battery to be used in later studies was evaluated for its relevance to dementia and treatment during a 6-month study of Alzheimer's disease patients and their carers (Chapter 3). Memory tasks were found to be especially sensitive to clinical outcomes of dementia treatment (Chapter 4). An observational study of Indonesian elderly found a positive relationship between physical activity and memory performance on the same tests. This effect was strongest in women and in those with no pre-existing cognitive impairment (Chapter 5). However, the relationship could be further modified by other demographic factors, such as education. Health was independently affected in this model by exercise and its association with engaging in physical activity in this cohort was further investigated in Chapter 6. A randomised controlled trial (Chapter 7) was conducted to assess the effect of a 12-week programme of non-aerobic physical activity in sedentary middle-aged adults. Results indicated that resistance training, but not flexibility exercises, influenced memory but not executive function. Overall, this thesis suggests that several types of physical activity may be effective at slowing cognitive decline in elderly groups who are at increased risk of dementia, such as those in middle age and elderly women (Chapter 8). These findings should be expanded with the aim to improve healthcare advice and influence policy-making.

Keywords: physical activity, cognitive impairment, dementia, aging, memory, resistance training

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General Introduction

As people age, cognitive abilities change and can range from superior performance to impairment that impedes activities of daily living. In pathological cases this decline takes the form of a clinical syndrome, or dementia. There are different types of dementia – the most common being Alzheimer's disease (AD) (Fratiglioni et al., 1991) – and the vast majority of sufferers are over 65 years old. With improving technology and healthcare, life expectancy is increasing around the world and the percentage of the UK population over the age of 65 years is expected to rise from 16.7% in 2011 to almost 23% by 2034 (Office of National Statistics [ONS], 2010). Dementia is therefore expected to continue to be a growing problem in the future, with the projected number of cases rising from 24.3 million in 2001 to 81.1 million worldwide by 2040 (Ferri et al., 2005).

There is currently no treatment that reverses the neural damage and symptoms of AD or other forms of dementia and many patients die from complications of the disease, such as pneumonia or severe malnutrition caused by immobility, infection and swallowing disorders. Disease progression lasts on average 7 years before death (Fitzpatrick, Kuller, Lopez, Kawas, & Jagust, 2005) but can be much longer, leaving patients in need of substantial financial, medical and practical assistance with daily living. According to Wimo, Winblad and Jönsson (2010), the financial cost of care for those with dementia worldwide totalled around $422 billion in 2009. People with dementia often need help with everyday tasks such as shopping, personal hygiene, housekeeping and managing money, and many caregivers are relatives of the patient which can bring its own social challenges. A focus group made up of carers reported feeling tired, frustrated at a lack of information and support, and guilty about the proxy end-of-life decisions they may be forced to make (Livingston et al., 2010). AD and other forms of dementia thus have additional impacts on patients and their carers beyond those caused directly by cognitive impairment.

The consequences of AD even in the earliest stages mean that research into the prevention of the disease is especially important. Brookmeyer, Johnson, Ziegler-Graham and Arrighi (2007) suggest that delaying AD onset in individuals by just 1 year would substantially reduce the burden of AD by 2050 by reducing the number of patients needing a high level of care, such as residential placement. The aim of this thesis was thus to investigate the effectiveness of lifestyle interventions for AD, which can be low cost and easily accessible to the majority of the public.

Physical activity as a lifestyle intervention for dementia has been explored previously and there are a wealth of studies showing strong associations between physical activity and cognitive abilities. Our aim, therefore, was not to establish presence or absence of a link but rather to identify variables that may influence the relationship to determine whether certain groups benefit more from physical activity than others, whether the cognitive benefits are domain specific, whether certain types of physical activity are more effective than others, and whether certain variables act as mediating or moderating factors.

Part One of this thesis discusses and reviews existing literature in this field. In Chapter 1, we describe the key features of AD and discuss the mechanisms by which physical activity interventions may reduce an individual's risk of developing the disease. In Chapter 2, we present a literature review that describes and compares studies investigating the effects of physical activity on cognitive performance. This review aimed to identify some of the possible mediating and moderating factors that will be addressed in the later sections of this thesis and identify why controversy exists within this field. The review was published as a chapter in the Handbook of Cognitive Aging: Causes, Processes and Effects (Clifford, Bandelow & Hogervorst, 2009). As effects of physical activity seemed most prominent in women from the literature review, another review (see Appendix A) focused on other midlife lifestyle interventions to prevent cognitive decline and dementia for women specifically (published as a full paper in Aging Health; Clifford, Yesufu Udechuku, Edwards, Bandelow & Hogervorst., 2009).

In Part Two, we introduce the cognitive tests that were used in the studies presented in this thesis and discuss their relevance to age-related cognitive decline and dementia. In Chapter 3 we discuss their relevance to the cognitive deficits seen in AD. In Chapter 4 we present the specific methods used and validate our versions of these tests in a 6-month treatment study of AD patients and their carers. This study showed high sensitivity to AD for most of our tests and showed that they were suitable for use in the physical activity studies.

Part Three (Chapter 5) describes an observational cohort study investigating the association between physical activity and cognition in Indonesia. The aims of this study were to assess the impact of sex and age on the relationship between everyday physical activity and cognition. Physical health measures were included to determine whether they act as a causal pathway. Age and sex were both found to mediate the relationship and

better physical health explained some, but not all, of the association between participation in physical activity and better memory. This study also revealed some cultural factors that should be considered in future research investigating physical activity interventions. Chapter 6 discusses the associations of health and exercise in more depth.

Part Four (Chapter 7) describes a pilot intervention study based in the UK that assessed the impact of a 12-week resistance-training programme on cognitive performance. This study recruited middle-aged men and women who had no evidence of cognitive impairment and built upon the findings of the literature review and previous observational study by assessing strength training, causal pathways and different cognitive domains measured. Significant associations were seen between resistance training and memory, but not executive function, independently of muscle strength changes. Effects were strongest in women, similar to findings in Chapters 2 and 5.

Part Five (Chapter 8) combines the results of the previous chapters and gives recommended directions for future research.

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Part One – Literature review

Chapter 1 – Introduction to dementia

1.1. Description of Dementia and Alzheimer's disease

The term 'dementia' refers to a group of acquired cognitive symptoms that impact on activities of daily living and that are most commonly seen in those over the age of 65 years. The idea of age-associated cognitive decline has been documented since Greco-Roman times (Karenberg & Forstl, 2006). However, we now know that there are several types of dementia, each with their own aetiologies, symptoms and progression. Some forms of dementia can be at least partially reversed or halted by removing the cause, such as vitamin deficiencies, endocrine disease, electrolyte imbalance, lead intoxication and alcoholism. Other types of dementia are progressive and non-reversible, showing gradual decline until death. Such dementias include Lewy Body dementia, Frontotemporal dementia, dementia with Parkinson's disease and Creutzfeld-Jakob disease. Alzheimer's disease (AD) accounts for around 50-70% of diagnosed cases of progressive dementia (e.g. Hardy, 1997) and often co-occurs with Vascular Dementia (VaD). Dementia can thus be considered an umbrella term for a range of disorders of which AD is the most common.

Many of the difficulties experienced in AD are with memory, both verbal and non-verbal. AD often becomes apparent due to a progressive decline in remembering new information, with more severe cases experiencing difficulties recalling events from many years previously (American Psychiatric Association [APA], 1994). For example, individuals may fail to recognise familiar people such as family and friends, forget recent events, and get lost in familiar surroundings. Not all symptoms of AD are related to memory, however, and other cognitive domains are usually also affected. These include reduced executive function abilities which manifest as difficulty in planning activities, such as making a meal, washing oneself and playing a game, and making judgements such as dressing appropriately for the occasion. Attention and language can also be affected, causing difficulties with following a conversation, remembering words and using the correct word in a sentence. Although these deficits are common in AD, they do vary widely between individuals and as such different cases can present with very different symptom profiles.

The heterogeneity of symptoms means that diagnosis of AD is not straightforward, especially since many older individuals experience some decline in memory ability and changes in brain activity as part of the normal aging process (Bishop, Lu & Yankner, 2010). In order to be diagnosed as having AD, a memory deficit should be accompanied by impairment in at least one other cognitive domain (e.g. language, object recognition, motor functions) that interferes with the ability to carry out daily tasks (Diagnostic and Statistical Manual of Mental Disorders 4th Edition; [DSM-IV]; APA, 1994). Memory impairments should normally be present for at least 6 months before a diagnosis can be made to help rule out potentially reversible syndromes, such as transient ischemic attack, brain trauma or hydroencephalus (International Statistical Classification of Disease and Related Health Problems 10th Revision [ICD-10]; World Health Organisation [WHO], 1992). Cognitive symptoms should also occur without impaired awareness or altered consciousness (i.e. delirium) but may be accompanied by mood changes, such as apathy or irritability (WHO,1992). In addition, the diagnostic procedure may be supported by neuroimaging and analysis of biomarkers of the disease (e.g. Dubois et al., 2010; McKhann et al., 2011). Those with a memory complaint who do not reach the criteria for probable AD (McKhann et al., 2011) may be diagnosed with possible AD or Mild Cognitive Impairment (MCI; Petersen et al., 1999), which is characterised by a memory impairment that does not affect activities of daily living. Approximately 64% of people who are diagnosed with MCI go on to be diagnosed with AD after 2 years (Geslani, Tierney, Herrmann & Szalai, 2005). However, some patients with MCI never develop AD, and it remains unclear whether MCI represents a transitional stage to AD or whether it is an independent disorder that makes an individual vulnerable to further decline.

An analysis of neuropathology reveals characteristic features of AD that are being increasingly considered as potential biomarkers. A loss of brain volume in the medial temporal lobe, especially in the hippocampus, temporal poles and temporoparietal junction, is seen in over 70% of AD patients (Dubois et al., 2007). These brain areas are thought to be responsible for memory and increased atrophy in these areas is associated with poor memory performance in AD as well as in healthy individuals (e.g. Golomb et al., 1994; Lind et al., 2006; de Toledo-Morrell et al., 2000). At a cellular level, AD patients tend to show increased levels of intracellular neurofibrillary tangles (NFTs), which consist of hyperphosphorylated tau protein, and extracellular protein plaques containing high levels of Amyloid-β (Aβ). Tau protein is involved in giving structure to the axon of a neuron and a

decline in its quality can cause the microtubules of the axon to lose their shape. Aβ is a peptide formed from the cleavage of Amyloid Precursor Protein whose own function is currently unclear but is thought to be involved in the passage of messages across synapses (Priller et al., 2006). Excess insoluble Aβ in the brain causes deposits (plaques) on the outside of the neuron, affecting neuronal quality and function. Although NFTs and Aβ plaques are seen in healthy aging (Hyman et al., 2012), they are generally seen in excessive amounts in those with AD and abnormal levels can be measured in cerebrospinal fluid years before onset of symptoms (Dubois et al., 2007). The dominant theory suggests that these features cause dementia symptoms (Mohajeri & Leuba, 2009). However, it remains controversial whether Aβ plaques cause AD or are simply a feature of it, especially since research into treatments that target these features has to date been relatively unsuccessful (e.g. bapineuzumab [Johnson & Johnson, 2012], tarenflurbil [Myriad Genetics, 2008] and semagacestat [Eli Lily, 2010]).

1.2. Non-modifiable risk factors: Genetics and AD risk

Despite extensive research using humans as well as mouse, rat and fly models, the cause of AD is currently unknown. Several genes have been identified that appear to increase an individual's risk of developing late onset AD (early onset AD has a clear familial genetic component but is relatively rare and is not the topic of this thesis). One of the better-known genes is called *Apolipoprotein E* (*ApoE*), where possession of two epsilon-4 alleles increases risk of AD in comparison to possession of just one, which itself increases risk of AD compared to possession of no epsilon-4 alleles (Corder et al., 1993; Tsai et al., 1994). In contrast, the epsilon-2 allele has been observed to be protective against AD (Tsai et al., 1994). *ApoE* has been linked to lipid transport and the breakdown of Aβ (Raber, 2008). The epsilon-4 allele appears to be less effective at this breakdown process than other variants (Baum, Chen, Ng & Pang, 2000) resulting in higher levels of amyloid plaques. Other genes implicated in AD susceptibility such as *CLU*, *BIN1* and *PICALM* are thought to be involved in mitochondrial energy metabolism and stress resistance, lipid metabolism, endocytosis and neuroinflammation (Harold et al., 2009; Hu et al., 2011; Liang et al., 2008). However, these genes predict a minority of AD cases (Rocchi, Pellegrini, Siciliano, & Murri, 2003) and so it is likely that external factors, including environment and chance, play a large part. Lifestyle behaviours may thus significantly contribute to an individual's risk of developing the disorder.

1.3. Modifiable protective factors: Lifestyle, physical activity and prevention of dementia

Physical activity refers to any type of sustained movement, including day-to-day activity such as walking as well as structured exercise such as sport and fitness classes. Physical activity has long been recommended to promote physical health in the elderly because it helps to maintain a healthy weight, lowers cholesterol and blood pressure (BP), and reduces risk of disorders such as diabetes, heart disease and cancer (Haskell et al., 2007). Even a small amount of physical activity can have a huge impact on health; Wen et al. (2011) showed that all-cause mortality over 8 years was reduced by 14% in those exercising to the equivalent of just 15 minutes per day compared to those who were inactive. However, less than 40% of middle- to older-aged adults meet the recommended amount of physical activity (which is 30 minutes, at least 5 times per week; Haskell et al., 2007). Physical activity can be low cost, there is choice of different activities, and it is accessible to most regardless of ability. Encouraging an active lifestyle in the elderly is therefore a sensible intervention that is worthy of consideration. Moreover, there is a social component to group activities, which may add to their appeal and possibly their effectiveness. Psychosocial mediators of the effect of physical activity on cognitive function are discussed in more detail elsewhere (Stock, Clifford & Hogervorst, 2012).

1.4. Mechanisms for protective effects of physical activity on brain function

Physical activity seems to be a sensible intervention for Alzheimer's disease but an equally important question is whether there are any theoretical mechanisms through which physical activity may impact on cognitive functioning. There are many plausible mechanisms that have been suggested, which are described below and presented in Figure 1.

1.4.1. Direct causal effects and the association of physical activity with cognitive reserve

Physical activity is believed to increase cell proliferation and promote the maturation of cells to fully integrated neurons (van Praag, Christie, Sejnowski & Gage, 1999; Kim et al., 2010; for a review see Schaeffer, Novaes, da Silva, Skaf & Mendes-Neto, 2009). Van der Borght, Havekes, Bos, Eggen & Van der Zee (2007) found that running increased the number of young neurons in the mouse dentate gyrus (see also

Kim et al., 2010). While previously controversial, it is now generally accepted that neurogenesis occurs in two regions within the adult brain, one of which is the subgranular zone of the dentate gyrus in the hippocampus (Zhao, Deng & Gage, 2008), an area implicated in memory (Diana, Yonelinas & Ranganath, 2007) that is particularly affected in AD (Rombouts, Barkhof, Witter & Scheltens, 2000). Reduced neurogenesis is not considered to be directly or solely responsible for AD but neurogenesis is known to decline in older age (Verret, Trouche, Zerwas & Rampon, 2007) and preventing cells from dividing impairs memory performance (Shors et al., 1995), potentially exacerbating the effects of dementia pathology. In addition, Acetylcholinesterase Inhibitor (AChEI) treatments – the primary treatment for AD that can temporarily help to slow symptom progression – increase the number of young cells and neuroblasts (cells that are mature but not yet integrated in neural networks), found *in vivo* and *in vitro* (DeCarolis & Eisch, 2010).

Levels of neurotrophins increase after physical activity, such as Insulin-Like Growth Factor-1 (IGF-1; Nakajima, Ohsawa, Ohta, Ohno & Mikami, 2010). Exercise induced IGF-1 is associated with increased neurogenesis (LLorens-Martín, Torres-Alemán & Trejo, 2010). This may reflect a downstream process as IGF-1 induces Brain-Derived Neurotrophic Factor (BDNF), which helps to promote the survival of neural stem cells (e.g. Zhao et al., 2008; Bothwell, 1995). BDNF supports cholinergic neurons and it is secreted by pyramidal neurons in the hippocampus (Schaeffer et al., 2009). Physical activity is also associated with increased levels of Granulocyte Colony Stimulating Factor (G-CSF) in the cingulate and prefrontal cortices in older human adults (Flöel et al., 2010). G-CSF helps to inhibit proinflammatory cytokines, such as IL1, TNFα and IFN-γ, which are released by microglia as part of an immune response by plaque deposition, potentially worsening dementia pathology through a cyclical relationship (Nichol et al., 2008). Inflammatory markers within the hippocampus have been observed to decrease following physical activity (Lovatel et al., 2013). Direct causal effects of physical activity on cognition are therefore plausible and this makes it important to evaluate physical activity as an intervention for AD. However, new cells take time to become functional and integrated into the dentate gyrus (Zhao, Teng, Summers Jr,, Ming & Gage, 2006), yet memory and attention improvements have been demonstrated after an acute bout of physical activity (e.g. Hogervorst, Bandelow, Clifford & Stock, unpublished raw data). Neurogenesis is

therefore not the only potential causal pathway through which physical activity can influence cognitive functioning.

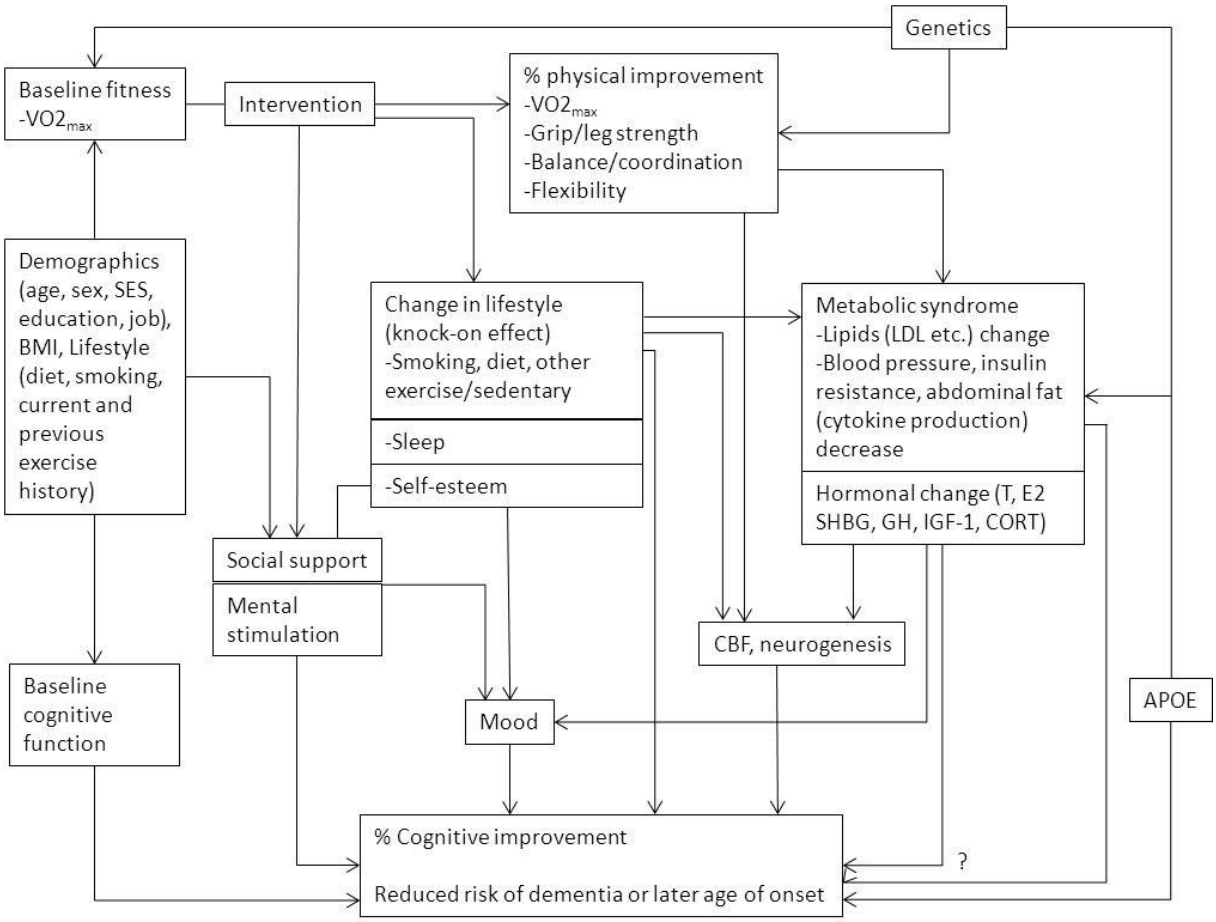

Figure 1
Theoretical mechanisms for protective effects of physical activity on cognitive function[1]

Physical activity that increases the heart rate encourages the flow of blood and oxygen around the body including the brain (Querido & Sheel, 2007; Ogoh, 2008; Rhyu et al., 2010), preventing loss of tissue through hypoxia to which the hippocampus is thought to be particularly sensitive (Di Paola et al., 2008). Brain volume is at least maintained in both gray and white matter areas after long-term physical activity (Colcombe et al., 2006) and perhaps particularly the right anterior frontal cortex (Flöel et al., 2010) and the

[1]Figure developed by Prof E Hogervorst

hippocampus (Yuede et al, 2009), both of which are involved in memory. Direct neurological effects of physical activity are purported to affect cognitive functioning through what has come to be known as “cognitive reserve”. Supporters of this theory suggest that the brain has the capacity to function relatively normally in the presence of disease pathology (Nithianantharajah & Hannah, 2009; Stern, 2002). This is supported by the observation that degree of AD pathology at post-mortem is not always indicative of decreased cognitive performance (Katzman et al., 1989). Increased cognitive reserve is not thought to significantly extend life expectancy but rather maintains cognitive abilities for longer during the lifetime of the individual (Marioni, van den Hout, Valenzuela, Brayne & Matthews, 2012). Although some accounts of cognitive reserve suggest that it is a predefined threshold, others consider cognitive reserve as adaptive and the proposed impact of physical activity on cognitive reserve is largely based on neural networks being modifiable. While education and childhood IQ (which are associated with early acquired cognitive reserve) predicted age at onset of both hypertension and dementia (Hogervorst, Clifford, Stock, Xin & Bandelow, 2012), education in most models remains independent of other risk and protective factors, suggesting scope for later-life interventions.

1.4.2. Association with cardiovascular risk factors

Healthy lifestyles may influence cognition through their effects on cardiovascular risk factors, which are also risk factors for AD. For example, the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study followed their 1449 participants from middle-age, beginning at around the mid 40th decade of their lives (Kivipelto et al., 2005). They found that being obese (Body Mass Index [BMI] >30kg/m^2), having a high BP and high total cholesterol in midlife increased the risk for AD 18 years later by a factor 1.5 to 2, i.e. these factors doubled the risk. When the three factors were present together, the risk for AD was increased by a factor 6. This was independent of reported fat intake or physical activity, age and education. Similarly, in the Honolulu-Asia Aging Study (Launer et al., 2000), increased BP in mid-life (in the 5th decade of life) was associated with an increased risk of AD after 25 years in non-treated individuals. In the Kaiser Permanente of Northern California Medical Group study, elevated levels of cholesterol at 40-45 years of age were associated with a doubled risk of AD and VaD after a 30 year follow-up (Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009) and being overweight or obese at 40-45 years of age was also associated with a 2 to 3 fold increase in risk of AD in later life (Whitmer,

Gunderson, Quesenberry, Zhou & Yaffe, 2007). The Swedish Adoption/Twin Study Aging study similarly suggested that higher BMI in the 4th decade of life was associated with lower global cognitive ability 25 years later and faster cognitive decline (Dahl et al., 2009). Physical activity reduces fat mass and lowers blood pressure and cholesterol levels (Hogervorst et al., 2012), and it is thus a cost effective way of reducing cardiovascular and dementia risk in midlife.

1.4.3. Association with an overall healthy lifestyle and diet

Active lifestyles may appear to influence cognitive functioning because they are accompanied by other healthy behaviours that exert an independent effect on cognition. For example, certain diets help to protect against cardiovascular risk factors (see section 1.4.2.) and they may also have direct neurological effects. A prospective study of older adults found a positive relationship between monounsaturated and polyunsaturated fatty acid intake and global cognition over 8.5 years (Solfrizzi et al., 2005). The Mediterranean diet is low in fat but does contain high levels of antioxidants, omega-3 fatty acids and vitamin B12, which are thought to be neuroprotective. Adherence to the Mediterranean diet was associated with a 24% reduced risk of AD after adjustment for age, sex, ethnicity, education, ApoE genotype, caloric intake, smoking, comorbidity index and BMI (Scarmeas, Stern, Tang, Mayeux & Luchsinger, 2006). Other research suggests that caloric restriction may be more important than specific diets in affecting cognitive performance; for example, Witte, Fobker, Gellner, Knecht and Flöel (2009) showed a significant improvement in memory scores in 50 healthy older adults who adhered to a calorie-restricted diet over three months compared to those who continued with their normal diet.

The associations between physical activity, diet and cognitive functioning may also be linked to insulin sensitivity. Insulin resistance is a risk factor for AD even in those who do not have diabetes (Rönnemaa et al., 2008; Luchsinger, Tang, Shea & Mayeux, 2004). Increasing insulin resistance through feeding a high fat diet can lead to impaired ability on task switching in rats (McNeilly, Williamson, Sutherland, Balfour & Stewart, 2011), reduced long-term potentiation in the dentate gyrus and impaired Morris Water Maze performance (Stranahan et al., 2008). In Witte et al.'s study of human elderly, significant relationships were found between increased insulin sensitivity and improvements in memory (Witte et al., 2009). Drugs for diabetes have also been found to improve or

maintain cognitive ability (Craft et al., 2012). Type 2 diabetes is particularly associated with lifestyle factors, including diet and physical activity, and reducing insulin resistance through a healthy lifestyle may help to prevent cognitive decline and AD. It could thus be suggested that those who choose to engage in physical activity will also choose healthier diets and evidence exists for this health 'knock-on' effect.

1.4.4. Physical activity may be most important in midlife

Despite evidence for strong associations in midlife, cardiovascular risk factors have been shown to change in the years before dementia becomes clinically apparent, possibly due to dysfunctional regulation in the central nervous system caused by pathological changes seen in AD. For instance, a meta-review of the literature (Qiu, Winblad & Frtaiglioni, 2005) showed that high BP in mid-life is associated with AD, whereas low BP in older age is associated with AD. In cross-sectional case control studies in those with established dementia, BP is often found to be lower (e.g. Hogervorst, Ribeiro, Molyneux, Budge & Smith, 2002). In a longitudinal study, high BP was found to be a risk factor in mid-life for later life dementia but was seen to drop in the years preceding the clinical onset of dementia (Skoog & Gustafson, 2006). Similarly, being overweight or obese in later life (>60 years of age) has been associated with a decreased risk of dementia (West & Haan, 2009) despite mid-life obesity being associated with increased risk. This has important implications for treatment; two Cochrane reviews found no evidence that reducing cholesterol through the use of statins or reducing BP with anti-hypertensive medications lowered risk of AD and dementia in individuals above the age of 70 years (McGuinness, Craig, Bullock & Passmore, 2009; McGuinness, Todd, Passmore & Bullock, 2009).

The neurological benefits of physical activity also suggest the benefit of midlife intervention as exercise does not appear to have an effect on Aβ once plaques and memory impairments are already present (Richter et al., 2008). These data thus suggest a need for early midlife (rather than later life) interventions, as these risk factors tend to become unstable in later life. In addition, in midlife after menopause, levels of sex steroids (both estrogens and testosterone) drop dramatically in women and men also start to show a gradual decline (Hogervorst et al., 2012). Physical activity affects levels of sex hormones, which may have a knock-on effect on cognitive functioning. For example, free testosterone, which decreases with age (Shkurnikov, Donnikov, Akimov, Sakharov &

Tonevitsky, 2008), affects many factors implicated in pathological brain aging and reduced levels have been associated with dementia risk (Hogervorst, Bandelow, Combrinck, & Smith, 2004). Estrogen also has various potential protective effects on brain function (Hogervorst, Henderson, Gibbs & Brinton, 2009). Part of the effect of exercise may thus be mediated by its effects on sex steroids but this remains to be further investigated.

1.5. Conclusion

In all, physical activity presents as a potential lifestyle intervention with evidence pointing towards the need for midlife intervention before dementia pathology is present. There appear to be multiple mechanisms through which physical activity can affect cognitive performance and reduce the risk of dementia through associations with other lifestyle behaviours, cardiovascular risk factors and cognitive reserve. In practice, it is likely that the beneficial effects of physical activity and cognitive function are due to a combination of factors, both direct and indirect. The study of mediating and moderating factors is therefore important to determine optimal conditions for the relationship between physical activity and cognitive functioning. In the next chapter, we present a literature review of exercise studies to identify such factors for investigation in Parts 3 and 4 of this thesis.

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Chapter 2 – Review of previous studies investigating physical activity and cognition

2.1. Introduction

Physical activity appears to be a potential lifestyle intervention for AD with many possible mechanisms for maintaining cognitive performance into older age. There is a wealth of studies that have looked into the effects of physical activity on cognitive function in the elderly, many of which have found increased scores on cognitive tests or a reduced risk of developing dementia for those who participate in physical activity versus those who do not. However, there are also many studies that have failed to replicate this, finding instead that physical activity has little or no effect on cognitive function. Here we aimed to critically review these studies and their findings to establish possible reasons for these discrepancies.

By reviewing the physical activity and cognition literature we have tried to answer the following questions. Our first question was whether physical activity has any long-term effect on cognitive function in healthy elderly adults, and, second, whether it can protect against or delay the onset of dementia. Finally, we wanted to know if exercise can improve cognition or offer protection from further decline in those who have already been diagnosed with dementia. There have been previous reviews of this literature, such as Kramer, Erickson and Colcombe (2006) and Rockwood and Middleton (2007). However, here we provide an up-to-date review of a wide range of human behavioural studies with a focus on the different types of physical activity and cognitive measures used. Specifically, we looked at whether the effect of physical activity is general to all cognitive functions or selective for only a few. We also considered the different types and intensities of exercise and physical activity measures and which may be most effective in showing improved or maintained cognitive function in the elderly. Finally, we looked at a range of potentially confounding and moderating variables that may have affected the results of these studies.

Earlier meta-analyses, such as those by Angevaren, Aufdemkampe, Verhaar, Aleman and Vanhees (2008) and Colcombe and Kramer (2003), have found overall positive effects of exercise on cognition. However, one meta-analysis (Etnier, Nowell, Landers & Sibley, 2006) did not fully support this view, claiming that any small differences

in cognition after exercise are in fact due to factors independent of the physical activity. This discrepancy may be related to the different studies that were included in the analyses and differences in inclusion criteria of studies. For instance, most of these reviews focused on aerobic activity only. We therefore included studies that investigated the effect of aerobic and/or non-aerobic activity.

2.2. Methods

To identify studies relevant to this review, we performed searches of PubMed, PsycInfo and Cochrane Controlled Trials Register (date range unrestricted) using combinations of the keywords “exercise, physical activity, Alzheimer, dementia, cognition, cognitive function, memory, executive function”. Full texts of articles that appeared to answer the research question were retrieved for further assessment. Inclusion criteria were all experimental, cross-sectional or prospective studies that investigated the long-term effect of any kind of physical activity on cognition (measured in the form of cognitive tests or risk of dementia) in middle- to older-aged humans. Randomised controlled trials (RCTs) could include exercise programs of any type and duration. We also manually searched bibliographies of studies identified in these initial searches for further papers. The literature search was completed in February 2009.

For inclusion in this review, papers had to include both a measure of physical activity and a measure of cognitive performance, cognitive impairment or a clinical syndrome (dementia, AD, VaD or MCI) in humans only. For the studies investigating healthy adults, we selected studies in which the mean age of participants was over 40 years, and there was no upper age limit. Treatment trials were excluded if they did not include a control group, or if the exercise group also undertook social or mental activities, as this may have confounded the results reported. For instance, a study by Diesfeldt and Diesfeldt-Groenendijk (1977) showing better memory with group gymnastics after a 4 week RCT was excluded from this review as it was unclear what level of (neurological) disability or cognitive status participants had. A study by Fabre, Chamari, Mucci, Masse-Biron and Prefaut (2002) was also not included as the intervention, sample and results matched those in an earlier article (Fabre, Masse-Biron, Chamari, Varray et al., 1999). Data was extracted based on pre-defined criteria (see Tables 1-4). The identified studies were grouped into categories for critical review. Firstly we looked at cross-sectional and

RCT studies that assessed the effect that physical activity has on cognitive function in healthy adults using cognitive tests as the outcome measure. The next set of studies investigated whether higher levels of physical activity reduced the risk of developing dementia. The final studies reviewed examined whether physical activity affected ability on cognitive tests in adults with an existing diagnosis of cognitive impairment or dementia. It is important to distinguish between the effect of exercise on cognitive function in healthy adults and that in adults with dementia, as the same overall effect may be due to different processes and therefore have slightly but meaningfully different features, such as the type of exercise or the specific cognitive modality on which it has an effect. This would in turn lead to different recommendations for interventions. Therefore, we will review separately the studies that have included each of these groups.

2.3. Results

2.3.1. Cognitive Function in Healthy Middle-aged Adults: Observational studies

A large proportion of the studies found through our search of the literature were cross-sectional studies without follow-up (details of these studies are given in Table 1). Generally, participants had their recent physical activity levels rated and they then completed a selection of cognitive tests. A variety of results were seen across these studies, with seven (Christensen et al., 1996; Colcombe et al., 2004; Bixby et al., 2007; Deeny et al., 2008; Newson, & Kemps, 2006; van Gelder et al., 2004; Barnes, Yaffe, Satariano & Tager, 2003) finding a clear benefit of exercise on all cognitive tests completed, and eight finding a benefit on some tests, but not on others (Clarkson-Smith & Hartley, 1989; Shay & Roth, 1992; Christensen & Mackinnon, 1993; van Boxtel et al., 1997; Etnier et al., 999; Lindwall, Rennemark & Berggren, 2008; Newson, & Kemps, 2008; Petrella, Miller & Cress, 2004). One study of very healthy elderly participants (van Boxtel, Langerak, Houx & Jolles, 1996) found no main effect of exercise, but did report an interaction between age and activity on cognitive speed. No studies found a negative effect of exercise on cognition.

Table 1

Details of cross-sectional studies investigating the association between exercise and cognitive function in healthy adults.

Author	**Year**	**n (%F)**	**Mean age: years (SD)**	**Age range: years**	**Country**	**Groups**	**Exercise / fitness measure**	**Tests**	**Outcome**	**Covariates**	**Notes**
Clarkson-Smith	1989	124 (N)	69.74 (N)	55-88	USA	High exercise (>3100 kcal/week + > 1 1/4 hr exercise) vs. low exercise (<1900 kcal/week + < 10 min exercise)	All activity requiring physical exertion (<1kcal/min/kg of body weight), including sport and non-recreational activity	Letter sets, Digit span backwards and Reading span, Simple, 2- and 4-Choice RT, Analogies, Progressive matrices, Letter series completion	High exercise group performed significantly better than the low exercise group on: Letter sets, Reading Span, Simple, 2- and 4-Choice RT, Analogies, Matrices, Series Completion.	Age, education, self-rated health status. Collapsed across sex	Fitness significantly increased (HR and vital capacity) for high compared to low exercise group
Shay	1992	38 (0%)	65 (N)	60-73	USA	High fit (above median for age group) vs. low fit (below median for	Predicted VO2max	WMS Visual reproduction immediate and delayed recall, Hooper Visual Organisation test, ReyOsterreith	Significant differences between groups for: WMS Visual Reproduction immediate and	WAIS-R Verbal Intelligence	Have considered here only older group for review. Fitness groups relative to each other.

						age group)		Complex Figure, WAIS-R Digit Symbol, SCWT, TMT, Verbal fluency, Digit span, WMS Logical Memory immediate and delayed, Critical Flicker Threshold, Finger Tapping speed	delayed recall, ReyOsterreith Complex Figure copy and recall.		17.9% of subjects' self-reported activity not correlated with fitness measure. Activity measured over past several months
Christensen	1993	56 (N)	76.7 (N)	70+	Australia	High education vs. low education	Scale 1 based on Schonfield (% hours a day spent active v passive). Scale 2 based on number of hours a day spent in physical, social and mental activity - 7 point score	Symbol-Digit Modalities test, Progressive Matrices, Similarities subtest from WAIS-R, NART, WMS Visual Reproduction, 5 purpose-designed tests	Physical activity from both Scale 1 and Scale 2 positively related to fluid intelligence but not memory or crystallised intelligence	Age, GHQ-30, health, education,	Have considered here only older group used in this study. The two scales associated high activity with opposite levels of education so may not be reliable measures.

van Boxtel	1996	80 (N)	67.14 (N)	55+	Netherlands	One group	APAQ	Word learning, SCWT colour-word part III, Concept-shifting task part C, Concept-shifting parts O, A and B, SCWT colour-word part I and Continuous tapping, Letter digit modalities, Verbal fluency	Exercise explained little variance on all cognitive tests	Age, sex, intelligence, health	Recruited relatively active and healthy older adults. APAQ not validated with direct measures of caloric expenditure e.g. VO2max. Many tests were modified or based on others.
Christensen	1996	703 (N)	(N)	70-89	Australia	One group	Current levels of sport, walking, heavy gardening, cleaning	MMSE, memory for a figure, Word recall, Address recall, Face recognition, Word recognition, Symbol-Letter Modalities test, NART, WAIS-R Vocabulary, Information Knowledge, WAIS-R Similarities, Cube	Activity contributed significantly but modestly to variance accounted for in fluid and crystallised intelligence, memory and MMSE (change in R2= .01-.02)	Age, sex, sensory functioning, health, education, ADL, past medical conditions, activity x education, age x activity, age x education	Current levels of activity measured only, does not take into account levels over past several months.

								Drawing, Verbal Fluency, Simple and Choice RT			
van Boxtel	1997	132 (42%)	47 (N)	24-76	Netherlands	Participation v non-participation in additional cycling session	Endurance cycling (reach HR70%) - VO2max; Weekly participation in aerobic sports	VVLT, Verbal Fluency, Continuous Tapping, Concept Shifting Test, Simple and Complex RT, Letter-Digit Subtraction test, SCWT colour-word test	Positive association between VO2max and SCWT colour-word (added .01 to R2) and Concept Shifting task (added .02 to R2)	Age, sex, IQ	Not controlled for general health but participating group rated themselves higher than non-participating group. Subjects with IQ scores <90 or >140 were excluded
Etnier	1999	98 (N)	(N)	56-80	USA	One group	6 min walk test of fitness	Fluid intelligence (Culture Fair Intelligence test) Working memory span (word recall) Processing speed (modified version of Digit-Symbol test) Reaction Inhibition (Negative Priming task)	6 min walk test added .17 to R2 for fluid intelligence and .20 for processing speed. Did not explain extra for working memory or reaction inhibition	Age, education, depression, pulmonary function	

Colcombe	2004	41 (N)	(N)	(N)	USA	High fit (above median fitness) vs. low fit (below median fitness)	VO2max	Flanker task	High fit group performed better on Flanker task than low fit group		High fit group had a greater level of activity in prefrontal and parietal cortex
Bixby	2007	120 (68%)	78.9 (5.8)	65-92	USA	One group	Frequency and intensity of physical activity (YPAS)	SCWT colour-word test	Physical activity intensity explains 4% of variance in SCWT interference scores	IQ, education, age	Physical activity must have been stable for 3-5years to be reported.
Lindwall	2008	1402 (N)	75.1 (10.2)	60-92	Sweden	Non-active (never - 1-3 times/month) vs. active (several times/week - every day) over last 12 months	Light intensity e.g. walking, golf; high intensity e.g. jogging, skiing, ball sports	MMSE, free recall, recognition of positions, Digit Span backwards, Digit Cancellation, Comparing Figures, Vocabulary	Active participants who did light intensity activity showed higher scores compared to non-active on Vocabulary, recognition of positions, free recall, Digit Span, Digit Cancellation and	Age, education, depression, functional status, co morbidity	

									MMSE for men only. No significant effects of high intensity activity on any task		
Deeny	2008	54 (44%)	59.9 (4.6)	50-70	USA	One group	Total caloric expenditure per week	Sternberg task	Physical activity significantly predicted RT for both six- and eight-letter conditions for e4+ only	Age, education, sex, stratified for ApoE4+ and e4-	Both heterozygous and homozygous ApoE4 carriers were included
Newson	2008	96 (53%)	70.79 (5.23)	65+	Australia	High vs. low fitness	>3 hours/week of vigorous activity causing sweating or increase in HR or breathing vs. no activity	SRT Attention (SCWT, Map search task), Working memory (Letter-number sequencing, Corsi blocks) Processing speed (Digit symbol substitution, Boxes test) Memory (Names test, Doors test) Executive Function	High fit group performed better on SRT, working memory and processing speed. No difference on tests of memory, attention or executive function.	Age, sex, education, general wellbeing, crystallised intelligence (NART-R and Spot the Word test)	Only older group considered for this review. Activity had to be stable for 2 years to be reported.

								(Six element test, Zoo map test)		
Newson	2006	100 (67%)	young: 20 yrs; young-old: 69; middle-old: 77; old-old: 86 yrs all SD=2	18-26, 65-74, 75-84, 85-92	Australia	One group	VO2max	Attention (SCWT, Map search) Working memory (Letter-number sequence of WAIS-III, Corsi blocks) Processing speed (Digit symbol substitution, Boxes test) Executive Function (Zoo map test, Six elements test) Memory (People test, Names test)	VO2max contributes additional 26% of variance in attention, 11% in working memory, 23% in processing speed, 8% in executive function and 7% in memory.	Age, sex, education, psychological and physical wellbeing, biomarkers of aging
Petrella	2004	35 (69%)	77.2 (6)	(N)	USA	Independent vs. marginally dependent	High vs. low leg extensor power	Cognitive Stability Index (RT, psychomotor speed, memory, attention)	Independent group showed higher scores on RT, psychomotor speed and memory compared to marginally dependent group. No	Age, education

									significant differences on attention.		
Longitudinal studies											
van Gelder	2004	295 (0%)	74.91 (N)	(N)	Finland, Italy, Netherlands	Increase, stable or decrease duration of activity; Increase, stable or decrease in intensity of activity over follow-up	Walking, bicycling, hobbies, gardening, odd jobs, sport	MMSE	Decrease in duration and intensity of activity associated with a decline in MMSE scores. Increase in duration and intensity of activity show no change in MMSE scores.	Age, education, country, alcohol consumption, smoking status, mental activities, physical activity and duration ADL, depression, BMI, antihypertensive drugs, HDL, cholesterol, BP, baseline cognitive functioning	Follow up 10 years
Barnes	2003	349 (N)	69 (N)	59-88	USA	Tertiles of fitness	VO2peak	MMSE, TMT B, SCWT, Digit Symbol Substitution Test, CVLT, Verbal fluency	Participants with lowest baseline VO2peak showed decline in scores on all tests, while	Age, years of education, intelligence, hypertension, thyroid disorder, self-rated	Follow up 6 years

	participants with highest baseline VO2peak remained stable.	health, smoking, and baseline mMMSE score. Stratified by sex

Abbreviations: (N) - information unavailable; RT - Reaction Time; HR - Heart Rate; WMS - Wechsler Memory Scale; WAIS-R - Wechsler Adult Intelligence Scale; TMT - Trail Making Test; NART - National Adult Reading Test; GHQ - General health Questionnaire; APAQ - Actual Physical Activity Questionnaire; MMSE - Mini Mental Status Examination; VVLT - Visual Verbal Learning Test; YPAS - Yale Physical Activity Scale; SRT - simple RT; BP - Blood pressure; ADL - Activities of Daily Living; BMI - Body mass index; HDL - High-density lipoprotein; CVLT - California Verbal Learning Test

2.3.1.1. Test specificity

There are several possible reasons for the variety in results seen among the cross-sectional studies. Firstly, physical activity could have a specific effect on some cognitive domains, but not on others. These cross-sectional studies tended to include many cognitive measures, as they were looking at cognitive function in general terms. This is useful as this can tell us more about possible effects across different cognitive domains. However, it also increases the risk of chance findings, especially when only one test for each domain is used. The most common domains tested were i) memory, ii) cognitive speed, iii) executive function and iv) response inhibition[2]. Of these, none proved to have a consistent association with physical activity. All domains showed positive effects after exercise in some studies but not in others. The most reliable function to be improved in those who exercised was cognitive speed, with memory and response inhibition showing positive associations of exercise in around half of all tests used. When these tests were broken down further into individual tasks, the most common tests showing positive associations with physical activity were: i) the Trail-Making Test B (TMTb), ii) the SCWT test, iii) Simple Reaction Time tests (SRT), iv) Complex Reaction Time tests (CRT), v) the Digit Symbol Substitution Test, vi) Verbal Fluency and vii) tests measuring word or letter learning such as the Digit Span, measuring short term memory capacity. Again, there were no tests that showed a consistent advantage for groups that were more physically active. Thus, while we cannot rule out selectivity for specific cognitive domains, this cannot explain all of the variance seen in these data.

2.3.1.2. Measures of physical activity

The variety of results seen in these cross-sectional studies may be influenced by the type of activity or the exercise measures used. Some studies analysed only participation in activity that caused sweating or increased heart rate (e.g. Newson & Kemps, 2008), while others included lower intensity exercise such as walking (e.g. Lindwall et al., 2008). Some studies used objective measures of fitness, such as VO_{2max} (e.g. Newson & Kemps, 2006). We grouped the studies into those that used objective measures of fitness and those that used frequency of activity. Frequency of activity and objective fitness measures both showed similar inconsistent results for memory, executive

[2] See also Angevaren et al., 2008 for a similar classification and explanation of tests falling under these domains

control and inhibition. However, studies measuring activity frequency were more likely to report positive associations with better cognitive speed (SRT and CRT) than those that used objective measures of fitness. Shay and Roth (1992) found that in 17.9% of subjects, the self-reported level of activity did not correspond with their VO_{2max}. Self-report of exercise is thus not always related to objective fitness and other factors such as mental stimulation, improved mood and social interactions while exercising may be responsible for the positive associations found. However, two studies (Deeny et al., 2008; Clarkson-Smith & Hartley, 1989) considered energy expenditure and both found positive effects of exercise on memory and reaction time (RT). Therefore for future work, objective measures of energy expenditure and fitness should be used in addition to self-report of frequency of physical and other activities (e.g. mental stimulation because of exercise etc.) in order to obtain reliable and valid measures of physical activity and fitness.

2.3.1.3. Cross-sectional studies – general issues

Cognitive domain and exercise measures do not appear to explain all of the variance in these cross-sectional studies. However, these studies cannot establish causal relationships between variables. Many of these cross-sectional studies run the risk of self-report bias as they included questionnaires to determine level of activity that rely on accurate completion by participants. Self-report by definition is unreliable in those who have impaired cognitive function, which can result in artificially increased risks. However, we also found two prospective studies which both found that participants with lowest cardiovascular fitness over 6 years (Barnes, 2003) or a decline in self-reported physical activity over 10 years had a worse drop in scores on the Mini-Mental Status Examination (MMSE), a test sensitive to dementia (see Chapter 3). On the other hand, exercise may not have an influence on cognition so much as cognition has an effect on the amount of exercise a person does. For example, memory limitations may affect the ability to start or continue participating in exercise programs. Hence, a review of randomised controlled treatment studies (RCT) is required in order to determine the true causal effect of physical activity on cognitive function.

2.3.2. Cognitive Function in Healthy Middle-Aged Adults: Randomised Controlled Trials

The other type of studies identified for this review is RCTs (see Table 2 for details of studies). RCTs have the benefit over cross-sectional studies in that, by randomising participants into two groups, there is increased probability of a causal relationship between the two variables. Among the 20 RCT studies that we identified through our literature search, six studies (Hawkins, Capaldi & Kramer,1992; Colcombe et al., 2004; Lachman, Neupert, Bertrand & Jette, 2006; Cassilhas et al., 2007; Williams & Lord, 1997; Bakken et al., 2001) showed a clear benefit of exercise on cognitive function, while a further 13 studies (Molloy, Delaquerriere-Richardson & Crilly, 1988; Hassmen, Ceci & Backman,1992; Brown, Liu-Ambrose, Tate & Lord, 2008; Perrig-Chiello, Perrig, Ehrsam, Staehelin & Krings, 1998; Fabre et al., 1999; Oken et al., 2006; Hill, Storandt & Malley, 1993; Moul, Goldman & Warren, 1995; Smiley-Oyen, Lowry, Francois, Kohut & Ekkekakis, 2008; Zlomanczuk et al., 2006; Emery, Schain, Hauck & MacIntyre, 1998; Kramer et al., 2001; Hassmen & Koivula, 1997) showed some benefit of an aspect of exercise on some tests used, but not on others. The final seven studies (Blumenthal & Madden, 1988; Tsutsumi, Don, Zaichkowsky & Delizonna, 1997; Madden, Blumenthal, Allen & Emery, 1989; Blumenthal et al., 1989; Emery & Gatz, 1990; Panton, Graves, Pollock, Hagberg & Chen, 1990; Whitehurst, 1991) showed no effect of an exercise program on cognitive function. Again, no study found a negative effect of exercise on cognition.

2.3.2.1. Test specificity

Because of the high proportion of studies that showed effects of exercise on some tests but not on others, the contrasting results may be due to exercise having a specific effect on particular cognitive domains, such as those discussed for the cross-sectional studies. For the RCTs identified here, we were able to form groups for i) cognitive speed, ii) memory, iii) executive function, iv) inhibition and v) visual attention. Exercise appeared to have the most consistent effect on memory and visual attention, although only about half of the tests for each domain showed a positive effect of exercise.

Hall, Smith and Keele (2001) suggested that aerobic activity has selective benefits for executive control, and this was supported by a later meta-analysis by Colcombe and Kramer (2003). Chodzko-Zajko (1991) examined task difficulty, claiming that automatic

processes are less liable to age-related decline and show less benefit from exercise compared to those that require conscious thought and controlled processing. However, this idea does not seem to be supported by the data described here, as there appeared to be no overall consistent advantage on tests of executive control and inhibition for exercise groups compared to controls. Angevaren et al. (2008) also found in their meta-analysis comparing aerobic exercise vs. no intervention that only simple tests such as auditory attention (Digit Span forwards) and motor speed (Finger Tapping[3]) were significantly affected by exercise. While only half of the studies in our review reported a positive effect of exercise on Digit Span (forwards and backwards), this was also the only individual test to show a repeated positive effect. This was not the case for executive control or inhibition tests that require controlled information processing. Similarly, Etnier et al.'s (1997) meta-analysis of cross sectional studies found a larger effect size for simple than complex tasks.

As mentioned by Chodzko-Zajko (1991), there are very few studies that directly examined the relationship between task difficulty and exercise. One study, Hawkins, Capaldi and Kramer (1992) used two visual attention tests that each had two levels of difficulty: one was a single task, the other a dual task. They found that after the intervention period there were no differences between the exercise and no-exercise groups on the simpler task, but that time-sharing costs on the dual task were more reduced for the exercise than the no-exercise group. Evidence thus suggests that task complexity may indeed partly determine whether an effect of exercise is seen or not, although it is inconclusive which type of task (simple or complex) actually shows greatest benefit.

2.3.2.2. Type of exercise

The RCT studies reviewed included a wide variety of different exercise programs and so the different results reported may be due to specific exercise programs having an effect but not others. The exercises involved ranged from aerobic activity, such as jogging (e.g. Madden et al., 1989) to non-aerobic exercises, such as strength training (Tsutsumi et al., 1997) or yoga (Oken et al., 2006). For the studies that compared an exercise group with a no-exercise control group, we split the different exercises into the following groups:

[3] One test (the Ross Information Processing assessment A) also showed an overall significant effect of memory and abstract reasoning but was only done in one RCT of n=20 (Moul, 1995)

i) aerobic (endurance), ii) flexibility and iii) strength. Where the program fell into two or more categories of exercise type, the study was placed under the category where that type of exercise was performed most.

Nine out of the 13 studies that compared aerobic exercise against no exercise found a positive effect on at least some cognitive tests (Hassmen et al., 1992; Fabre et al., 1999; Hill et al., 1993; Moul et al., 1995; Hawkins et al., 1992; Bakken et al., 2001; Emery et al., 1998; Hassmen & Koivula, 1997; Whitehurst, 1991). Angevaren et al. (2008) reported from their meta-analysis that a 14% increase in VO_{2max} is required for a positive effect to be found on cognition. However, four out of six studies that compared strength exercise against no exercise also found an effect on cognition on at least some tests (Lachman et al., 2006; Molloy et al., 1988; Perrig-Chiello et al., 1998; Zlomanczuk et al., 2006), suggesting that strength exercise may not only add to the benefit of aerobic exercise but may in fact independently affect cognition.

There is further support for this idea from some other studies that compared groups undergoing different types of exercise. Interestingly, while Blumenthal and Madden (1988) found no differences between RT performance of aerobic and strength/yoga training groups, Colcombe et al. (2004) and Smiley-Oyen et al. (2008) found clear advantages of aerobic over flexibility exercises on a Flanker task and Stroop Colour Word Task (SCWT) respectively. Cassilhas et al. (2007) also found that resistance exercises benefitted participants on some memory tasks (Digit Span, Corsi blocks, Similarities and Rey-Osterreith immediate recall) compared to stretching. No study that compared flexibility exercises such as Yoga against no exercise found an effect on cognitive function. Hence, stretching and flexibility exercises do not seem to render much benefit for cognitive function. Colcombe and Kramer's (2003) meta-analysis suggested that participants benefitted most from a combined strength and aerobic exercise program compared to aerobic exercise alone. Williams and Lord (1997) indeed found a positive effect on cognition of combined aerobic, strength and stretching exercise but had only compared this to no exercise (instead of to individual interventions).

These results combined suggest that the greater the intensity of the exercise, the greater benefit it has on cognitive function. This would suggest that the exercise has a greater cognitive benefit if it is also has a physiological benefit. Just under half of the studies that reported an increase in VO_2 measures found a positive effect of aerobic exercise, and only one study that found *no* increase in physiological function reported a small positive effect of the aerobic exercise intervention over flexibility training (Smiley-

Oyen et al., 2008). This suggests that objective measures of fitness may be extremely important in determining whether an exercise intervention will have a positive effect on cognition. Nearly all of the studies that reported an increase in muscle strength found a positive effect of strength exercise on cognition. For instance, Lachman et al. (2006) found that the increase in resistance levels over time predicted memory improvement over 6 months of exercise. Thus, despite the literature focus on aerobic activity being important for cognition, muscle strengthening and resistance training may also have an effect.

Another factor that could influence whether an exercise intervention can benefit cognition is the length of the exercise program. It could be predicted that the longer an individual maintains regular physical activity, the more their fitness should increase thus potentially exerting a greater effect on cognition. The studies highlighted here ranged from just two months up to one year. Harada, Okagawa and Kubota (2004) investigated the effect of jogging on frontal lobe functioning in young adults and found that most of the improvement in cognition already occurred in the first six weeks, but with little improvement seen from 6 to 12 weeks. This study needs to be replicated in older participants and could indicate that the benefits of exercise are most apparent in the early stages of the programme. While there were more consistent effects of exercise on cognition for interventions lasting six months or more, there were some benefits already reported after a programme of just two months. For example, Bakken et al. (2001), Pierrig-Chiello et al. (1998) and Fabre et al. (1999) already showed improvements of programmes with duration of only 8 weeks and Hawkins et al. (1992) after 10 weeks, respectively. A 6- week follow-up assessment from baseline may help to determine optimal effects in future studies.

Table 2 also indicates that more time spent exercising per week does not necessarily equate to more significant cognitive improvements. This supports Angevaren et al.'s (2008) claim that it is not the amount of exercise that is done but the intensity at which it is done that has a positive effect on cognition. No single study has directly examined this statement so it is difficult to draw firm conclusions. On the other hand, Lachman et al.'s (2006) findings (see above) do support the statement that the degree of objective improvement over time (as well as baseline ability levels) should be taken into account in analyses of results.

Perhaps related to this issue is the problem of relatively low rates of adherence to the exercise programmes. For example, in Brown et al. (2008), attendance ranged from

just 3 to 51 classes out of 52. This means that some individuals who were in the exercise group may actually fit more appropriately into the no-exercise control group. However, keeping them in the exercise group for analysis affects the mean change in cognitive scores. This is also seen in Oken et al. (2006), where mean attendance at the classes was 69% for the aerobic group, and participants claimed to have completed home practice on only 54% of all days. This is relatively low and may explain why they found no effect of exercise on cognition. Studies of this type must set a required adherence rate for an individual to be included in the exercise group as well as include an objective assessment of the degree of improvement, with any that were assigned to the exercise group but fail to meet the minimum requirements perhaps making up a "some exercise" group or by analysing the effect of the intervention as a continuous measure (e.g. degree of improved $VO_{2\,max}$ or improved strength predicting improved cognitive function).

2.3.2.3. Potential confounding variables

There are several additional variables that may confound the results of these kinds of study if they are not taken into account. For example, Blumenthal and Madden (1988) found that baseline fitness predicted RT after 12 weeks of physical exercise, but that change in fitness levels over the intervention did not affect the follow-up scores. Individuals who chose to take part in one of these exercise studies may have been interested in doing so because they already led an active lifestyle and had relatively high levels of baseline fitness. Therefore, the variance in improvement may have been too small to predict cognitive improvement. This could suggest that baseline fitness may significantly affect results of studies that have not taken this into account. Variability in high- and low- fitness individuals may affect results in that in high baseline fitness participants perhaps little improvement can be found, whereas for low fitness participants adherence may be difficult, but also the largest gains can be expected which may, however, take some time to become apparent (e.g. to build up adequate fitness levels, loss of weight etc.).

When participants began an exercise intervention program it is also possible that they took up other health behaviours, such as a better diet or quitting smoking, perhaps because the directing of attention to their own health by participation in the program encouraged them to have healthier lifestyles overall. This means that the results of

studies that did not monitor other health behaviours may have been confounded by one or a combination of major lifestyle changes other than engaging in exercise.

Another issue that is important is that of age. While some studies investigate the effect of exercise in healthy middle-aged adults (e.g. Blumenthal & Madden, 1988), others recruited much older participants who were more likely to be experiencing at least some degree of age-related cognitive decline or pathology placing them at high risk (e.g. Brown et al., 2008). This age difference may mean that results of these studies cannot really be compared. On the other hand, several observational studies have suggested that the long-term effects of exercise in reducing dementia risk by reducing obesity, improving blood cholesterol and reducing blood pressure may be most important when activity is engaged with in middle-age (e.g. Kivipelto et al., 2005). The studies in this review showed that there were positive effects of exercise occurring in participants with mean ages from 60 years up to over 90 years. Hassmen, Ceci and Backman (1992) split their sample into young (mean age 62.9 years) and old (mean age 69.2 years) age groups, and found that there was a positive effect of exercise on the Digit Span test in both age groups. However, the fact that another observational study did mention an interaction of age by activity (van Boxtel et al., 1996) suggests that all studies should a) control for age but b) should also investigate this possible interaction or stratify for age in analyses. The effect of sex should also be investigated. Whereas most studies used mixed groups, those that included only men (Blumenthal et al., 1988, Cassilhas et al., 2007) found little to no effects of exercise. As we see later, some observational studies found stronger effects in elderly women than in elderly men. Possible mediating effects of hormones related to this should therefore be investigated.

2.3.4. Summary

The results of treatment studies using healthy elderly adults suggest that some aspects of cognition can be improved after moderate and high intensity exercise and through increased strength and/or fitness. However, the variety of cognitive tests used in these studies make it difficult to determine exactly which cognitive domains may be positively affected. While much focus is placed on the benefits of aerobic exercise, strength-training exercises may also help to improve cognitive ability. Objective measures of strength and fitness should be used, as they may be more reliable in predicting

physiological improvement and therefore cognitive improvement than are self-reported accounts of recent activity. Researchers should take care to consider different potential confounding variables, such as baseline and change in fitness, changing other health behaviours, adherence to the program, age and sex, as it is difficult to compare different studies without addressing these issues.

Table 2
Details of controlled trials investigating the effect of exercise on cognition in healthy adults.

Author	Year	n (%F)	Mean age (SD)	Age range	Country	Exercise groups and types	Frequency of Exercise	Duration	Tests	Outcome	Notes
Hawkins	1992	36 (72%)	68 (N)	63-82	USA	Exercise (water aerobics) vs. No exercise	45min, 3x/week	10 weeks	Time Sharing test, Attentional Flexibility test	Greater decrease in time sharing costs for exercise than no-exercise group in both tests	Older group only considered for this review. RT for simple task was similar for both groups
Blumenthal	1988	28 (0%)	43.3 (8.8)	30-58	USA	Aerobic exercise (walking/jogging) vs. Non-aerobic exercise (strength training)	30-45min, 3x/week	12 weeks	Memory Search RT	No significant difference in RT between groups	Aerobic group increased in VO2max by 15% while non-aerobic group increased by 3%. Time 1 fitness accounted for 19% of the variance in Time 2 RT

Tsutsumi	1997	45 (80%)	68.8 (5.7)	61-86	USA	High intensity strength training vs. Low intensity strength training vs. No exercise	3x/week	12 weeks	Count backwards in 7s, Mirror Drawing	Both groups showed similar improvement on both tests post-intervention	Muscle strength, body fat, BP, and physical self-efficacy improved for active groups but not control group
Madden	1989	85 (48%)	67.1 (N)	60-83	USA	Aerobic exercise (cycling/jogging) vs. Non-aerobic exercise (Yoga) vs. Wait list control	Aerobic exercise: 1hr, 3x/week; Non-aerobic exercise: 1hr, 2x/week	16 weeks	Letter Search RT, Word Comparison RT	No significant differences between groups on any task	Only older group considered in this review. Participants showed good compliance to programme (>90%). Aerobic capacity increased in aerobic exercise group between time 1 and time 2.

Cassilhas	2007	62 (0%)	68.1 (N)	65-75	Brazil	Moderate intensity resistance training vs. High intensity resistance training vs. No exercise (stretching class)	1hr, 3x/week	24 weeks	Similarities, Digit span, Corsi Blocks, Rey Osterrieth Complex Figure, Toulouse-Pieron Concentration Attention test	Both exercise groups showed higher scores on Digit span, Corsi Blocks backwards, Similarities, and Rey Osterrieth immediate recall compared to control group. High intensity exercise group performed higher on Toulouse Pieron errors than controls.	Lean mass was significantly different for high intensity group and control post-intervention. Exercise attendance >75%
Molloy	1988	45 (100 %	82.7 (N)	73-90	Canada	Exercise (balance coordination and muscle strength training) vs. No	10-35min, 3x/week	3 months	Colour Slide recall and recognition, Digit Span, Logical Memory, Digit Symbol, Word	Exercise group showed less decline on Word Fluency after	Exercise attendence 31-94%, average 71%.

						exercise			Fluency, MMSE	intervention period. No differences on any other test.	
Hassmen	1992	30 (100 %	66.1 (N)	55-75	Sweden	Exercise training (walking) vs. Mental training (mental arithmetic, problem solving and logical thinkgin)	20mins, 3x/week	3 months	Face recognition, Digit Span, Simple RT, Choice RT	Increase in Digit Span after exercise training group but not mental training. No differences on any other test.	Exercise group was asked to walk at least 3 times per week, the control group was given 3 assignments per week. No differences between groups in VO2max post-intervention but the exercise group had lower systolic BP compared to controls.
Colcombe	2004	29 (62%)	65.6 (5.66)	58-77	USA	Aerobic exercise (walking) vs. Toning and stretching (whole body	10-15 up to 40-45mins, 3x/week	6 months	Flanker task	Aerobic group showed 11% reduction in conflict on task compared	Aerobic exercise group showed an increase in VO2max

						stretching/flexibility)				to 2% in controls.	
Oken	2006	135 (54%)	72.1 (N)	65-85	USA	Yoga vs. Aerobic exercise (walk outdoor 400m track) vs. No exericise	Yoga: 90mins, 1x/week + home practice. Aerobic: 1hr, 1x/week + home exercise	6 months	SCWT Colour-word test, 10-word List Learning, Letter-number sequencing	No differences between groups on any task	Participants attended 69% of classes and exercised 54% of all days for exercise intervention; attendance 78%, exercised 64% of all days for yoga class. Groups did not differ on all physical measures
Brown	2008	154 (88%)	79.6 (6.3)	62-95	Australia	General exercise (walking, resistance, flexibility and balance) vs. Flexibility and relaxation (gentle bending and rotation of	1hr, 2x/week	6 months	Similarities, Arithmetic, Picture Completion, Digit Symbol, Digit Span, Visual Paired Associates, Verbal Paired Associates, TMT, SCWT Colour-word test, Verbal Fluency	General exercise group showed improvements in similarities and arithmetic only. Flexibility and no exercise groups did not	Range of attendance 3-51 classes out of 52

						joints) vs. No exercise				improve on any tasks	
Perrig-Chiello	1998	46 (39%)	73.2 (N)	65-95	Switzerland	Exercise (strength training) vs. No exercise	1x/week	8 weeks	Immediate and delayed recall and recognition, Digit Symbol	Significant increase for immediate and delayed recall and recognition in exercise group only. No differences between groups for cognitive speed	Exercise frequency was very limited. There was a significant increase in muscular strength for exercise group.
Fabre	1999	32 (84%)	65.9 (N)	60-76	France	Aerobic training (walking/running) vs. Mental training (memory and perceptive activity) vs. Aerobic and mental training vs. Control	Aerobic: 2 x 1hr/week walking. Mental training: 1 x 90min/week mental activity	8 weeks	WMS, BEC96	Aerobic and mental activity group showed highest increase in WMS score, followed by aerobic only, then mental only, then control. No	Aerobic groups showed an increase in VO2max.

										change on BEC96 for any group	
Blumenthal	1989	101 (50%)	67.0 (4.9)	60-83	USA	Aerobic exercise (cycling and jogging) vs. Yoga vs. Waiting list control	Aerobic: 1 hr, 3x/week. Yoga: at least 1 hr, 2x/week)	16 weeks	Short Story module of the Randtman Test, Digit Span, Benton Revised Visual Retention test, Selective Reminding, TMT, SCWT, Digit Symbol, Visual Scanning, Fluency test (verbal and non-verbal)	Aerobic group showed no difference in any cognitive scores post intervention compared to control groups	Yoga not done as often as aerobic activity: aerobic = 48 sessions, yoga = 32 sessions. Good adherence rate (96%). There was an increase in VO2peak for aerobic group only.
Hill	1993	87 (51%)	64 (3.1)	60-73	USA	Exercise (flexibility, walking and running) vs. No exercise	50mins, 3-5x/week	1 year	Logical Memory, Digit Symbol, Crossing-off task	Exercise group stayed stable over time on Logical Memory but control group declined. No differences between	

										groups on other tasks	
Moul	1995	30 (63%)	69.1 (.79)	65-72	USA	Aerobic exercise (walking) vs. Strength training vs. Control (mild stretching)	30-40mins, 5x/week	16 weeks	Immediate memory, Recent memory, Temporal Orientation, Problem Solving and Abstract Reasoning, Organisation, Auditory Processing	Aerobic group improved by 7.8% on Organisation and Auditory Processing. Strength and Control group did not improve on any task.	Aerobic group only showed increase in VO2max by 15.8%.
Smiley-Oyen	2008	57 (72%)	70.2 (N)	65-79	USA	Aerobic exercise vs. Flexibility (e.g. Yoga)	50mins, 3x/week	10 months	Simple RT, Choice RT, Incongruent RT, SCWT, WCST, Go/No-go	Aerobic group showed significant decrease in SCWT errors and latency while Flexibility group showed small initial decrease in latency but increase in	There were no significant differences in VO2peak change between groups

										errors. No change on RT, WCST or Go/No-go tasks for any group.	
Zlomanczuk	2006	41 (100 %	64 (N)	57-72	Poland	Exercise (strength and endurance) vs. No exercise	45 mins, 3x/week	3 months	SCWT, Face/Name Association	Exercise group showed improvement in association test performance over time. No changes on SCWT or for control group on any task	
Williams	1997	149 (100 %	71.7 (N)	60+	Australia	Exercise (aerobic, strength and stretching) vs. No exercise	60 mins, 2x/week	12 months	Digit span forwards and backwards, Picture Arrangement, Cattell's Matrices	Exercise group improved on all cognitive measures but control group did not	Mean adherence of 59 (range 26-82) weeks of exercise intermittant with weeks off. Exercise group improved in physiological

											measures over time. Improvement in Digit Span associated with improvements in muscle strength
Emery	1990	39 (83%)	72 (6)	61-86	USA	Exercise (aerobic) vs. Social interaction (card games, art projects etc.) vs. Wait list control	1hour, 3x/week	12 weeks	Digit Span, Digit-Symbol Substitution, writing digits and writing words	No change in any group on any cognitive test	Attendance in exercise group ranged from 61-94%, social group from 10-94%. No differences over time between groups for cardiovascular factors
Lachman	2006	210 (78%)	75.3	60-94	USA	Exercise (resistance) vs. No exercise	35mins, 3x/week	6 months	Digit Span backwards	Change in resistance level over the exercise period predicted improvement in Digit Span	Exercises were delivered by video tape at home. Large range in participation rates. Upper and lower body

										in exercise group.	strength improved in the exercise group only.
Bakken	2001	10 (60%)	82.5 (N)	72-91	USA	Exercise (calisthenics, bicycling and walking) vs. No exercise	6-39mins, 3x/week	8 weeks	Finger Tracking test (measured as accuracy index)	Exercise group showed improved accuracy index whereas no-exercise group showed a decline in accuracy index over time	Attendance to exercise group ranged from 71-100% (mean 90.2%). No improvements were seen in physiological measures for either group.
Panton	1990	49 (53%)	72.04 (N)	70-79	USA	Aerobic (walking/jogging) vs. Strength training vs. No exercise	Aerobic: 30-55mins (increased over weeks), 3x/week. Strength: 30mins, 3x/week	26 weeks	RT	No differences between groups on RT post-intervention. Significant correlation between changes in VO2max and change in RT.	The aerobic group did more exercise than the strength group.

Emery	1998	79 (53%)	66.6 (6.5)	50+	USA	Exercise (aerobic) + education + stress management vs. Education + stress management vs. Control	Exercise: 45-90mins (increased over weeks), 3x/week	10 weeks	Digit Vigilance test, Finger Tapping, TMT (A and B), Digit-Symbol Substitution, Verbal Fluency.	Exercise group showed improved Verbal Fluency compared to control groups. No change on other tasks.	16% gain in VO2max in exercise group only.
Hassmen	1997 (a & b)	40 (50%)	66	55-75	(N)	Exercise (walking) vs. no exercise (3 home assignments per week)	3x/week	3 months	Simple RT, Complex RT, Immediate recall, Delayed recall, Face recognition, Digit span	Significant differences on complex tasks whereas only minor differences on simple tasks	
Kramer	2001	124 (73%)	(N)	60-75	(N)	Aerobic (walking) vs. flexibility (stretching and toning)	10-40mins (increased over weeks), 3x/week	6 months	Visual Search, Response Compatibility task, Task-Switching paradigm, Stopping paradigm, Spatial Attention, Rey Auditory Verbal learning task,	Aerobic group showed significant improvements over the flexibility group on Task-switching,	Aerobic group showed 5.1% increase in VO2max, flexibility group showed 2.8% decrease in VO2max. There were significant

									Pursuit Rotor task, Spatial working memory, Verbal working memory, Face recognition task, Digit-digit and Digit-symbol task, Digit Span forwards and backwards	Stopping, Response-Compatibility and Rey Auditory Verbal Learning task. Other tasks non-significant.	differences between groups for tasks involving executive function but not for tasks involving little or no executive control. There were also no differences for tasks of working memory.
Whitehurst	1991	14 (100 %)	65	61-73	(N)	Exercise (bicycling) vs. no exercise	35-40mins, 3x/week	8 weeks	Simple RT, Choice RT	No differences between groups for either task	Aerobic group showed significantly higher VO2max compared to the control group

Abbreviations: (N) - information unavailable; RT - Reaction Time; BP - Blood pressure; MMSE - Mini Mental Status Examination; WMS - Wechsler Memory Scale; HR - heart rate; WCST - Wisconsin Card Sort task; TMT - Trail-Making Test

2.3.3. The Effect of Exercise on Risk of Dementia

The second question we investigated was how physical activity can affect an individual's risk of developing dementia. We identified prospective studies that examined healthy older adults at baseline and determined the odds ratios of being either i) dementia-positive (cases) or ii) remaining dementia-free (controls) over time depending upon their level of physical activity. Dementia classification could include cognitive impairment (CI), AD, Vascular Dementia (VaD) or dementia as one group. Our search highlighted 13 prospective studies that fitted these criteria. All studies identified were prospective observational studies. Details of the studies identified can be seen in Table 3Table 3. Exercise measures tended to be either frequency of specific exercises, such as walking or swimming (e.g. Larson et al., 2006) or the number of calories expended in a given timeframe (Podewils et al., 2005; Ravaglia et al., 2008). Out of the 13 studies, five found a reduced risk of dementia for those who exercised more often. Significant risk reduction ranged from 31% (AD and VaD; Lindsay et al., 2002) to 88% (CI; Sumic, Michael, Carlson, Howieson, and Kaye, 2007). A further four studies (Larson et al., 2006; Laurin, Verreault, Lindsay, MacPherson & Rockwood, 2001; Podewils et al., 2005; Ravaglia et al., 2008) found a reduced risk for certain types of dementia only, while four (Wang, Karp, Winblad & Fratiglioni, 2002; Verghese et al., 2003; Carlson et al., 2008; Rovio et al., 2007) found no reduced risk of dementia following regular exercise. No study found an increased risk of dementia for individuals who exercised more.

2.3.3.1. Differences in dementia type

While most of the studies identified found that exercise either had a positive effect on both AD and VaD, or had no effect on either, four studies found different results for the different types of dementia. Larson et al. (2006), Laurin et al. (2001) and Podewils et al. (2005) found that exercise reduced the risk of AD (and CI in Laurin et al., 2001) but did not affect the risk of VaD. However, Ravaglia et al. (2008) found a reduced risk of VaD but not for AD. This was the only study that found a significant risk reduction for VaD. While this may suggest that exercise exerts an effect at the neural level that favours AD over VaD, it may also be due to methodological limitations. Risk factors for AD and VaD show great overlap, such as smoking, obesity, homocysteine, high blood pressure and

high cholesterol (Kivipelto, Ngandu, Fratiglioni, Viitanen et al., 2005; Hogervorst, Ribiero, Molyneux, Budge & Smith, 2002); therefore, it is unlikely that this result is due to biased control of these covariates in favour of AD or VaD across these studies. Rockwood and Middleton (2007) also found a lack of effect of exercise for VaD and suggested that it was due to too small numbers of individuals being classified as having VaD, which is less common than AD. A second explanation is that inter-rater agreement on classification of dementia type is often moderate at best, even between experienced medical professionals (Hogervorst, Barnetson, Jobst, Nagy et al., 2000). However, these suggestions are based on a limited number of studies and should be regarded with caution.

Table 3

Details of longitudinal studies investigating the effect of exercise on risk of developing dementia.

Author	Year	n (%F)	Mean age at baseline	Age range	Country	Duration	Measure of exercise	Dementia classification	Outcome	Covariates	Notes
Wang	2002	776 (79%)	81.1 (4.9)	>75	Sweden	7 years	Swimming, walking or gymnastics (daily vs. weekly vs. monthly vs. annually)	Dementia	No reduced risk of dementia for more active group than less active groups.	Age, sex, education, cognitive functioning, comorbidity resulting in hospitalisation (CHD, cerebrovascular disease, diabetes, malignancy, hip fracture), depressive symptoms and physical functioning at baseline	Limited types of exercise were included. Regular social and mental activity were positively associated with reduced risk of dementia. Outcome was the same for ApoE4 positive and negative groups.

Larson	2006	1740 (60%)	75.7	>65	USA	6.2 years (SD 2.0)	Walking, hiking, bicycling, aerobics or calisthenics, swimming, water aerobics, weight training or stretching, or other exercise. (Active: 15mins >3 times per week vs. Inactive: <3 times per week)	AD, VaD, other	Active group had 32% reduced risk of any type of dementia and 31% reduced risk of AD compared to inactive group	Age, sex, ApoE4 status, diabetes, hypertension, cerebrovascular disease, CHD, self-rated health, physical performance, depression, and cognitive functioning.	Exercise gives greatest risk reduction in those with poor performance-based physical function at baseline
Rovio	2005	1449 (62%)	50.6 (6.0)	39-64	Finland	21 years	Leisure-time physical activity that causes breathlessness and sweating (Active: 20-30mins at least twice per week vs. Inactive: activity less than twice per week)	Dementia, AD	Active group had 52% reduced risk of dementia and 62% reduced risk of AD compared to inactive group.	Age, sex, education, follow-up time, locomotor disorders, vascular risk factors, ApoE status, smoking, alcohol consumption	Outcome especially pronounced for ApoE4 carriers. Outcome showed a similar pattern for men and women

Laurin	2001	4615 (60%)	(N)	>65	Canada	5 years	High active: high intensity >3x/week vs. Moderate active: moderate intensity >3x/week vs. Low active: activity <3x/week	CI, AD, VaD, other specified dementia, other non-specified dementia	High active group had 53% reduced risk of cognitive impairment, 73% reduced risk of AD and 55% reduced risk of any type of dementia compared to low active group for women only.	Age, sex, education, family history of dementia, smoking, alcohol consumption, use of nonsteroidal anti-inflammatory drugs, ADL, IADL, self-rated health, health status	Individuals doing activity <3 times per week were classed as low activity even if it was at a high intensity. Was not clear how long each session of exercise must last to qualify for inclusion.
Verghese	2003	469 (64%)	79.1 (N)	75-85	USA	5.1 years	Tennis, golf, swimming, cycling, dancing, group exercise, team games, walking, climbing more than two flights of stairs, housework, babysitting (Active: daily - several days per week vs. Inactive: once weekly - never)	Dementia (AD, VaD, mixed dementia, other dementia)	No reduced risk of dementia for active compared to inactive group.	Age, sex, education, health status (cardiac disease, hypertension, diabetes, stroke, depression, hypothyroidism), baseline Blessed scores	Mental activity is related to risk of dementia. A limited number of activities were included.

Podewils	2005	3375 (N)	74.8 (4.9)	>65	USA	5.4 years	High energy expenditure (>1657kcal/week) vs. Low energy expenditure (<248kcal/week). High participation (>3 activities) vs. Low participation (0-1 activities) in previous two weeks	AD, VaD	High energy expenditure group had 32% reduced risk of AD compared to low energy expenditure group. High participation group had 56% reduced risk of dementia and AD compared to Low participation group.	Age, sex, ethnicity, ApoE status (stratified), education, ADL, IADL, social support, baseline 3MS score, white-matter grade	Reduced risk of dementia was seen for ApoE4 non-carriers only
Abbott	2004	2257 (0%)	77 (N)	71-93	Honolulu-Asia cohort	6 years	Active: walk >2miles/day vs. Inactive: walk <1mile/day vs. Sedentary: walk <.25mile/day	AD, VaD, overall dementia	Active group had 43% reduced risk of overall dementia compared to Inactive group. Active group had 55% reduced risk of AD compared to Sedentary group.	Age, ApoE status, professional status, hypertension, diabetes, CHD, education, BMI, childhood years spent living in Japan, cholesterol level	Reduced risk of dementia was seen for both ApoE4 carriers and non-carriers

Ho	2001	988 (47%)	77.4 (6)	>70	Hong Kong	3 years	Active: participate in physical activity vs. Inactive: do not participate in physical activity	CI	Active group had 55% reduced risk of CI compared to Inactive group in women only	Age, education, stratified by sex	Was not clear what was defined as exercise and no exercise (e.g. was walking classed as exercise)
Lindsay	2002	4088 (61%)	73.3 (N)	>65	Canada	5years	Active: participate in physical activity vs. Inactive: do not participate in physical activity	AD	Active group had 31% reduced risk of AD compared to Inactive group	Age, sex, education	Not clear what was defined as exercise and no exercise (e.g. was walking classed as exercise)
Carlson	2008	294 (0%)	44.7 (N)	67-85	USA	28-36 years	Active: participate in physical activity vs. Inactive: do not participate in physical activity. Outdoor activities, sports, gardening, home improvement, physical activity after age 35	Dementia	Active group had no reduced risk of dementia compared to inactive group.	Age, General Intellect Demand score, stratified by zygosity and ApoE4	This was a twin study (61% monozygotic). Cognitive activity reduced dementia risk by 26% in ApoE4 carriers only. The active group had activity frequency from sometimes to daily. This

											study looked at midlife activity.
Ravaglia	2008	749 (54%)	73.2 (6.0)	>65	Italy	3.9 (SD=.7)	Tertiles of energy expenditure for walking, stair climbing, moderate activity, vigorous activity, total activity. Participation vs. non-participation in 30mins moderate intensity activity 4x/week	Dementia, VaD, AD	VaD risk lower for upper tertiles of walking, moderate activity and total activity compared to lowest tertile No reduced risk of dementia overall or AD. Participation group had no reduced risk of dementia, VaD or AD compared to non-participation group.	Education, comorbidity (2 or more vascular risk factors/history), ADL, age, sex, ApoE4 status	No effect of ApoE4 was seen but this may be due to low numbers of ApoE4 carriers
Rovio	2007	1449 (62%)	50 (N)	65-79	Finland	20.9yrs (SD=4.9)	Daily work commuting time (not at all v <59mins, >60mins/day); Occupational activity (sedentary, physical)	AD	Work-related physical activity had no effect on risk of AD	Age, sex, education, follow-up time, locomotor symptoms, occupation, midlife income, leisure time physical activity, ApoE4 status,	Those with active jobs were less likely to exercise outside of work

										vascular disorders, smoking status	
Sumic	2007	66 (59%)	88.5 (2.74)	>85	USA	4.7yrs (SD=2.71)	Walking, biking, dancing, jogging, swimming, farm work, hunting, skiing, tennis, hiking, home maintenance (Active: >4hours/week vs. Inactive <4hours/week)	CI	Active group had 88% reduced risk of CI compared to Inactive group for women only	Age, sex, race, education, SES, place of residence, living arrangements, IADL, ApoE4 status, baseline walking speed, depression, baseline delayed recall scores	Limited types of exercise were included.

Abbreviations: (N) - information unavailable; AD - Alzheimer's Disease; VaD - Vascular dementia; ApoE - Apolipoprotein E; CHD - Coronary heart disease; IADL - Instrumental Activities of Daily Living; ADL - Activities of Daily Living; BMI - Body Mass Index; SES - Socioeconomic status

2.3.3.2. Differences in exercise measures

Among the studies in this category, there was a huge variety in the exercise measures used and this may have had an effect on variation in the risk reduction ratio in these studies. The studies that found no effect of exercise on dementia risk (but also many of those that did find an effect) used self-report measures of activity frequency. However, as discussed in the previous section, these measures do not always correlate well with objective fitness measures, as they depend upon participants being honest and accurate in their recollection of physical activity. By the very nature of the disease, those with dementia or in the prodromal phases of dementia may have inaccurate recall of their health-related behaviours (e.g. see for hormone use Petitti, Buckwalter, Crooks & Chiu, 2002). Alternatively, being part of this kind of study may have encouraged healthy participants to take up more physical exercise or other health behaviours such as healthy diet, quitting smoking etc. (see also section above). Behaviour has the potential to change greatly over several years between baseline and follow-up measurements, and without knowing exactly how stable the activity has been over time it is difficult to know how accurate the odds ratios really are. This could be partly overcome by assessing changing exercise behaviours over time and taking into account other health behaviours at regular intervals over the follow-up period, although the reliability of self-report measures is never perfect. Therefore, using objective measures such as improvement in strength and VO_{2max} and perhaps blood measures of oxidative stress and vitamin levels could better validate this type of research.

There were also several methodological limitations among the exercise measures used in these studies. For example, many studies such as Wang et al. (2002) and Verghese et al. (2003) selected only common sports and activities, meaning that some individuals were classed as inactive even though they may have taken part in some unusual but intense activities. Carlson et al. (2008) used criteria of activity being either ‘never’ or ‘sometimes’, with the “sometimes” category including ‘activities engaged in up to every day’. This means that this study cannot distinguish between those who did the activity every day and those who did it every few weeks, which may have made a large difference. These three studies were among the four that found no risk reduction for high exercise groups. Therefore some of the null results may be explained through the definitions of exercise and control groups.

We mentioned in the previous section that aerobic and possibly resistance training both appeared to have an effect on cognition, whereas flexibility exercise did not. A general observation of the studies in dementia risk was that there was a focus on high intensity aerobic activity and little mention of yoga and resistance exercise. Thus it was not clear how much of a risk reduction might be seen in individuals who regularly participated in strength exercises alone. Again future work may consider looking specifically at resistance exercises to see if there is a connection between the beneficial effects of this type of exercise seen on cognition in healthy older adults and the subsequent risk of dementia and CI.

2.3.3.3. Moderating variables

Some of the studies that have looked at how exercise affects dementia risk have investigated the ways in which genetics can act as a moderator variable between exercise and risk of dementia. As mentioned in Chapter 1, carriers of two ApoE ε4 alleles are much more likely to develop AD than those with one ApoE ε4 allele, while those with one ApoE ε4 allele are about 2 times more likely to develop dementia than those with no ApoE ε4 alleles (Corder, Saunders, Strittmatter, Schmechel et al., 1993). While some studies that had the genetic data on their participants found that both ApoE ε4 carriers and non-carriers benefited from exercise, Rovio et al. (2005) found that those with at least one ApoE ε4 allele showed greatest risk reduction. In contrast, Podewils et al. (2005) found that non-carriers of the ApoE ε4 allele benefited most from exercise. The ApoE ε2 allele is thought to provide protection against cognitive decline (Berlau, Corrada, Head & Kawas, 2009), while ApoE ε3 is associated with median cognitive decline (Wilson, Bienias, Berry-Kravis, Evans & Bennett, 2002). Therefore, individuals without two ApoE ε4 alleles may have carried either the ApoE ε2 or the ApoE ε3 allele, and this could potentially have confounded some of the results in these studies. Thus, a different classification should be used that takes into account the relative protective effects of ApoE ε2 compared to the negative effects of ApoE ε4 rather than to focus on ε4 alone, although this type of classification requires a very large sample.

Another potential moderating variable between exercise and risk of dementia is sex. Women are twice as likely to be diagnosed with AD as men (Launer, 1992). There is some evidence that the reduction in female hormone estrogen at menopause is linked to the increased risk of AD (Hogervorst, Williams, Budge, Riedel & Jolles, 2000). Some studies have found similar patterns of

cognition after exercise for both men and women (e.g. Rovio et al., 2005). However, other studies have found more pronounced protective effects of exercise in protecting against dementia and cognitive impairment for women when compared to men (Laurin et al., 2001; Ho et al., 2001; Sumic et al., 2007). Exercise may therefore have a particularly protective effect on women who are more vulnerable to the risk of dementia. The potentially mediating effects of sex steroids in this association should be further investigated (see Clifford et al., 2009).

2.3.3.4. Summary

Most studies have found that participation in regular physical exercise helps to significantly prevent or delay the onset of AD, although whether the same is true for other types of dementia is less clear. The wide range of quoted risk ratios (from 0% to 88%) may be due to differences in the considered activities, age and duration of follow-up (as the risk for dementia increases with age, see Chapter 1) and a lack of standardised objective fitness measures or only moderate inter-rater agreement in diagnoses. Many factors appear to interact with effects of exercise, including genetics and sex. Based on the findings from the previous section, future work may wish to consider different types of exercise as their activity measures in addition to the potentially moderating factors mentioned above.

2.3.4. The Effect of Exercise in Patients with Existing Cognitive Impairment

Although exercise has generally been researched to be a potential preventative activity against the onset of dementia, our final question was whether, like in healthy adults, exercise could improve cognitive functioning of those with dementia. Some longitudinal studies mentioned previously (van Gelder et al., 2004; Barnes et al., 2003) found associations between frequent exercise and better scores on the MMSE, which is a test sensitive to dementia. Although there are very few studies that directly answer this question, making it difficult to draw conclusions, we believe it is crucial for discussion within this review as there are potential benefits to those already diagnosed with the disease. There has been a recent meta-analysis of the literature concerning exercise and cognition in those with dementia. Forbes, Forbes, Morgan, Markle-Reid et al. (2008) concentrated on RCTs but, through use of very strict inclusion criteria, the authors were only able to run the analysis on two studies (Francese, Sorrell & Butler, 1997; Rolland, Pillard,

Klapouszczak, Peynish et al., 2007). They found that there was insufficient evidence of a positive effect of exercise on cognition. However, with only two studies it is perhaps not really possible to draw firm conclusions at this stage. Our search of the literature also only identified four RCTs that fit our criteria for review, so we too are unable to make statements about the findings. However, we discuss the studies briefly in terms of their methodologies and how their results compared to those performed with healthy adults. These studies shared similar characteristics with the RCTs seen in the healthy adults except that the participants were diagnosed with mild cognitive impairment (MCI), AD or dementia. Details can be seen in Table 4.

2.3.4.1. Cognitive domain measured

Several different tests of cognitive function were used in these studies, such as the MMSE, Verbal Fluency and TMT. While one of the studies found a 30% improvement on MMSE scores after an exercise intervention (Kwak, Um, Son, & Kim, 2008), the other three studies all found no effect of exercise on the MMSE or any memory test. Also, while Scherder et al. (2005) found a positive effect of exercise on TMT performance, van Uffelen, Chinapaw, van Mechelen and Hopman-Rock (2008) found no such effect on the SCWT and Digit-Symbol Substitution Tests. The most consistent test to show positive effects of exercise in healthy adults was again the Digit Span test. This test also showed most consistent improvement with exercise in healthy elderly (see section 3 and Angevaren et al., 2008). On the other hand, Scherder et al. (2005) found that results on this test were unchanged after exercise. Thus, there is again no consistent pattern of which specific cognitive domains or tests are affected by exercise.

2.3.4.2. Type of dementia

The studies reviewed looked at patients with different classes of cognitive impairment. Arcoverde et al. (2008) recruited participants diagnosed with AD, Kwak et al. (2008) recruited participants with dementia, and van Uffelen et al. (2008) and Scherder et al. (2005) both recruited participants with MCI. Observational studies suggested that exercise appeared to have a potentially selective effect for reducing the risk of AD over other types of dementia. However, Arcoverde et al. (2008) found no effect for exercise in AD and the two studies

investigating the effect of exercise on cognition in MCI patients both found opposite results, so results were not consistent with this idea.

2.3.4.3. Exercise measures

We saw that for adults without dementia the different results may be due to the type or intensity of the exercise performed. Because of the age of the groups and disabilities concerned in these studies with dementia patients, many of the exercises were low intensity, such as seated gymnastics or walking. Kwak et al. (2008) used weight-training exercises and, if they led to changes in strength, this may explain why they found a positive effect on MMSE scores in comparison to Arcoverde et al. (2008) who used less intense exercises. Therefore, there may have been an influence of exercise type in these four studies. Walking showed inconsistent effects but was done at different intensities and compared against different control programmes. It is also not known whether participants of these studies experienced any improvement on physiological measures, which may be crucial in treatment studies as discussed previously.

The treatment studies for participants with CI or dementia looked at measures of cognition after 6 weeks, 6 months or a year of regular exercise. As with the RCTs in healthy adults, length of intervention did not appear to have an effect on the benefit to cognition. However, Scherder et al. (2005) showed a positive effect of exercise on cognition after just 6 weeks, again suggesting that the benefits can be seen very quickly after the start of an exercise intervention. Low rates of adherence to the exercise program were also an issue in these studies. One of the studies that found no difference between exercise and control groups had relatively low adherence rates (van Uffelen et al., 2008). Although the median adherence was 63%, it ranged from 2-81%. As discussed previously, if a participant only attends 2% of classes, they are likely to not have benefitted in the same way as those who had attended 81%, and thus these two participants should probably not be treated the same for purposes of analysis.

2.3.4.4. Moderating and confounding variables

Kwak et al. (2008) found that exercise improved MMSE scores in a woman-only group. This could be a chance result; however, this bias was also seen with the interventions in healthy adults and the observational studies so it is worth considering in future research. None of the studies reported included ApoE ε4

status as a variable so it cannot be determined whether the presence or absence of ApoE ε4 alleles facilitated or inhibited the effect of exercise on cognition. This might also be the subject of future research, as knowledge of the genetic status of patients may help determine who may benefit from an exercise intervention and who may not.

Activities of Daily Living (ADL) is a scale that measures functional ability (Berlau, Corrada & Kawas, 2009), and deficits on this scale are common in those with dementia (Reisberg, Finkel, Overall, Schmidt-Gollas et al., 2001). An observation made by some of the studies here was that exercise groups showed improved ADL scores compared to the no exercise groups (e.g. Kwak et al., 2008). Arcoverde et al. (2008) found that ADL scores were the best predictor of MMSE scores for active AD patients. The physiological benefits of exercise may improve an individual's ability to perform certain actions like walking, encouraging autonomy and indirectly leading to enriched mental activity and experiences. Mental stimulation has been associated with maintenance of cognitive function into old age (e.g. Verghese et al., 2003). Thus, it may in fact be an increase in mental stimulation rather than physical exercise that has driven the increase in cognitive scores seen in some of these studies.

2.3.4.5. Summary

The review by Forbes et al. (2008) concluded that there was insufficient evidence that there was a clear benefit of exercise on cognitive function in the elderly with existing cognitive impairment. Despite some studies showing positive effects of exercise, we would have to agree with this conclusion at present. There is a distinct lack of studies that have investigated this topic and this makes it very difficult to establish a clear conclusion. However, we can benefit from these few studies by learning about which factors to control in the future, such as early 6 weeks assessment, stratification by sex and genotypes and assessment of improvement in ADL function.

Table 4

Details of RCT studies investigating the effect of exercise on cognitive function in patients with a diagnosis of dementia.

Author	Year	n (%F)	Mean age (SD)	Age range	Country	Duration	Dementia type	Exercise groups and types	Frequency of exercise	Tests	Outcome	Covariates	Notes
van Uffelen	2008	152 (44%)	75 (2.8)	70-80	Netherlands	1 year	MCI	Exercise (moderate intensity walking) vs. Low intensity (relaxation, ADL, balance, glexibility and posture)	1hr/day, 2days/ week	AVLT, verbal fluency, SCWT colour word test, DSST	No significant main effects of intervention on cognition	education, baseline activity level, vitamin status, adherence and supplementation, stratified by sex	Median adherence to program was 63% (2-81%).
Arcoverde	2008	37 (N)	76.7 (N)	>65	Brazil	6 months	AD	AD active (Respiratory exercises, static and dynamic balance training, gait circuits, ADL, coordination PLUS cognitive stimulation) vs.	1hr/day, 2days/ week	MMSE	AD groups showed no difference on MMSE scores over time.		AD active group were much older than AD sedentary group and controls. There were no differences in final fitness levels between AD active and AD sedentary groups. Exercises were

								AD sedentary vs. Control active (dance and gym)					different for AD and control active groups.
Kwak	2008	30 (100%	80.97 (6.22)	>60	Korea	12 months	Dementia	Exercise (stretching and strength) vs. control	30-40mins/ week	MMSE	30% MMSE and ADL improvement in intervention group only		The control group was slightly older. Long term intervention better than short term.
Scherder	2005	43 (88%)	86 (N)	76-94	Netherlands	6 weeks	MCI	Exercise (self-paced slow walking) vs. Hand/face (hand stretching and facial expressions) vs. social control (social visits) vs. control	30mins/ day, 3x/ week	Category Naming, TMT, Digit Span, VLMT, Face recognition, Picture recognition	Category Naming and TMT better in walking group and hand/face group than control group immediately after treatment. No difference for memory tasks	Pre-treatment scores	The advantage was not maintained over time

Abbreviations: (N) - information unavailable; AD - Alzheimer's Disease; MCI - Mild Cognitive Impairment; ADL - Activities of Daily Living; AVLT - Auditory Verbal Learning Test; DSST - Digit Symbol Substitution Test; MMSE - Mini Mental Status Examination; TMT - Trail Making Test; VLMT - Verbal Learning Memory Test

2.4. Conclusions

This review aimed to evaluate the conflicting findings of past studies that have investigated the effect of physical exercise on cognition in older adults to determine whether physical activity may help to maintain cognitive function in older age. In particular, we looked at the individual cognitive domains that were examined in each study and the type of exercise measure that was used.

No firm conclusions could be made concerning which specific cognitive domains are affected by exercise, and the results here did not always support those found by other reviews such as Colcombe and Kramer (2003). The tests used in these studies are so varied that some results may have been seen by chance. However, the range of cognitive tests showing positive effects may also indicate that exercise benefits general cognitive ability to some degree. More replication is needed using standardised cognitive tests to determine how specific the effect of exercise is. In terms of risk of dementia, there was some evidence that exercise may have a specific effect on AD, although again this was based on very few studies and was complicated by methodological differences between studies. However, if this finding can be replicated, it would suggest that specific neural mechanisms may be targeted by physical activity and that would have further implications for which cognitive domains are affected. This idea is purely speculative, but it may be worth attention as it could determine what the specific cognitive benefits of exercise are.

Clearer patterns were seen when we looked at the type of exercise intervention used in these studies. The main focus has been on aerobic activity, which did appear to have an effect on cognition and risk of AD. However, strength-training exercises also seemed to be beneficial to cognition in both healthy adults and those with dementia. This is especially true when there is an additional measured increase in objective physiological measurements, such as VO_{2max} and muscle strength. This is important, as strength training exercises may be easier for some elderly to participate in and may thus be a more successful intervention (or at least compliment more aerobic activity) in terms of promoting adherence. While participation in aerobic activities appeared to help to delay dementia onset, it is less clear whether strength training can do the same and research may attempt to highlight these sorts of activities in future studies.

Future work must control for variables that may moderate the relationship between exercise and cognition. Adherence to the exercise program must be controlled in RCTs as low adherence by a large proportion of the sample can disguise a real effect of exercise. Fluctuations in physical activity habits as well as change in

other health behaviours, such as diet and smoking, should be monitored over the course of an intervention or follow-up period. Behaviour can change over time so a single measurement may not be sufficient to map a person's exercise habits over a given timeframe. Genetics must also be taken into account where possible when considering dementia risk and cognition in those with dementia, as there is evidence that ApoE status can affect whether an individual would benefit from exercise or not (e.g. Podewils et al., 2005; Rovio et al., 2005). As mentioned previously, a new categorisation for determining ApoE allele status needs to be considered to take into account the protective effect that the ApoE ε2 allele may have. There is also evidence that women may benefit more from exercise interventions than men (Sumic et al., 2007), which has additional implications for targeted healthcare recommendations. A review published in Women's Health (Clifford, Yesufu Udechuku, Edwards, Bandelow & Hogervorst, 2009; see Appendix A) discusses effects of physical activity and other lifestyle interventions for women in midlife specifically.

In summary, this review has found inconsistent evidence that physical activity can have positive effects on cognition and may delay the onset of AD. The inconsistencies appear to be partly due to the different types of exercise measures used, but they may also be influenced by a variety of different moderating variables such as sex, adherence and genetics. The data presented here suggest that more research into this area is warranted, and this review has highlighted some important variables that must be investigated in future studies. Later in this thesis we explore the effect of some of these variables, for example sex and cognitive status, in a community-dwelling sample of elderly adults in Indonesia (Chapter 5). We also describe an RCT looking at the effects of resistance training to expand knowledge about how this type of activity can influence cognition in midlife (Chapter 7).

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Part Two - Methods and cognitive test selection

Chapter 3 – Cognitive test selection and covariates

A clinical diagnosis of AD is ultimately the most desirable outcome measure when studying disease prevention. However, the lengthy follow-ups required to conduct adequate prospective studies into AD are not possible within the time constraints of a doctoral thesis and cognitive testing is often used as an alternative measure to assess short-term changes in cognitive function. The heterogeneous nature of AD means that relying on the outcome of a single cognitive test may not yield a fair impression of an individual's cognitive ability as it relates to the disorder. In addition, a key finding of the literature review presented in Chapter 2 was that physical activity might affect cognitive domains differently. Therefore, a battery of cognitive tests was used to measure abilities and changes over time in cognitive domains commonly affected in AD, with a focus on memory, executive function (e.g. focused attention, inhibition, task switching) and word generation.

For inclusion in this battery, the tests had to show some degree of sensitivity and specificity to the cognitive impairment seen in AD. The sensitivity of a test refers to the percentage of cases that are correctly identified, while specificity refers to the percentage of non-cases that are correctly identified (Ghaaliq Lalkhen & McCluskey, 2008). Both values are given as a percentage, with 100% for both indicating optimal discriminability between cases and non-cases. A value of around 50% suggests that the test is no better than chance at discriminating between cases and controls. In addition, the tests had to be relatively short in length and be appropriate for administering to participants with a range of abilities (i.e. show no ceiling/floor effects). This chapter introduces the cognitive measures used in this thesis and describes their relevance in AD research.

3.1. Global Cognition

The Mini Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) was included in the test battery as a clinical measure of global cognition and as a screening tool for serious cognitive decline including, but not restricted to, dementia. This allowed appropriate samples to be selected based on their baseline level of cognitive functioning. The MMSE takes the form of a "question-answer" test that is administered by a researcher. It tests a variety of cognitive domains, such as short-term memory, orientation, visuospatial construction, object naming and language. The

MMSE is scored out of a maximum 30 points, with 30 suggesting no impairment. Scores less than 27 are generally considered to indicate cognitive impairment with a sensitivity and specificity of 0.89 and 0.91 respectively (O'Bryant et al., 2008), while cut-offs specifically for dementia are considered to be one or two points lower (e.g. Kuslansky et al., 2004). A comprehensive review of fourteen papers found that estimates of test-retest reliability for the MMSE were between 0.80 and 0.95 in those with and those without age-related cognitive impairment (Tombaugh & McIntyre, 1992). This test takes around 3-4 minutes to administer. There are more recent tests of global cognition (e.g. Test Your Memory test, Brown, Pengas, Dawson, Brown & Clatworthy, 2009; Addenbrooke's Cognitive Examination-Revised [ACER], Mathuranath, Nestor, Berrios, Rakowicz & Hodges, 2000; Montreal Cognitive Assessment [MoCA], Nasreddine et al., 2005), some of which are reported to have equal or superior sensitivity and specificity to the MMSE in some samples (e.g. Brown et al., 2009; Smith, Gildeh & Holmes 2007; Chen et al., 2011). However, the MMSE is commonly used in memory clinics to aid the diagnosis of AD (including in the validation study in Chapter 4) and it has been validated for cross-cultural applicability (Hogervorst et al., 2011). Therefore, the MMSE was chosen as a screening test for cognitive impairment for the purposes of this thesis.

3.2. Memory

Severe short-term memory deficits are the main feature of AD with extensive neuropathology occurring around memory regions, such as the hippocampus (Du et al, 2001). The literature review presented in Chapter 2 suggested that many of the changes in cognitive performance following physical activity are seen in the memory domain. Memory tests that met our inclusion criteria described previously were therefore included in the test battery.

3.2.1. Hopkins Verbal Learning Test

The Hopkins Verbal Learning Test (HVLT; Brandt, 1991) is a verbal measure of short-term, explicit memory in which participants are read aloud a list of 12 words that they are then asked to recall. This is done three consecutive times in total, giving a total immediate recall score of up to 36 points (delayed recall after 30 minutes can also be given [Benedict, Schretlen, Groninger & Brandt, 1998] but this is covered by copyright). There are six equivalent forms of this test, and each word list contains three categories of four words. Scoring high on the HVLT requires the recruitment of memory

strategies, such as chunking the words into categories, making the task particularly difficult for those with disrupted memory networks (De Jager, Hogervorst, Combrinck & Budge, 2003). This test can take around 6-8 minutes to administer but has the advantage of not showing ceiling effects, as healthy controls often do not score full marks (Hogervorst et al., 2002).

The HVLT appears able to successfully predict dementia cases from healthy controls, with an optimal cut-off point for mild dementia of 18/19 out of 36 points (sensitivity 0.96, specificity 0.80; Frank & Byrne, 2000; see also Hogervorst et al., 2002). Test-retest reliability estimates within acceptable limits (around 0.75) have been reported for the HVLT in healthy elderly (Benedict et al., 1998; Wesnes, 2012). Data from the OPTIMA project (e.g. Schrijnemaekers, De Jager, Hogervorst & Budge, 2006) revealed that those with AD showed a small decline on this test over time while healthy controls improved after repeated exposure to the test stimuli, even after a 2-3 year interval (Schrijnemaekers et al., 2006). On the other hand, those with MCI tended to remain stable over time (Schrijnemaekers et al., 2006), suggesting that the HVLT is able to differentiate between levels of cognitive impairment (see also De Jager et al., 2003). A further advantage of this task for our RCT (Chapter 7) is the availability of equivalent forms, which make it resistant to learning effects where repeat testing over a short time is needed (Benedict & Zgaljardic, 1998).

3.2.2. Verbal Fluency

Word generation deficits in those with dementia have been reasonably well documented (Sailor, Antoine, Diaz, Kuslansky & Kluger 2004; Taler & Phillips, 2008). Word generation recruits neural networks particularly implicated in semantic memory (Kitabayashi et al., 2001), and recalling one word often prompts generation of semantically or physically similar words. The Verbal Fluency task, or the number of words from a given category that can be named in 60 seconds, is a way of measuring these abilities. The category ‘animals’ is often used, however ‘fruits and vegetables’, ‘cities and towns’ and ‘items of clothing’ have been validated as alternatives for repeated testing (Cunje, Molloy, Standish & Lewis, 2007). Patients with AD tend to produce fewer words, especially atypical ones (Sailor et al., 2004), and word generation also declines in healthy adults several years before dementia onset (Taler & Phillips, 2008; Nutter-Upham et al., 2008). Gomez and White (2006) demonstrated that category fluency had greater ability to differentiate patients with mild Dementia of Alzheimer’s Type from healthy controls (CDR = 0.5 vs CDR = 0) than did other tasks such as Logical Memory, Digit Symbol or the Boston Naming task and verbal fluency

scores correlate highly with MMSE scores (Kitabayashi et al., 2001). Category fluency shows higher sensitivity (100% [specificity 92.5%]) to dementia compared to letter fluency (89% [specificity 85%]; Monsch et al., 1992; Cerhan et al., 2002), an alternative form that involves naming as many words as possible that begin with a given letter. Studies have reported good test-retest reliability (around 0.83) for category fluency in the elderly with and without Alzheimer's disease (Solomon et al., 1998; Diesfeldt, 1985).

3.3. Executive Function

The term executive functioning encompasses the cognitive skills that control the planning, initialisation, sequencing and monitoring of complex goal-directed behaviour (Royall et al., 2002). Executive function deficits occur early in AD (Perry & Hodges 1999; Baddeley, Baddeley, Buck & Wilcock, 2001; Bracco et al., 2007), and impairments may also be indicators of pathology in healthy individuals at increased risk of developing AD (Parasuraman, Greenwood & Sunderland, 2002; Rosen, Bergeson, Putnam, Harwell & Sunderland, 2002). Although the previous literature review did not support it, Hall, Smith and Keele (2001) suggested that physical activity mainly affects these complex abilities. Therefore, tests of executive function were included in the test battery to try to clarify these discrepancies.

3.3.1. Trail-Making Task

The Trail-Making Task (TMT; Reitan, 1955) is a test of concept shifting that comes in two parts. In TMT part A (TMTa), participants are given a series of randomly positioned circled numbers (1-25) that they must connect sequentially (1-2-3-4 and so on) by drawing a continuous line between them. TMTa serves as a baseline measurement of psychomotor speed and visual scanning. In TMT part B (TMTb), the stimuli include both numbers (1-13) and letters (A-L), and participants must connect them by alternating between the two systems (1-A-2-B-3-C-4 and so on). Participants are asked to complete both parts as quickly as they can and the time taken to complete each part is recorded. The added cognitive demand of set switching for the TMTb creates an interference effect, where TMTb takes longer to complete compared to TMTa and elicits more errors. Patients with dementia and cognitive impairment find TMTb particularly difficult (e.g. Amieva et al., 1998; Lafleche & Albert, 1995), and reaction times and errors increase with dementia severity (Ashendorf et al., 2008; Catherine, Ronald & Gerard, 1985). The TMT has sensitivity (specificity) of 81% (71%)

for dementia using a cut-off of ≤40 correct connections on average over two test trials (Heun, Papassotiropoulos & Jennssen 1998). Performance on the TMT is also associated with MMSE scores in adults without AD (Ashendorf et al., 2008). Test-retest reliability estimates have been reported to be moderate for the TMT. For example, TMT reliability coefficients of <0.65 were observed in healthy elderly who were part of the Alzheimer's Disease Neuroimaging Initiative (ADNI; Wesnes, 2012). However, assessments were conducted over the course of 1 year which would allow for some deterioration of cognitive functioning acting as a confound (see also Snow et al., 1998).

3.3.2. Stroop Colour-Word Test

The Stroop Colour-Word Test (SCWT; Stroop, 1935) is a commonly used test of selective attention and automatic response inhibition. The full version of the SCWT has four conditions: reading a word written in black ink, naming a block of colour, and naming the colour of the font that a word is written in, which may be congruent or incongruent with the meaning of the word. For example, in congruent conditions, the word 'blue' would be written in blue font, while in incongruent conditions the word "blue" may be written in red font. As the automated response when seeing a word is to read it, this task requires relatively low cognitive effort when naming the font colour in congruent conditions. However, when the font colour is incongruent to what the word says, the viewer has to inhibit the reflexive response and switch attention to the font colour. The result is an interference effect with the incongruent condition taking longer to complete and eliciting more errors.

Performance on the SCWT declines with age (Cohn, Dustman & Bradford, 1984) but those with AD also show significantly larger interference effects compared to healthy controls (Bondi et al., 2002; Amieva et al., 2004). Performance also declines with disease severity, with MCI patients performing midway between healthy controls and AD patients (Kramer et al., 2006) and possible AD patients performing midway between probable AD patients and healthy controls (Berardi, Parasuraman & Haxby, 2005). Those who score under half marks on the full SCWT test have a 7.3-fold increased risk of dementia over 7 years compared to those who score higher (Sarazin et al., 2007). Intraindividual variation on the incongruent SCWT trials is also significantly larger in those with mild Dementia of the Alzheimer's type (CDR=0.5) than in healthy controls (CDR=0; Duchek et al., 2009). Not all studies have found clear differences on the SCWT between AD patients and controls (e.g. Binetti et al., 1996) and sensitivity for dementia has been reported to be low (41%; Sarazin et al., 2007). In addition, test-retest reliability estimates have been shown to vary widely in elderly

adults, ranging from as low as 0.48 to 0.96 depending upon the method of scoring (Lemay, Bédard, Rouleau & Tremblay, 2004; Seo et al., 2008). On the other hand, intraindividual variation on the incongruent trials is higher in healthy ApoE e4+ carriers (Duchek et al., 2009) and correlates positively with biomarkers and neurological signs of cognitive impairment at post-mortem (Bondi et al., 2002).

3.4. Conclusion

This chapter has identified two tests of memory and two commonly used tests of executive function that appear suitable for inclusion in our test battery according to the criteria set. Although not specifically a measure of dementia diagnosis or neuropathology indicative of the disease, these tests are all highly sensitive to AD and performance on some correlate with indicators of the disease, such as ApoE status or biomarkers. These tests are able to assess a wide range of cognitive abilities and are of limited duration. Different versions of these tests are also available, allowing reliable repeated assessment. These tests should therefore be suitable for inferring changes in cognitive ability. While many other cognitive tests are available, we chose those tests that are most commonly used in physical activity and dementia/cognitive impairment research to allow cross-study comparison. The versions selected for the later studies have been assessed for their usefulness, with the findings presented in Chapter 4.

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Chapter 4 – Validation of cognitive tests

4.1. Introduction

In Chapter 3 we identified a group of cognitive tests on which those with dementia and those at risk for dementia perform poorly compared to healthy age-matched controls. This chapter describes a study investigating whether the specific versions of the cognitive tests available and the scoring methods intended for use in the present test battery can discriminate between the two groups and whether responses are associated with disease severity in a similar manner to the versions discussed in Chapter 3. Research studies often use different versions of cognitive tests and analyse them in different ways, which can affect their levels of sensitivity to AD. For example, computerised versions of tests can be a highly sensitive measure of reaction time compared to a manual stopwatch, while speed/accuracy trade-offs can mean that error rates alone do not discriminate well between groups. It is therefore important to assess whether our methods are sensitive to cognitive impairment relevant to AD to ensure their usefulness in the later studies of this thesis. The aims were to investigate a) whether scores on these tests could predict group membership with a high level of accuracy; b) whether performance on the cognitive tests correlated with a clinical measure of AD; c) whether performance on these cognitive tasks at baseline differed between those who declined on a clinical measure of AD over 6 months and those who did not; and d) whether learning effects over time differed between groups.

4.2. Method

4.2.1. Participants

A total of 26 community-dwelling men and women aged 50 years and over were recruited for this study. The experimental group (*n*=13) consisted of patients who had been diagnosed with mild to moderate AD and who were attending a memory clinic in the UK to start treatment with *Reminyl* (galantamine). Galantamine is not a cure for AD but aims to slow the progression of dementia by preventing the breakdown of acetylcholine in the synapses between neurons, thus helping to compensate for the loss of neurons that respond to acetylcholine. At baseline these participants were *not*

taking medication for AD or any other medication affecting mental function (e.g. lithium). AD diagnosis was based on ICD-10 criteria (WHO, 1992) and was established by clinical evaluation using a consensus group-based decision-making process in the memory clinics before referral to the study. The control group (*n*=13) had no subjective cognitive impairment and were required to have an MMSE score ≥27. Control participants were either an age-matched carer (in all cases this was the spouse) of a participant in the experimental group (*n*=10) or an age- and sex-matched volunteer recruited through word-of-mouth (*n*=3). Exclusion criteria for both groups consisted of presence of a co-morbid psychiatric disorder, other neurological disease, substance abuse and previous use of AChEIs or other medication affecting cognition. None of the volunteers for either group had a visual impairment that affected their ability on the cognitive tasks and that could not be corrected by prescription glasses (verified using a visual assessment described in section 4.2.4). Written informed consent was gained from all participants before the study commenced as approved by the Newcastle & North Tyneside 2 Research Ethics Committee. Consent was also given on behalf of the patients by their respective carer regardless of whether the carer participated themselves.

4.2.2. Cognitive assessments

All participants completed the Mini-Mental State Examination (MMSE) as a clinical measure of disease severity and as a screening tool for allocation to the control group. Participants also completed the Trail Making Test (TMT), Stroop Colour Word Test (SCWT), Verbal Fluency and the Hopkins Verbal Learning Test (HVLT) as described in Chapter 3. Specific methods are described below:

- The TMT was a paper-and-pencil version with black, circled numbers presented on white A4 paper. A practice trial was given before each part using 8 items to ensure that the participant understood the instructions before starting the main test. Participants were asked to complete both parts as quickly and as accurately as possible. The TMT was scored in terms of an interference effect for reaction time (TMTb – TMTa), measured with a manual stopwatch and given in seconds. If participants made a mistake, they were given three seconds to correct themselves; otherwise they were referred back to the last correct item and reminded of the strategy (number to number or alternating).

- Verbal Fluency was measured as the total number of animals named in 60 seconds. Category fluency was chosen over letter fluency due to its higher sensitivity to AD in previous studies (Monsch et al., 1992; Cerhan et al., 2002). Any living animal

was accepted and duplicates were ignored. Responses were recorded using a Dictaphone for accurate scoring after testing.

- The SCWT was a computerised version with two conditions: naming a word written in black ink (baseline condition) and font colour naming (incongruent condition). The test included 20 trials in the baseline condition and 40 trials in the incongruent condition. Each trial consisted of presentation of the stimulus in the centre of the screen, flanked by one target word and one distracter (see Figure 2). The participant was asked to respond by pressing either a left or right arrow to indicate the spatial location of the target (left or right side of the stimulus) as quickly as possible. Six practice trials were given with accuracy feedback ("correct" or "incorrect") before each condition began. Reaction time for each trial was automatically recorded, and baseline mean reaction time was subtracted from the incongruent condition mean reaction time to gain an interference score. Standard deviation (*s.d.*) on each condition was also calculated for each participant as a measure of intra-individual variation, thought to be sensitive to decline in AD. The SCWT test was displayed on a Toshiba 15" laptop screen.

- The HVLT list A was used and it was scored as both a trial 1 score and as a total immediate recall score (adding all correct words recalled over 3 trials). Trial 1 was used as a proxy for digit span, which was shown to be affected by physical activity in the literature review (Chapter 2). Total immediate recall showed similar sensitivity as delayed recall for dementia and MCI (Hogervorst et al., 2002) so only the immediate recall was used to reduce the length of the testing session. As per the standardised instructions for this test, words were read aloud at a rate of 1 per second and participants were given 90 seconds per trial to recall as many words from the list as they could.

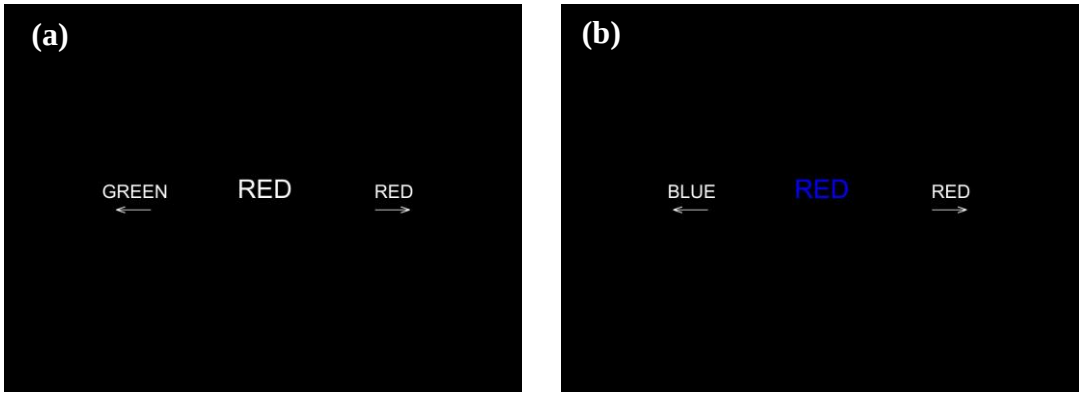

Figure 2
Screen shot of the SCWT task (a) baseline condition and (b) incongruent condition

4.2.3. Questionnaires

Demographic information on participants including age, gender, education obtained (years), lifestyle factors (e.g. smoking, alcohol consumption) and medical history was surveyed using a questionnaire (Appendix B) and were confirmed by the carer who was present. Participants also completed the Geriatric Depression Scale (GDS; Yesavage et al., 1983; Sheikh & Yesavage, 1986) to assess mood, which itself may have an impact on cognitive performance (Kliegel et al., 2005; Lee & Sternthal, 1999). The GDS short-form is a 15-item questionnaire to which participants answer 'yes' or 'no' to each statement, making it simpler for those with dementia to complete than questionnaires with more response choices (Appendix C). The GDS has been found to be valid for those with AD who do not deny having cognitive complaints (Feher, Larrabee and Crook, 1992) and, since all our participants acknowledged their cognitive difficulties, it was deemed a suitable measure of mood in this group.

4.2.4. Visual assessment

Visual impairments are common in older people and in those with AD (Kirby, Bandelow & Hogervorst, 2010) so a visual assessment was used to rule out permanent visual impairments that may have impeded participants' ability to complete the cognitive tasks. Participants were asked to name a mixed sequence of the following letters: C, D, H, K, N, O, R, S, V and Z. These letters decreased in size and were presented at two distances. At 0.6 metres, the letters decreased gradually in size from approximately 9 x 9mm to 2 x 2mm. At 6 metres, the letters decreased from approximately 102 x 94mm to 31 x 28mm. These letters were in a dark grey font printed on a white background, and at each distance there were 55 letters displayed one at a time. The letter order was different for the two distances but was consistent for all participants.

4.2.5. Design

This was a repeated-measures study designed to investigate how sensitive scores on the cognitive tests selected for this test battery were to the cognitive deficits seen in AD. Participants were visited in their own homes and visits varied between 30 and 60 minutes for each participant depending mostly upon session number (with the first session lasting longer than follow-up due to informed consent) and each

participant's ability. Participants were offered frequent breaks during each session in case of fatigue; however, none chose to take a break and the testing procedure was well tolerated by all participants. Age, education, alcohol intake (units) and GDS scores were used as covariates. Smoking had been considered as a covariate, but only one participant reported past smoking so it was not included.

4.2.6. Procedure

Patients of a memory clinic who were eligible for participation in this study and their carer were given the information by clinic staff during a routine visit. The investigator contacted them by telephone around 2 days later having given them time to consider. This call gave the opportunities for the carer to ask any questions that they had about the study and, if they were happy to take part, to arrange a meeting at their home before the patient received their first prescription for galantamine. Where the carer did not participate in the study, they remained the contact person for the patient and were in the home during the testing session. For those control participants who were not the carer of an AD patient, the meeting took place at the participant's earliest convenience. At the start of the visit, informed consent was gained and participants completed the demographic questionnaire followed by the GDS. They then completed the visual assessment and finally the cognitive tasks. Both cases and controls completed the same procedure and were tested separately to avoid exposure to the test items. Willing participants were revisited six months later and they completed the GDS, visual assessment and cognitive tasks only.

4.2.7. Analysis

The data from this study were analysed using SPSS Version 18.0 with a required p value of ≤.05. To test the hypotheses a number of statistical tests were conducted on the data. First, a Multivariate Analysis of Variance (MANOVA) was performed to assess differences between AD patients before starting on medication and controls on the cognitive tasks at baseline. Analysis of histograms, Q-Q plots and the Shapiro-Wilk statistical test revealed no significant violations of normality for the HVLT trial 1, HVLT total, TMT or Verbal Fluency tasks, but SCWT scores (interference scores and standard deviations [*s.d.*]) were normalised using a Log Transformation. Receiver Operating Characteristic (ROC) analysis was also conducted for each task to determine optimum cut-offs and their respective sensitivity and specificity of each test for group membership (AD patient vs. control).

Partial correlations were performed between MMSE scores (as a clinical measure of AD) and the other cognitive tests to assess the strength of the associations while controlling for the covariates. As MMSE scores had been used as a grouping variable, these correlations were performed on AD patients only. Spearman's Rank correlations were also conducted between baseline test scores and MMSE change (delta) scores. MMSE delta scores were compared between those with poor cognitive performance and those with high performance at baseline. MMSE delta scores were coded as '0' if the delta score <0 (indicating a decline) or a '1' if the delta score was ≥0 (indicating stability or improvement). Cognitive test scores were stratified into below- and above-median score. Fisher's Exact Test (FET) was used due to MMSE delta scores not being normally distributed.

Finally, a repeated-measures Analysis of Variance (ANOVA) was performed to assess whether there were any differences in scores from baseline to follow-up at six months between AD patients and controls. Levene's test for homogeneity of variance was not significant for any test meaning the required *p* value remained at ≤.05.

4.3. Results

Baseline demographic information and cognitive test scores at baseline and at follow-up are shown in Table 5. No significant differences in age ($t(24)=-.019$, $p=.985$), sex ($Chi^2=0.16$, $p=.694$), education level ($Chi^2=0.00$, $p=1.000$), GDS score ($t(24)=-0.61$, $p=.549$) or alcohol consumption ($t(24)=0.59$, $p=.559$) were seen between AD patients and controls at baseline. However, as expected, participants in the control group had significantly higher mean MMSE scores than the experimental group ($t(13.05)=7.93$ $p<.001$).

Of the original group of 26 participants, 16 completed both baseline and follow-up assessments. Baseline characteristics did not differ between those who completed follow-up assessments and those who chose to leave the study before completion (Age: $t(24)=-1.00$, $p=.330$; Education: $Chi^2=0.14$, $p=.712$; GDS: $t(24)=1.52$, $p=.141$; MMSE: $t(24)=-0.08$, $p=.936$; Sex: $Chi^2=0.00$, $p=1.000$; Alcohol: $t(24)=0.87$, $p=.391$). Scatterplots revealed linear relationships between the covariates and moderate correlations (<0.55) were seen between them. There were, however, no significant correlations between the covariates and performance on the cognitive tests.

Table 5
Baseline demographics and mean scores on cognitive tasks.

Variable	AD patients	Controls
Baseline		
N	13	13
Mean age in years (*s.d.*)	69.0 (9.9)	69.1 (8.4)
Education (%)		
Secondary	69	69
Uni Degree	31	31
Female (%)	46	62
Mean alcohol consumption (units per week)	2.2 (5.4)	3.58 (6.2)
Mean GDS score	2.4 (1.3)	2.1 (1.3)
Cognitive scores		
Mean MMSE (*s.d.*)	22.7 (3.1)	29.6 (0.6)
Mean HVLT Trial1 (*s.d.*)	1.6 (1.7)	7.2 (1.6)
Mean HVLT Total (*s.d.*)	7.1 (4.5)	26.3 (4.5)
Mean TMT interference (*s.d.*) [a]	122.3 (80.6)	38.67 (12.7)
Mean Verbal Fluency words recalled (*s.d.*)	11.6 (6.6)	20.8 (7.1)
Mean SCWT interference score (*s.d.*) [b]	2355 (2265)	463.6 (265)
Mean SCWT *s.d.* [b]	482	3545
Follow-up		
N	8	8
Female (%)	63	50
Cognitive scores		
Mean MMSE (*s.d.*)	20.6 (3.1)	29.7 (0.5)
Mean HVLT Trial 1 (*s.d.*)	1.8 (1.6)	9.1 (2.0)
Mean HVLT Total (*s.d.*)	8.3 (4.0)	28.9 (3.9)
Mean TMT interference (*s.d.*)[a]	116.0 (108.9)	37.1 (22.5)
Mean Verbal Fluency words recalled (*s.d.*)	9.7 (5.9)	25.7 (4.8)
Mean SCWT interference score (*s.d.*) [b]	2184 (2295)	342.9 (408)
Mean SCWT *s.d.*[b]	1923	698

Abbreviations: s.d. – Standard Deviation; GDS – Geriatric Depression Scale; MMSE – Mini Mental State Examination; HVLT – Hopkins Verbal Learning Task; TMT – Trail Making Test; SCWT – Stroop Colour Word Test
[a]given in seconds
[b]given in milliseconds

4.3.1. Comparison of cognitive test scores for AD patients and controls

The MANOVA showed a significant difference between AD patients and controls on the cognitive tests ($F(4, 11)=19.88$, $p=.000$, Pillai's Trace=.88, $\eta^2=.88$). Because HVLT total scores and SCWT s.d. scores showed high correlations ($r>.80$, see Table 6) with scores on the other tasks they were excluded from the initial MANOVA to avoid collinearity. No univariate or multivariate outliers were identified for any of the dependent variables, and observed power for this model was high (>.8).

Using a Bonferroni adjusted *p* value ($p \leq .01$) to account for multiple testing, AD patients recalled an average 10 fewer words than the controls on the Verbal Fluency task ($F(1,14)=15.94$, $p=.001$, $\eta^2=.53$) and 5 fewer words than the controls on the HVLT trial 1 ($F(1,14)=36.80$, $p=.000$, $\eta^2=.72$). Compared to controls, AD patients also showed larger TMT interference scores (average 59 seconds longer; $F(1,14)=10.93$, $p=.005$; $\eta^2=.44$) and SCWT interference scores (average 2 seconds longer per trial; $F(1,14)=20.04$, $p=.001$, $\eta^2=.59$). Inclusion of the HVLT total score and SCWT *s.d.* in the model did not affect results from the other tasks but HVLT total scores were significantly reduced in AD patients compared to controls ($F(1,13)=85.70$, $p=.000$, $\eta^2=.87$). SCWT *s.d.* was also higher by over 3 seconds in AD patients compared to controls ($F(1,13)=22.41$, $p=.000$, $\eta^2=.63$).

Table 6
Correlations between cognitive test scores at baseline

	HVLT trial 1	HVLT total	SCWT interference	SCWT s.d	Verbal Fluency
HVLT trial 1					
HVLT total	.94**				
SCWT interference[a]	-.41*	-.55**			
SCWT s.d[a]	-.78	-.78**	-.41		
Verbal Fluency	.65*	.69**	.44*	-.69**	
TMT interference[a]	-.21	-.21	.41	.00	-.09

Note: Correlation significant at **$p<.01$ and *$p<.05$ level.
Abbreviations: HVLT – Hopkins Verbal Learning Task; SCWT – Stroop Colour Word Test; TMT – Trail Making Test
[a]Lower score indicates better performance

Results of the ROC analysis are shown in Table 7. All cognitive tests were able to significantly predict group membership (AD patient v control) with a high degree of sensitivity and specificity (≥70%). The Area Under the Curve (AUC) for each test suggested good to excellent discrimination (>.80) between groups by all tests at their respective cut-off values except for the SCWT. Baseline HVLT trial 1 and total scores were especially sensitive to AD compared to the other tasks.

Table 7
Details of ROC analysis for each of the cognitive tests

Test	Cut-off score	Sensitivity	Specificity	AUC (%)	*P*
HVLT trial 1[a]	4.5	100	100	100	.000
HVLT total[a]	16.5	100	100	100	.000
Verbal Fluency[a]	12.5	78	92	82	.007
TMT interference[b]	76	77	100	82	.006
SCWT interference[c]	1717	70	100	23	.035
SCWT s.d.[c]	543	20	20	06	.001

Abbreviations: AUC – Area Under Curve; HVLT – Hopkins Verbal Learning Task; TMT – Trail Making Test; SCWT – Stroop Colour Word Test
[a]a score below the cut-off indicates allocation to the experimental group
[b]given in seconds; a score above the cut-off indicates allocation to the experimental group
[c]given in milliseconds; a score above the cut-off indicates allocation to the experimental group

4.3.2. Disease severity

There were small and non-significant correlations between MMSE scores and SCWT interference scores (r=-.06, *d.f.*=10, p=.877) and SCWT standard deviations (r=-.39, *d.f.*=10, p=.300). However, there were moderate to high positive correlations between baseline MMSE scores and scores on the HVLT trial 1, HVLT total score and Verbal Fluency (Table 8). In addition, there was a negative correlation between MMSE scores and TMT interference. These correlations indicate that poorer performance on the cognitive tasks was associated with lower MMSE scores and thus increased severity of AD. With the exception of HVLT total scores, these correlations were only borderline significant and an adjustment for multiple comparisons using the average correlation between the variables (p<.027) meant that none of these correlations reached significance.

Table 8
Partial correlations[a] between baseline MMSE scores and cognitive tasks (AD patients only)

	HVLT trial 1	HVLT total	Verbal Fluency	TMT interference[b]	SCWT interference[b]	SCWT *s.d.*[b]
MMSE	.56*	.72**	.42*	-.63*	-.06	-.39

Note: correlation significant at *p<.10, **p<.05
Abbreviations: MMSE – Mini Mental State Examination; HVLT – Hopkins Verbal Learning Task; TMT – Trail Making Test; SCWT – Stroop Colour Word Test.
N=13, *d.f.*=10.
[a]Adjusted for age
[b]Lower score indicates better performance

The repeated-measures ANOVA found a group*time interaction for the HVLT trial 1 when adjusting for the covariates ($F(1,10)=8.53$, $p=.015$, $\eta^2=.46$). Controls showed greater learning effects from time 1 to time 2 on this task (average 1.5 words improvement) compared to AD patients (average no improvement; Figure 3). There was also a similar trend for Verbal Fluency scores ($F(1,8)=4.56$, $p=.065$), but there were no significant interactions for the HVLT total, SCWT or TMT interference scores. Instead, similar learning effects from time 1 to time 2 were seen for both groups on these tasks.

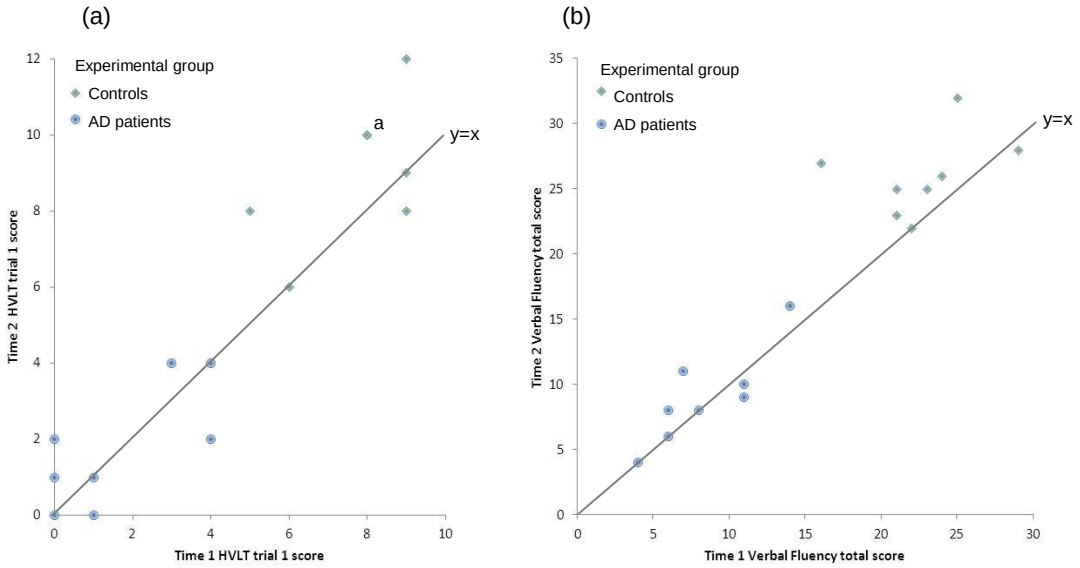

Figure 3
Scatterplot of (a) HVLT trial 1 scores and (b) Verbal Fluency total scores, both at Time 1 and Time 2 for AD patients and controls.

[a]Data point for 3 participants

A high correlation was seen between TMT scores at baseline and MMSE change scores ($r=-0.805$, $p=.000$), indicating that worse (higher) TMT interference scores were associated with a decline in MMSE scores over the 6 months. The same correlation was not seen between SCWT baseline scores (interference or *s.d.*) and MMSE change scores ($r=0.396$, $p=.084$) nor was this seen for the memory tests ($p>.25$).

When participants were stratified based on whether they declined or improved/remained stable on the MMSE over time, a significant association was seen

between TMT baseline scores and MMSE change scores (*p*=.010) which was especially pronounced in the AD group (Figure 4). A cut-off of 77.5 seconds TMT interference score had optimum sensitivity and specificity of 83% and 90% respectively (AUC=.933; *p*=.005) to identify decliners in MMSE performance over time. Again, the same was not seen between SCWT baseline scores and MMSE change scores, nor was this seen for the HVLT and Verbal Fluency tests. Low baseline TMT interference scores thus appeared to predict a lack of response to standard treatment with AChEIs (as assessed by the MMSE) in AD patients, whereas memory tests did not.

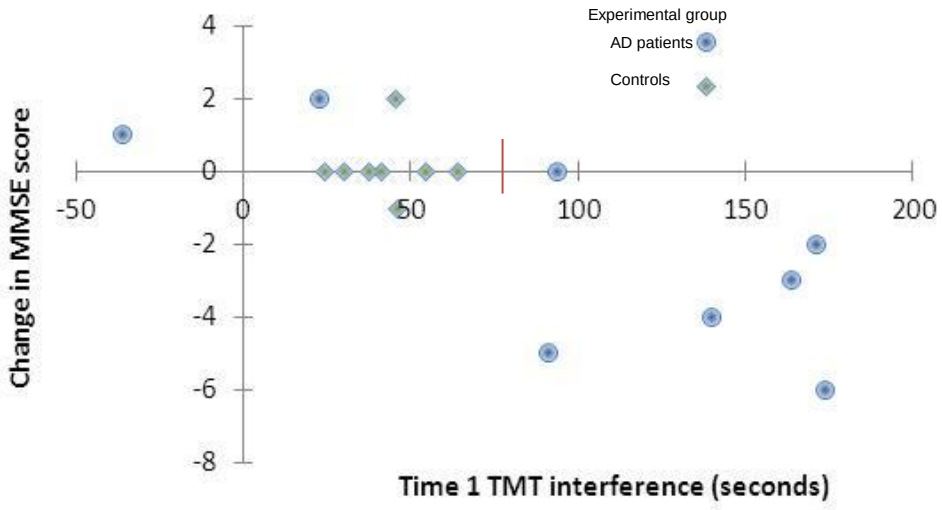

Figure 4
Plot to show MMSE change scores against baseline TMT interference scores.
Note: Red line marks optimum cut-off of 77.5 seconds

4.4. Discussion

The aims of this study were to examine the relevance of our versions of easy to administer and well-tolerated cognitive tests to the cognitive difficulties experienced in AD. This study found that performance on these tests showed good discrimination between varying levels of cognitive ability relevant to AD. HVLT scores were particularly sensitive with optimal cut-offs comparable to those by Frank et al. (2000) (18/19 points) and Hogervorst et al. (2002). The Verbal Fluency task and TMT interference scores were also highly sensitive for AD, although not as strongly as the

HVLT. Similar findings were reported previously in other cohorts (De Jager, Hogervorst, Combrink & Budge, 2003). Both SCWT interference scores and *s.d.* were on average significantly smaller in controls compared to those with AD. However, the SCWT showed low discriminability between groups, which has also been reported previously (Binetti et al., 1996; Sarazin et al., 2007) and is possibly due to high variance in both groups on both conditions of this task. Performance on the memory tasks and TMT correlated with dementia severity in AD patients. These tasks therefore appear be consistent with what would be expected of tasks that act as domain-specific assessments of abilities affected in AD.

Poor TMT performance at baseline predicted decline in clinical outcomes of AD after 6 months particularly in AD patients. Early executive function deficits have been demonstrated as a marker of early AD symptoms (Parasuraman, Greenwood & Sunderland, 2002). TMT performance can predict conversion to AD (Chen et al., 2000; Rapp & Reischies, 2005) and Ewers et al. (2012) also found that TMT performance was one of the best predictors of conversion from MCI to AD over 2 years with accuracy of 64.6% (95% CI: 55.5, 73.4%). Low TMT performance may therefore be indicative of particularly severe pathology or dementia with accompanying vascular changes that are less likely to respond to AChEI treatment (Kramer, Reed, Mungas, Weiner & Chui, 2002). Our findings may be due to the small sample size but they are consistent with previous understanding of executive function deficits. The SCWT test did not show this same pattern, despite previous research finding that deficits on this task predicted decline in MMSE scores (Clark et al., 2011).

The SCWT requires attention inhibition, but not task switching as seen in the TMT, which may indicate that the TMT is more complex and difficult for those with AD-type impairment. However, it was also noticed that AD patients in this study often forgot the rule for the incongruent condition of the SCWT and reverted to the congruent condition rule, meaning that no interference effect was created as participants in effect responded in the same way to both conditions. The computerised version of this task does not allow for correcting mistakes, however the TMT allows for the participant to go back and correct all errors, meaning that an error leads to a time penalty and is reflected in the interference effect. In sum, low executive function in AD patients, as assessed by TMT interference (but not SCWT) may predict a lack of response to 6 months of AChEI treatment and this should be investigated further.

The HVLT trial 1 (and to some degree the Verbal Fluency task) showed a difference between groups over time. The control group tended to improve slightly at the second meeting, while AD patients tended to show no learning effects from baseline to six months. In contrast, implicit learning effects were seen in both groups

on the tasks of executive function, although AD patients showed reduced scores compared to controls at both assessments. Learning effects on the HVLT trial 1 (and Verbal Fluency) may rely on episodic memory while learning effects on the executive function tasks is possibly based more heavily on procedural memory, which can be relatively preserved in AD (Deweer et al., 1994; Hirono et al., 1997). The HVLT trial 1 and Verbal Fluency tasks thus appear to measure a specific memory ability that is affected by AD. In our RCT we will control for learning effects in controls on these AD sensitive tests by using an order-balanced design with practice trials before baseline measurements (Chapter 7).

A strength of this study is that it assessed AD patients before starting treatment, removing any possible effect that treatment could have had on their baseline cognitive scores. It also allowed us to determine the relationship between our versions of cognitive tests and response to treatment over the six months. A limitation of this study is the high drop-out rate, although there were no differences between those who stayed in the study and those who left after the first testing session. Bias caused by attrition is therefore unlikely to account for these findings. However, small sample sizes throughout the study preclude generalised conclusions from being made on the appropriateness of using these cognitive tests in acting as a proxy for AD. For further understanding of the way that these tests respond to AD in different populations and over different stages of AD, a multi-centre study is needed to expand the sample size and inter-patient variability on covariate measurements.

This study aimed to validate the cognitive test battery as being sensitive to cognitive impairment such as that seen in dementia. These tests appear to offer domain-specific tests of cognitive function that are relevant to the impairment seen in AD and as such they are used in the studies presented later in this thesis. The HVLT trial 1 and Verbal Fluency tasks may be especially relevant to assessing changes over time, although the TMT also appears sensitive to early or severe cognitive deficits. These tests therefore measure specific abilities that are affected in AD and that are thus appropriate targets for interventions based on the cognitive reserve hypothesis. Performance on our version of the SCWT test was not consistent with previous research and so it has been excluded from the cognitive test battery for the following treatment studies presented in this thesis. However, the HLVT (trial 1 and total), Verbal Fluency and TMT tasks were included.

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Part Three – Observational Study

Chapter 5 – The relationship between physical activity and cognition in an elderly Indonesian cohort

5.1. Introduction

The literature review presented in Part One (Chapter 2) identified several important factors that may influence the relationship between physical activity and cognitive performance. Firstly, three studies showed that physical activity was associated with reduced risk of cognitive impairment or dementia over 3-5 years for women only in stratified analyses (Laurin, Verreault, Lindsay, MacPherson & Rockwood, 2001; Ho, Woo, Sham, Chan & Yu, 2001; Sumic, Michael, Carlson, Howieson & Kaye, 2007). However, other studies that included only men did still find an association, including a 43% reduced risk of dementia over 6 years (Abbott et al., 2004; see also Cassilhas et al., 2007). It is unclear whether associations between physical activity and cognitive performance in general are stronger in women compared to in men or whether the differences are incidental due to study methodologies as few studies report a direct comparison of effect sizes.

Secondly, the relationship between physical activity and cognitive performance appears to be lessened when cognitive decline is more advanced, as few improvements were seen in elderly with clinically diagnosed cognitive impairment or dementia after RCTs of physical activity (see Chapter 2). Thus, the strongest associations may be seen in younger rather than older elderly who are more likely to show dementia pathology. It is important to note that few studies have directly compared these two groups so this finding may be due to a lack of evidence or to study design. On the other hand, as physical activity is thought to prevent rather than reverse cognitive decline, younger and high functioning adults may show a stronger association of physical activity and cognitive performance.

Thirdly, the literature review suggests that physical health may act as a pathway between physical activity and cognitive performance. In the next chapter we show that physical activity is significantly associated with activities of daily living and health-related Quality of Life (QoL) measures (Chapter 6). The physical autonomy that comes from improved fitness and physical ability may lead to increased social and mental stimulation that in turn has a protective effect on cognition. This may be instead of, or in addition to, a direct physiological effect of physical activity on neural systems. Functional disability is associated with impaired cognitive function (Perneczky et al.,

2006) and Arcoverde et al. (2008) found that Activities in Daily Life (ADL) scores correlated with MMSE scores in AD patients. However, few studies have used ADLs or QoL as a specific variable of interest. It is also unclear whether these associations would be affected by other factors mentioned above such as age and sex.

To test these hypotheses, data were analysed from an observational study of a large community-dwelling sample in Indonesia. The data were collected as part of the Study of Elderly's Memory Impairment and Associated Risk factors (SEMAR) study, which was developed through a previous collaboration between Loughborough University and University of Indonesia (described in detail in Yesufu, 2009). Baseline data were collected in 2006 by collaborators at University of Indonesia, with follow-up data collected in 2009. The author was not responsible for study design or implementation but rather performed secondary data analysis on this cohort to investigate the impact of age, sex and physical health on the relationship between physical activity and cognitive functioning.

5.2. Method

5.2.1. Participants

A total of 719 men and women over the age of 60 years were recruited from three sites in Indonesia: Central and South Jakarta (*n*=298), Borobudur (near Yogyakarta; *n*=214) and Citengah (near Bandung; *n*=207). Jakarta is an urban area, whereas Borobudur and Citengah are both rural. Local residents and those in surrounding villages were given study information by village elders or staff at local community centres and care homes. None of those who were invited to participate declined. Participants were tested at their local community centre (*n*=667) or care home (*n*=49) where possible. Participants with limited mobility were tested at home (*n*=3). Of the initial sample, 135 participants from the Borobudur area were revisited 3 years later for follow-up measurements, a follow up rate of 63%. Reasons for attrition to follow-up included death and moving away from the area. Written informed consent was gained from all participants before study onset and, if participants brought a carer with them, they too signed a consent form. Ethical approval was obtained from Loughborough University (UK) and the University of Indonesia (Jakarta) prior to study onset, as were governmental and local permits.

5.2.2. Outcome measures

Participants completed the Mini Mental State Examination (MMSE) and the Hopkins Verbal Learning Test (HVLT), as described in Chapters 3. The HVLT was scored in terms of both trial 1 and a total immediate recall score as in Chapter 4. Stimuli from both tests were adapted slightly for local knowledge and illiterate respondents. Specifically, the precious gems category in the HVLT and the backwards-spelling task and seasons question in the MMSE were changed. In these study waves, Verbal Fluency and the TMT were not included.

5.2.3. Measures

Aided by trained research assistants at community health centres, participants were asked to complete an extensive questionnaire that included questions on demographic characteristics and lifestyle behaviours (Appendix D). Forward- and back-translations (English and Indonesian) were completed prior to study onset to ensure that the questionnaire maintained its intended meanings, and all questions were administered verbally by a native speaker. Participants were assessed using the Mahoney scale of Activities of Daily Living (ADL; Mahoney & Barthel, 1965; Appendix E) and the Lawton scale of Instrumental Activities of Daily Living (IADL; Lawton & Brody, 1969; Appendix F) scales. These scales rate an individual's ability to perform basic activities, such as eating and bathing (ADL), and more complex activities, such as cooking, banking and preparing medication (IADL). Higher scores on both scales indicate more independence and less reliance on help from others. The questionnaire also included the Symptom Checklist questionnaire (SF-36; Ware and Sherbourne, 1992; Appendix G), a measure of health-related QoL. This questionnaire includes scales on physical, emotional and mental health that are averaged to give a total score out of 100 (a higher score indicates higher rated QoL).

5.2.4. Design

This was a cross-sectional study examining the relationship between self-reported frequency of participation in physical activity and cognitive performance (global and memory) and the impact of possible mediating (ADL, IADL, QoL) and moderating (sex, age) factors. A subgroup of participants completed a second cognitive assessment three years after baseline as prospective studies have demonstrated previously that participation in physical activity is predictive of cognitive

status at follow-up several years later (e.g. Laurin et al., 2001; Sumic, et al., 2007; see Chapter 2).

Physical activity variables included regular participation in sport and gardening (each scored *yes* or *no*) and walking frequency (rated on a 5-point scale from *never* to *very often*)[4]. The dependent variables were HVLT trial 1 score, HVLT total score and MMSE total score, all continuous variables.

Covariates included in the analysis were age (years), education (years) and smoking status. Increased age, low education and cigarette smoking are known risk factors for AD (Lindsay et al., 2002; Reitz, den Heijer, van Duijn, Hofman & Breteler, 2007; Cataldo, Prochaska & Glantz, 2010). ADL, IADL and SF-36 scores (continuous) were also considered as potentially mediating variables because functional ability and health may interfere with participation in physical activity. Alcohol consumption was measured with the intention to use as a covariate but was excluded as no participants reported drinking alcohol (this was mainly a Muslim sample).

5.2.5. Procedure

All participants were seen individually between 8am and 11am to limit the effects of circadian rhythms and heat. After an information session in which informed consent was gained, participants completed the demographic questionnaire and SF-36 questionnaire with the researcher. They were then asked to do the HVLT and MMSE, followed by the ADL and IADL assessments. Three years later, participants were invited back to repeat the cognitive tasks.

5.2.6. Analysis

The data were analysed using SPSS v18.0 with a required p value of .05. Demographic characteristics and mean cognitive scores for the baseline and follow-up samples were calculated using cross tabs and descriptive analyses for means. Bivariate correlations were calculated to determine each covariate's suitability for inclusion in the model, showing that the independent variables were all moderately correlated with the outcome measures. In addition, the independent variables were moderately correlated with each other but not so high as to suspect multicollinearity (r<.7). Hierarchical regression analyses using the 'Enter' method were performed to determine which physical activity variables uniquely predicted cognitive scores while

[4] Participation in gymnastics and dancing was also included in the questionnaire but final response rates to this question were too low to include the variables in the analysis

accounting for the selected covariates. Step 1 of all regression models included the covariates age, education and smoking status. Sport, walking and gardening were added in Step 2 and ADL and IADL scores were added in Step 3. In Step 4, QoL scores were added. Because walking was recorded as an ordinal rather than scale variable, dummy coding was used to transform it into dichotomous variables using backwards difference contrasts. Each contrast compared a level of the variable with the previous level (e.g. 'often' v 'sometimes'), creating four new variables for each physical activity. Walking was then only considered significant in a regression model if all four contrasts had a significant beta value (Stockburger, *n.d.*).

To assess the impact of sex on the association between physical activity and cognitive functioning, moderated regression models were run for each of the outcome measures. Each model included an interaction term between the three physical activity variables and sex entered as Step 5. Because of the large difference in sample size for men and women, the dichotomous sex variable was weighted proportional to the total sample (men -0.65, women 0.35) before calculating the interaction terms. Similar models were run with interactions between the three physical activity variables and age entered as Step 5. The age variable was centred to avoid collinearity with the interaction terms by subtracting each value from the mean before calculating the interactions.

For follow up analyses, a regression model was conducted to examine the relationship between physical activity at baseline and cognitive performance after 3 years. In addition, odds ratios were calculated using crosstabs to determine the risk of being in a low functioning group dependent on baseline physical activity. Participants who had an MMSE score <24.5 and a HVLT score <14.5 were classed as having low cognitive functioning based on earlier data (Hogervorst, Rahardjo & Bandelow, 2011).

The required sample size for each regression analysis was determined as $N>50+8m$, where m is the number of independent variables (Tabachnick & Fidell, 2001), giving a minimum group size to give sufficient power for each model as $n=146$. Missing cases were deleted listwise. Analysis of residual statistics and plots revealed no violation of normality or outliers for any regression model.

5.3. Results

5.3.1. Baseline Analysis

Table 9 shows the baseline demographic information of the whole group, which was subsequently stratified by sex and by median age. Women had higher IADL

(*t*(703)=-2.01, *p*=.045) and HVLT total (*t*(573.7)=-2.44, *p*=.015) mean scores compared to men. Smoking was seen in few cases in women, with men significantly more likely to smoke (see Table 9). Women were also more likely to have fewer years of education (chi^2=8.81, *p*=.003). Men and women were, however, of similar age and had similar proportions of those at risk of dementia based on combined MMSE and HVLT scores.

Table 9
Demographic characteristics and mean cognitive test scores at baseline

Variable	Total	Sex		Median age split	
		Men	Women	<68 years	>68 years
N	719	255	464	337	382
Mean age (*s.d.*); years	69.4 (7.9)	70.1 (7.7)	69.0 (7.9)	62.7 (2.6)	74.8** (5.5)
Mean IADL score (*s.d.*)	13.3 (3.9)	12.9 (4.0)	13.5* (3.8)	14.7 (2.1)	12.6** (4.1)
Mean ADL score (*s.d.*)	19.7 (1.1)	19.6 (0.9)	19.7 (1.2)	19.9 (0.5)	19.5** (1.4)
Ever smoked; %	31.8	70.8	4.0**	21.4	26.7*
Education; %					
<Elementary	76.6	60.6	88.0	33.5	56.3
>Elementary	22.9	38.2	12.0*	60.5	47.3**
Mean MMSE (*s.d.*)	24.2 (5.6)	24.3 (5.3)	24.3 (5.7)	25.7 (4.3)	23.1** (5.8)
Mean HVLT total score	19.7 (10.7)	18.5 (9.2)	20.4* (8.2)	16.8 (7.3)	12.8** (7.2)
(*s.d.*)	3.9 (2.4)	3.7 (2.2)	4.0 (2.5)	4.5 (2.4)	3.4** (2.2)
Mean HVLT trial 1 (*s.d.*)					
Dementia risk; (%)	29.9	28.2	30.8	20.5	38.2**

Note: contrast (men v women OR age <68 years v age >=68 years) significantly different, *p<.05, **p<.001.
Abbreviations: SD – Standard Deviation; IADL – Instrumental Activities of Daily Living; ADL – Activities of Daily Living; SF-36 – Short Form 36 Questionnaire; MMSE – Mini Mental State Examination; HVLT – Hopkins Verbal Learning Task
[a]Based on HVLT (<14.5) and MMSE (<24.5)

The young and older groups were different on all measures, with older participants having lower IADL (t(562.9)=9.04, p<.001), ADL (*t*(446.4)=4.91, *p*<.001), MMSE (*t*(663.6)=9.04, *p*<.001), HVLT total (*t*(670)=7.95, *p*<.001) and HVLT trial 1 (*t*(671)=7.23, *p*<.001) scores. Older participants had lower levels of education (chi^2=19.61, *p*<.001) and were also more likely to smoke (chi^2=4.69, *p*=.030). Older participants had increased dementia risk compared to the younger group (chi^2=38.87, *p*<.001).

Frequencies of participation in the different activities at baseline are shown in Table 10. A higher proportion of women played sport than men (chi^2=19.45, p<.001) while a higher proportion of men participated in gardening than women (chi^2=7.52, p=.006). No differences were seen in walking between men and women (chi^2=3.39, p=.495). Older elderly were more likely not to play sport (chi^2=23.91, p<.001). No differences were seen between age groups on gardening frequency (chi^2=0.84, p=.360) but a higher proportion of younger elderly walked often compared to elderly (chi^2=37.54, p<.001).

Table 10
Frequency of participation in different physical activities

Activity	Response	Whole group	Men	Women
Sport	No	404	172	232
	Yes	311	82	229
Gardening	No	613	204	409
	Yes	100	48	52
Walking	Never	10	3	7
	Seldom	95	38	57
	Sometimes	163	57	106
	Often	389	140	249
	Very often	58	15	43

5.3.1.1. Whole group

After controlling for the covariates, physical activity significantly explained additional variance in cognitive scores (approx 2.8-4.3%). Sport and walking specifically were associated with higher MMSE, HVLT trial 1 and HVLT total recall scores (Table 11). Gardening was associated with lower cognitive scores although this relationship did not reach significance. IADL scores were also associated with all cognitive scores, while ADL scores were associated with MMSE scores only. Although IADL and ADL scores attenuated the relationship between walking and cognitive performance, the relationship remained significant for sport. Adjustment for ADL and IADL scores also led to a stronger and significant negative association between gardening and HVLT trial 1 score. Further adjustment including SF-36 scores had little effect on the associations.

Table 11

Regression analysis for whole group

	Variables	*Model 1*[a]		*Model 2*[a]		*Model 3*[a]	
		β	SE	*β*	SE	*β*	SE
MMSE	Walk seldom	5.48***	1.57	2.69*	1.45	2.62*	1.46
	Walk sometimes	4.48***	1.24	1.72	1.16	1.64	1.17
	Walk often	3.59***	0.91	1.25	0.86	1.18	0.87
	Walk very often	1.71**	0.63	0.63	0.59	0.61	0.59
	Sport	1.86***	0.43	1.60***	0.39	1.61***	0.39
	Gardening	-0.02	0.50	-0.41	0.45	-0.40	0.46
	ADL			0.47**	0.16	0.45**	0.16
	IADL			0.50***	0.06	0.49***	0.06
	SF-36					0.01	0.01
		$F_{(9, 653)}$=35.44		$F_{(11, 651)}$=47.15		$F_{(12, 650)}$=43.19	
		R^2 change=.043		R^2 change=.115		R^2 change=.000	
HVLT trial 1	Walk seldom	2.14**	0.72	1.49**	0.72	1.30*	0.72
	Walk sometimes	1.80**	0.57	1.16**	0.58	0.92	0.58
	Walk often	1.38***	0.42	0.85**	0.43	0.67	0.43
	Walk very often	0.82**	0.30	0.57*	0.30	0.49*	0.30
	Sport	0.74***	0.20	0.68***	0.20	0.72***	0.20
	Gardening	-0.13	0.23	-0.22	0.23	-0.17	0.22
	ADL			0.13	0.09	0.06	0.09
	IADL			0.11***	0.03	0.07**	0.03
	SF-36					0.012**	0.01
		$F_{(9, 626)}$=32.03		$F_{(11, 624)}$=29.39		$F_{(12, 623)}$=28.42	
		R^2 change=.029		R^2 change=.026		R^2 change=.012	
HVLT total	Walk seldom	6.54**	2.15	3.98*	2.11	3.36	2.10
	Walk sometimes	5.29**	1.71	2.76	1.70	1.98	1.69
	Walk often	4.48***	1.26	2.40*	1.26	1.79	1.26
	Walk very often	2.43**	0.89	1.45*	0.87	1.19	0.87
	Sport	1.98***	0.60	1.74**	0.59	1.87**	0.58
	Gardening	-0.93	0.68	-1.28*	0.66	-1.14*	0.65
	ADL			0.42	0.26	0.20	0.26
	IADL			0.45***	0.09	0.34***	0.09
	SF-36					0.06**	0.02
		$F_{(9, 626)}$=43.13		$F_{(11, 624)}$=42.08		$F_{(12, 623)}$=40.68	
		R^2 change=.028		R^2 change=.043		R^2 change=.013	

[a]all models adjusted for age, education and smoking

***p=≤.001; **p=≤.05; *p=<.10

Abbreviations: SE – Standard Error; IADL – Instrumental Activities of Daily Living; ADL – Activities of Daily Living; SF-36 – Short Form 36; MMSE – Mini Mental State Examination; HVLT – Hopkins Verbal Learning Task

5.3.1.2. Effect of sex

To assess whether the relationship between physical activity and cognitive performance is different for women compared to for men, regression analyses were stratified by sex (data not shown). Physical activity explained an additional 2.5-4.3% of the variance in cognitive scores in men and an additional 2.6-5.0% of the variance in

cognitive scores in women, but the association was only significant in women. Adjustment for ADL, IADL and SF-36 scores did not affect these observations except that the strength of the association between sport and HVLT trial 1 scores was similar between men and women after full adjustment.

To statistically test whether sex moderated the relationship between physical activity and cognitive functioning, moderated regression analyses were performed using the following interaction terms: walking*sex, sport*sex and gardening*sex (Table 12). These models showed that the interaction term of sport*sex was consistently significant for all outcomes, suggesting that sex acted as a moderating variable between sport and cognitive functioning. The interaction of gardening*sex was also significant for HVLT trial 1 but no other interaction terms were significant.

Table 12
*Regression analysis using interaction terms for physical activity*sex*[a]

Cognitive test	Interaction term	*t*	*β*	*SE*
MMSE	Walk*sex	-1.79	0.27	0.15
	Sport*sex	1.98*	1.41	0.71
	Gardening*sex	0.66	0.60	0.91
			$F_{(14,648)}$=37.49*	
			R^2 change=.01*	
HVLT trial 1	Walk*sex	1.44	0.32	0.22
	Sport*sex	2.24*	2.33	1.04
	Gardening*sex	-2.10*	-2.76	1.32
			$F_{(14,621)}$=34.87*	
			R^2 change=.01*	
HVLT total	Walk*sex	1.43	0.43	0.30
	Sport*sex	2.42*	3.42	1.41
	Gardening*sex	-1.94	-3.48	1.79
			$F_{(14,620)}$=38.29*	
			R^2 change=.02*	

Note: significant at *$p \leq .05$
[a]All models adjusted for age, education, smoking, walking, sport, gardening, ADL, IADL and SF-36
Abbreviations: SE – Standard Error; MMSE – Mini Mental State Examination; HVLT – Hopkins Verbal Learning Task

5.3.1.3. Effect of age

To examine whether the relationship between physical activity and cognitive performance is reduced with increased age, another group of moderated regression models were performed for each outcome using the following interaction terms:

walking*age, sport*age and gardening*age (Table 13). The interaction terms between age and sport were significant for HVLT trial 1 and total scores, suggesting that age played a moderating role on the relationship between sport and memory. No other interactions were significant.

Table 13
*Regression analysis using interaction terms for physical activity*age*

Cognitive test	Interaction term	*t*	*β*	*SE*
MMSE	Walk*age	0.25	0.01	0.03
	Sport*age	1.63	0.07	0.05
	Gardening*age	0.01	0.00	0.06
		$F_{(15, 644)}$=34.62*		
		R^2 change=0.00		
HVLT trial 1	Walk*age	0.18	0.00	0.01
	Sport*age	-3.18*	-0.08	0.02
	Gardening*age	0.52	0.02	0.03
		$F_{(15, 617)}$=23.78*		
		R^2 change=0.01*		
HVLT total	Walk*age	-0.04	-0.00	0.04
	Sport*age	-2.20*	-0.16	0.07
	Gardening*age	0.42	0.04	0.09
		$F_{(15, 617)}$=32.40*		
		R^2 change=0.01*		

Note: significant at *p=≤.05
[a]All models adjusted for age, education, smoking, walking, sport, gardening, ADL, IADL and SF-36
Abbreviations: SE – Standard Error; MMSE – Mini Mental State Examination; HVLT – Hopkins Verbal Learning Task

5.3.1.4. Odds ratios

We documented 215 cases of high dementia risk based on combined test cut-offs of HVLT (<14.5) and MMSE (<24.5). Those who participated in sport had a 78% reduced risk of being in an at-risk group for dementia (OR: 0.22, 95% CI 0.15, 0.33) while those who walked a lot (walked often or very often) had a 45% reduced risk of being in that group (OR: 0.55, 95% CI; 0.39, 0.76). Participating in gardening was also associated with reduced risk but this did not reach significance (OR: 0.64, 95% CI: 0.39, 1.05).

5.3.2. Follow-up analysis

Demographic information about the participants who were retained to follow-up after 3 years are shown in Table 14**.** There were no relationships between any type of physical activity at baseline and cognitive function at follow-up, including odds of being in an at-risk group for dementia (data not shown).

Table 14
Demographic information for participants at follow-up

Variable	
N	135
Mean age (SD); years	70.4 (8.0)
Female; %	63.0
Mean ADL score (*s.d.*)	19.8 (0.5)
Mean IADL score (*s.d.*)	12.8 (3.7)
Ever smoked; %	29.6
Education; %	
< Elementary	76.3
> Elementary	23.0
Mean MMSE (*s.d.*)	23.2 (4.5)
Mean HVLT total (*s.d.*)	14.2 (6.9)
Dementia risk; %	39.3

5.4. Discussion

The aims of this study were to examine the influence of a range of mediating and moderating factors identified by the literature review presented in Chapter 2 on the relationship between physical activity and cognitive functioning in a large elderly cohort. Participation in sport and walking was associated with better memory and general cognitive abilities. The associations between walking and performance on each of the three tasks were explained by improved physical health measures (as assessed by IADL, ADL and SF-36), suggesting that walking may promote cognitive health through maintaining physical autonomy and health. However, the association of sport with cognitive performance was relatively independent of physical health and suggests other mediating factors are involved. The data showed that the relationship between participation in sport and cognitive performance was strongest in women compared to in men after adjustment for physical health. Age also appeared to act as a

moderator of the relationship between sport and memory, with the relationship weakening in the oldest-old. Participation in physical activity was not associated with cognitive performance or risk of cognitive impairment after 3 years.

Surprisingly, participation in gardening was associated with *decreased* memory performance and an *increased* risk of cognitive impairment relative to non-participation in women. This was generally a weak association and post hoc analysis showed that it was explained by those who worked in farming (*n*=258). Farmers were more likely to participate in gardening perhaps to grow produce to sell or for private consumption and were also more at risk of having lower cognitive scores. Culture and its associations with socio-economic or other lifestyle factors may thus heavily influence the relationships between particular types of physical activity and memory. On the other hand, engaging in sports was similarly (to European and US based cohorts) protective against poor memory in this middle-income country. Different types of physical activity should thus be considered individually in relation to the country under investigation in observational studies.

Our study found that the association between physical activity and cognitive functioning was stronger in women compared to in men, which is consistent with previous findings. For example, a study of a Chinese cohort found a 55% reduced risk of cognitive impairment over 3 years in women only who took part in physical activity (yes v no) compared to those who were inactive (Ho et al., 2001). This sex difference has also been seen in Western countries (Laurin et al., 2001; Sumic et al., 2007). These consistencies suggest that this impact of sex may not be due to sociocultural factors, as these would differ between geographical regions, and thus supports the role of hormones as a possible mediating factor in the relationship. We also found that the association was strongest for memory in younger elderly, who also had significantly higher MMSE scores and lower risk of dementia. This may be because those with cognitive impairment misreported their physical activity habits in this study, but these findings are also consistent with the premise that the association is weakened when dementia pathology is likely to be more advanced. This therefore supports the need for midlife interventions before dementia pathology develops, as discussed in Chapter 2 and in the review presented in Appendix A.

Unlike in Ho et al. (2001), physical activity was not associated with cognitive functioning after 3 years. This may indicate that physical activity has only short-term effects that do not last if physical activity is stopped or that other factors (such as morbidity) interfere with both physical activity and cognitive decline (unfortunately no follow-up physical activity or health data was available to further investigate this). However, the mean age at follow-up was 70 years and since no association was seen

in the older-age group at baseline, it is uncertain whether the lack of an association is actually due to the age of the participants. The small sample retained to follow-up meant that the group size was too small to stratify to gain a meaningful comparison based on age. In the literature review in Chapter 2, few studies recruited participants under the age of 65 years at baseline and those that did investigated dementia risk (not cognitive ability/impairment) and showed conflicting findings (Rovio et al., 2005; Rovio et al., 2007; Carlson et al., 2008). Further longitudinal research with regular cognitive assessments and measurements of physical activity is needed in this area to determine whether long-term associations change as risk of having underlying dementia pathology increases.

The strengths of our study include the large sample size, which allowed for direct comparisons of the effect size between groups stratified by sex and by age. The community sample also allowed the investigation of everyday activities rather than in an artificial environment. Our study has several limitations. The measure of physical activity was not comprehensive, although the questionnaire did include those activities that were most commonly performed. The selective effects seen in the regression models may be due to the method of self-report, which can be unreliable as those with existing cognitive impairment can find it difficult to accurately report activities that they are engaged in. In addition, walking was measured on a scale that depends upon each respondent's own interpretation of the response levels (e.g. seldom vs. sometimes). This would most likely bias the findings towards the null. Objective measures of physical activity/fitness are needed (e.g. daily caloric expenditure, cardiovascular fitness, muscle strength, balance, grip strength) to improve the reliability of the independent variable and the sensitivity of statistical outcomes.

In sum, this study has identified specific groups for whom physical activity may be especially beneficial. We provide evidence that engaging in sport is associated with better cognitive ability and memory particularly in elderly Indonesian women. This finding in a middle-income country is novel but important as the majority of people with dementia are estimated to live in developing countries and this is where the largest growth in incident cases is expected to be (Wimo, Winblad, Aguero-Torres & von Strauss). Indonesia is the world's fourth most populous country with a rapidly growing elderly population (Wibowo et al., 2004) and these results may have important implications for lifestyle behaviours in the middle- to older-age groups. Due to time and resource constraints, only the MMSE and HVLT tests were used and so we cannot generalize our findings to executive function abilities, but this study provides evidence that memory is affected by physical activity. However, being a cross-sectional study, these results may simply reflect lower exercise adherence in those with existing

cognitive or physical problems and also cultural factors that cannot be controlled for. Thus, controlled studies that use objective measures of physical activity need to be conducted in this region to determine causal direction. Methodological improvements may also help to determine if amount or intensity of physical activity is related to future cognitive ability as this may have implications for healthcare advice for this region. In the following chapter we include a study further investigating the association between health and physical activity. In Part Four we then present an RCT investigating physical activity effects in middle-aged adults for whom this type of intervention may be most appropriate.

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This chapter involves analysis of data collected as part of the study described in Chapter 5 and is currently in press.

Chapter 6 – A Cross-sectional Study of Physical Activity and Health-Related Quality of Life in an Elderly Indonesian Cohort

6.1. Introduction

Average life expectancy is increasing rapidly around the world (World Health Organisation 2011) and with this comes a higher rate of age-related illness and disability. Poor health has high social and economic costs, especially where there are long recovery times. Health-related Quality of Life (QoL) is a measure of the physical, psychological, social and functional well-being of an individual (Fallowfield 2009; Hennesey et al 1994). QoL measures are increasingly used as prognostic indicators for a variety of conditions and are predictive of future hospitalisation and mortality (Dorr et al 2006; Efficace et al 2006; Mapes et al 2003). They can also be used to aid the selection of treatment by balancing efficacy with side effects (Fallowfield 2009) that may contribute to relapse or require further care. Improving QoL in community samples may help to lower the demand on medical services and reduce number of person years lost to illness and/or disability in the future. Assessing and improving QoL therefore has possible wide reaching clinical implications.

Sedentary lifestyles are common in many parts of the world (van der Bij et al 2002), despite the fact that physical activity is often recommended in later life due to its benefits to cardiovascular and cognitive health (e.g. Houde and Melillo 2002; Clifford et al 2009). Physical activity has been associated previously with improved QoL in middle- to older-aged adults. Acree et al's (2010) cross-sectional study found that participation in regular physical activity was associated with increased QoL in men and women aged around 70 years. Intervention studies have found similar results. For example, Cakar et al (2010) found that completing stretching, strength and cardiovascular exercises three times per week for six weeks led to improvements in QoL for those in long-term care. In addition, men completing six months of structured aerobic activity showed improved QoL compared to a control group continuing their daily routine (Antunes et al 2005). Physical activity in general therefore appears to have positive effects on QoL.

It is unclear whether all types of physical activity have a positive effect on QoL. While Antunes et al (2005) found benefits of aerobic activity, three months of resistance training was also associated with increased ratings on a QoL mental health subscale (Kimura et al 2010). However, Oken et al (2006) found that a group of elderly

adults who performed yoga once per week for six months showed increased QoL whereas a walking group did not. This suggests that some types of physical activity may be more strongly associated with QoL than others, perhaps due to intensity or specific characteristics, such as whether it is a social activity or not. On the other hand, a review of the literature found consistent increases in QoL as a result of physical activity regardless of the type (Rejeski and Mihalko 2001). In addition, the social interaction and mental stimulation a participant receives while taking part in an intervention study may contribute more to QoL than does the physical activity. The first aim of this study was thus to examine whether different types of physical activity are associated with self-rated QoL within one large, community-based, observational study.

The second aim of this study was to identify other factors that may contribute to the relationship between physical activity and QoL. Improved functional ability as assessed by Instrumental Activities of Daily Living (IADLs) may at least partially mediate the relationship between physical activity and QoL. Functional ability and reliance on help from others have been shown previously to be associated with QoL in the elderly (Patrick et al 2000; Wlodarczyk et al 2004; Andersen et al 2004). Improved muscle strength and flexibility that come from regular physical activity may enable individuals to carry out tasks without the need for help from others, thus increasing QoL ratings. Although physical activity does not appear to reduce disability, reviews of the literature have found that it does lessen “functional limitations” and increases independence (Keysor 2003; Paterson and Warburton 2010; Spirduso and Cronin 2001). This relationship has been little explored in previous literature. Therefore, the present study also aimed to investigate whether IADL abilities mediate the relationship between physical activity and QoL.

6.2. Method

6.2.1. Participants

A total of 719 community-dwelling men and women aged 52-98 years were recruited from three sites around Indonesia: Central and South Jakarta (*n*=298), Borobudur (near Yogyakarta; *n*=214), and Citengah (near Bandung; *n*=207). Local residents and those in surrounding villages were given information about the study by village elders or staff at local community centres and care homes. Participants were tested at their local community centre (*n*=667) or care home (*n*=49) where possible. Participants with limited mobility were tested at home (*n*=3). Written informed consent was gained from all participants before study onset and, if participants brought a carer

with them, they too signed a consent form. Appropriate measures (assignment of participant ID, secure storage of data etc.) were taken to ensure anonymity and confidentiality of the data. Ethical approval was obtained from Loughborough University (UK) and the University of Indonesia (Jakarta) prior to study onset, as were governmental and local permits.

6.2.2. Measures and procedure

Participants were asked to complete an extensive questionnaire to provide information on demographic characteristics and lifestyle behaviours, including participation in several different physical activities. This questionnaire was used previously in Indonesia (Yesufu 2009) and a native speaker administered all questions verbally. Forward- and back-translations (English and Indonesian) were completed prior to study onset to ensure that the questionnaire maintained its intended meanings. Physical activity variables included regular participation in sport and gardening (both scored 'yes' or 'no') and frequency of participation in walking (rated on a 5-point scale from 'never' to 'very often'). Other measures of physical activity, such as gymnastics and dancing, were included on the original questionnaire; however, there was not enough variability in the answers to these questions to include them in the analysis. IADLs were assessed using the Lawton scale (Lawton and Brody 1969). This scale rates an individual's ability to perform activities such as cooking, shopping and preparing medication. Higher scores indicate more independence and less reliance on help from others.

Health-related QoL was assessed using the Medical Outcome Survey Short Form-36 questionnaire (SF-36; Ware and Sherbourne 1992). This questionnaire consists of 36 questions about the respondent's health and physical pain as well as how their health restricts their daily activities. The physical functioning and role physical dimensions were removed to avoid circular reasoning, leaving six dimensions in the final rating. Participants' responses to each dimension were standardised to a 0-100 point scale and were averaged to create a total score. Large UK population studies suggest that the SF-36 has high internal consistency (Brazier et al 1992; Jenkinson et al 1993) and high construct validity, with significant differences in SF-36 scores between those who report recent illness and those who do not (Jenkinson et al 1993; Lyons et al 1994).

This was a cross-sectional study examining the relationship between self-reported frequency of participation in physical activity and scores on the SF-36 while adjusting for age in years (as QoL has been seen to decline with age [Ho et al 2007]).

Years of education completed and smoking status were also included as covariates that may reflect on QoL. The IADL score was used as a possible mediating variable of interest. Weight was not available for these analyses but will be included in follow-up analyses of a smaller subset. Alcohol consumption was considered as a covariate but, as this was a largely Muslim sample, no participants reported drinking alcohol.

6.2.3. Statistical analysis

Hierarchical regression was used to examine the relationship between different types of physical activity and SF-36 scores while controlling for the selected covariates. Covariates (age, education and smoking status) were added as a block in Step 1, with the physical activity variables being added as a block in Step 2. IADL scores were added at Step 3 to examine whether they explained any relationship between physical activity and SF-36 scores. All variables were added using the Enter method. As walking frequency was scored on a Likert scale, coding was used to transform the variable into four separate dummy variables (each with two levels) by contrasting each level of walking with the previous level (e.g. 'often' versus 'sometimes'). These new dummy variables were then put into the regression model in the same step (Stockburger *n.d.*). Walking was classed as significantly explaining variance in SF-36 scores only if the beta values of all four dummy variables were significant. Analysis of residuals revealed no violation of normality or presence of outliers and multicollinearity was not suspected as no high correlations were seen between predictor variables. Analyses were carried out in SPSS v. 18.0 with a required alpha value of <.05.

6.3. Results

Of the original 719 participants, complete data sets were available for 677. Participants had a mean age of 69.2 years (*s.d.*=7.7 years) and 434 (64.1%) of the participants were women. SF-36 total scores ranged from 0 to 99 with a mean of 77.9 (*s.d*=15.7). IADL scores ranged from 0 to 16 with a mean of 13.3 (*s.d*.=3.9). The numbers of participants reporting participating in the different physical activities were: sport *n*=311; gardening *n*=100; walking often or very often *n*=447. Table 15 shows the Pearson correlations between each of the independent variables and SF-36 scores. Participation in walking and sport were both significantly correlated with SF-36 scores (*r*=.306 and *r*=.169 respectively), with those participating in more physical activity showing higher SF-36 scores. Similarly, IADL scores showed a significant positive correlation with SF-36 scores (*r*=.354) and walking (*r*=.238).

Table 15
Pearson correlations between walking and selected covariates

	Walking	Sport	Gardening	Age	Education	Smoking	IADL score
Walking	1						
Sport	.249**	1					
Gardening	.140**	.070	1				
Age	-.202**	-.188**	-.066	1			
Education	.174**	.540**	.087*	-.158**	1		
Smoking	-.071	-.196**	.081*	.049	-.012	1	
IADL score	.238**	.014	.069	-.284**	.001	.012	1
SF-36 score	.306**	.169**	.038	-.142**	.246**	-.049	.354**

Abbreviations: IADL – Instrumental Activities of Daily Living; SF-36 – Medical Outcome Survey Short Form-36
*significant at the p<.05 level
**significant at the p<.001 level

Table 16 shows the standardized beta values and significance levels for each variable at each step of the regression model, as well as changes in R^2. After accounting for age, education and smoking status, physical activity explained 10% of the variance in SF-36 scores. Of the three physical activities, only walking uniquely and significantly contributed to the model. After adjustment for IADL scores (which independently explained a further 9.5% of the variance in SF-36 scores, p=.000), walking remained significant in the model (see Figure 5) although the strength of the association between walking and SF-36 scores was reduced by approximately one third. A large part of the relationship between walking and SF-36 scores was therefore independent of IADLs. Standardised beta values revealed that the individual contributions of walking and IADL scores to SF-36 scores were comparable. Education also explained a significant amount of the variance in SF-36 scores in all steps of the regression model, while age was not a significant predictor after adjustment for IADL scores.

A compound score that included frequency of participation in all of the physical activities was not significant in another regression model (results not shown). When data were stratified by sex, similar results were found for men and women. Stratifying the sample by district also revealed no differences in the relationship of walking and SF-36 scores between those living in rural and those living in urban areas.

Table 16
Standardised beta values of each variable and R^2 and F values at each step of the regression analysis

Variable	Step 1	Step 2	Step 3
Age	-.137**	-.075*	.048
Education	.227**	.210**	.189**
Smoking	-.026	-.030	-.021
Walking seldom		.505**	.285**
Walking sometimes		.922**	.591**
Walking often		.983**	.622**
Walking very often		.397**	.267**
Sport		-.022	-.052
Gardening		-.005	-.022
IADL			.371**
R^2	.081	.186	.280
R^2 change	.081**	.105**	.095**

Dependent variable: Medical Outcome Survey Short Form-36 scores
Abbreviations: IADL – Instrumental Activities of Daily Living
*significant at the p<.05 level
**significant at the p<.001 level

6.4. Discussion

The aims of this study were to investigate whether different types of physical activity were associated with QoL in an elderly, community-based sample and whether increased IADL abilities mediated this relationship. This study found a strong association between participation in walking and higher QoL ratings. IADLs were also strongly associated with higher QoL ratings and they partially explained the association between walking and QoL. However, much of the relationship between walking and QoL was independent of IADL abilities. Participation in sport or gardening was not associated with QoL, which may indicate that the associations with these activities are confounded by other variables such as education. These findings may also be influenced by fitness; for example, Stewart et al (2003) showed that improved fitness as measured by VO2max and weight was associated with increased QoL. The physical activity scales are based upon subjective ratings and are thus vulnerable to self-serving bias and inaccuracies, and the Lawson scale of IADLs shares these weaknesses. Objective measures, such as accelerometer readings and functional ability tests, are thus recommended in future work to help lessen these limitations. Despite methodological limitations, this study provides evidence of a relationship between physical activity and QoL independent of IADLs and future work should aim to examine different types of physical activity to confirm which are most effective.

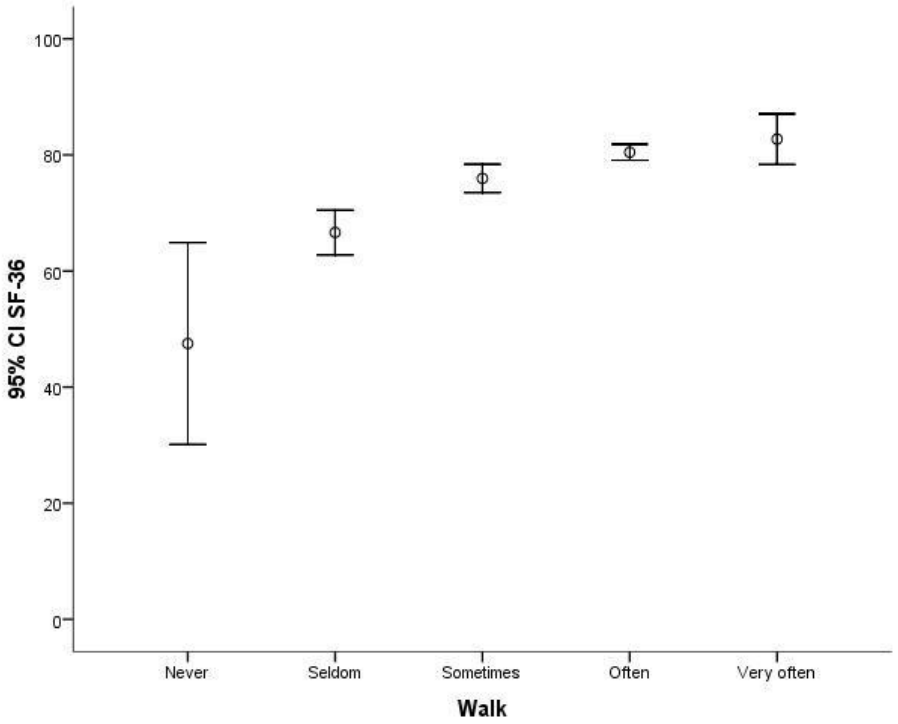

Figure 5
Error bar chart of walking frequencies and Quality of Life ratings

Abbreviations: 95% CI – 95% Confidence Interval; SF-36 – Medical Outcome Survey Short Form-36

Education was highly associated with QoL ratings in this study. Glasgow et al (1997) also found that those with increased years of education had higher ratings on the related SF-20 in a large sample of middle-aged diabetes patients. Education may be linked to better access to services or awareness of seeking health advice and support, or even taking preventative measures against serious illness or injury. Future research in this area should thus consider low education as a risk factor for low QoL and its associated outcomes. In addition, possible interactions between education level and physical activity should be investigated.

IADLs are often targeted during occupational therapy, and this study suggests that the individual contribution of walking to QoL may be comparable to that of IADLs. While walking should not be taken as an alternative to standard care, these findings do imply that treatment outcomes may be significantly improved through incorporating additional walking as part of treatment programmes due to its relationship with QoL. In addition, walking may be recommended to the older age community by occupational

health advisors as a convenient and accessible activity to act as a buffer against long recovery times in the event of illness or disability. These conclusions and implications are cautionary since this was an observational study and it is therefore difficult to establish a causal relationship between physical activity and QoL. Indeed, these findings are contrary to Oken et al's (2005) intervention study that found no association between walking and QoL. These differences may be due to the present study using a community sample with no exclusions made in relation to health, whereas the intervention study by Oken et al recruited relatively healthy adults. Other intervention studies (as mentioned in the introduction) have also shown improvements to QoL after physical activity and thus this relationship is worthy of further attention due to the importance of the possible health benefits.

The findings of this study may be especially pertinent to developing countries, and it is unclear how these findings translate to those living in developed areas with better access to public health services. Previous studies have suggested that these associations may be specific to certain population groups. For example, Luncheon and Zack (2011) found that the associations between physical activity and QoL were limited to white women in comparison to Latina, Asian and African American women living in California, USA. On the other hand, Rejeski and Mihalko's (2001) review suggested that race made no difference to the relationship although they too claimed that those results were based mainly on white middle-class samples. As this study assessed a population from a developing country, the results indicate that physical activity may be beneficial to other ethnic groups. Physical activity may also affect QoL in both men and women, as these associations were similar regardless of sex. Thus, the present study proposes that the effects of physical activity may be independent of demographic characteristics, although future controlled studies are needed to confirm this.

In summary, participation in walking is associated with improved QoL in this elderly South East Asian cohort, and this relationship stands independently of IADL abilities and education. Further evidence of a causal relationship would indicate that walking in addition to standard IADL-targeted treatment may be useful for health promotion and treatment outcomes, thus having wide reaching clinical benefits to a range of population groups. The role of fitness and other potential mediating variables should be further investigated to strengthen healthcare advice.

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Part Four – Randomised controlled trial

Chapter 7 – Randomised Controlled Trial of Resistance Exercise on Cognition in Healthy Middle-Aged Adults

7.1. Introduction

The literature review presented in Chapter 2 revealed that resistance training is a little-explored area but there is some evidence of a positive effect on cognitive performance. However, some of these studies looked at male- or female-only samples (e.g. Cassilhas et al., 2007; Zlomanczuk et al., 2006), or did not use tests of memory recall (e.g. Panton, Graves, Pollock, Hagberg & Chen, 1990; Tsutsumi, Don, Zaichkowsky & Delizonna, 1997). Lachman, Neupert, Bertrand & Jette (2006) found significant improvements of 6 months of strength training on the Digit Span test, but this study did not measure changes in executive function abilities. Perrig-Chiello, Perrig, Ehrsam, Staehelin & Krings (1998) compared strength training to no exercise over 8 weeks and found an improvement in memory but not in cognitive speed. Being a short intervention it is uncertain whether this is due to the exercises targeting memory alone or if the exercises were not sustained for long enough to have an effect on cognitive speed.

Resistance training is of interest as it does not focus on an aerobic component per se, but rather on physiological effects that come from strength changes. For example, Williams and Lord (1997) found that changes in muscle strength predicted cognitive change over 12 months. The observational study presented in Part Three found relationships between everyday physical activity and memory but also highlighted problems with observational and follow-up designs (e.g. causality and loss to follow-up as a confound). This section thus describes a Randomised Controlled Trial (RCT) that was designed to address some of these problems, especially those related to causality and the effect of potentially uncontrolled mediating variables over time. The study presented in this chapter aimed to investigate whether resistance training had a greater effect on cognitive performance over 12 weeks compared to a control activity, while also controlling for psychological factors that often accompany engaging in physical activities in everyday life. This study was conducted in middle-aged adults as our literature review suggested that interventions should be done in midlife to prevent later cognitive impairment.

7.2. Method

7.2.1. Participants

A total of 20 men and women completed this study (see Figure 6 for details of participation and attrition). Participants were all community-dwelling sedentary (<2 hours of activity per week) adults aged between 40 and 65 years at study onset. None had been diagnosed with any form of dementia and all participants had a baseline MMSE score of at least 27 points to exclude cases with cognitive impairment that could have interfered with daily life (e.g. dementia). Volunteers were asked to complete a health screen questionnaire (Appendix H) before they were recruited to the study to verify that they were physically able to complete the exercises and were not at high risk of suffering contraindications. If the researchers had any concerns from this questionnaire, participants would be asked to visit their GP for advice before starting on the study. Volunteers who were taking up new exercise regimes or diets of their own initiative, either for leisure or for medical reasons (e.g. to lower blood pressure), were asked to stabilise their routine for a minimum of two months before starting on the study (*n*=2). Volunteers were excluded from the study if they had a physical disability or illness preventing them from physical activity or had an illness that may have been exacerbated by the training programme (*n*=2; see Figure 6). Exclusion criteria also included of presence of a co-morbid psychiatric disorder, other neurological disease, substance abuse and previous use of medication affecting cognition. Participants were recruited through word-of-mouth and by contacting local community groups. Advertisements were placed in local newspapers (Leicester Mercury, Loughborough Echo), on the Loughborough University news website and in libraries, GP surgeries and shops around the local area in poster format. A radio interview was also conducted to spread awareness of the study. All participants gave full written informed consent approved by Loughborough University Ethical Advisory Committee before study onset.

7.2.2. Training programmes

This study had a crossover design in which all participants completed both a resistance-training programme and a control programme. Participants were randomly assigned to one of two groups. Group one completed the resistance-training programme and a sedentary control programme. Group two completed the resistance-training programme and a flexibility control programme, designed to control for the mental stimulation of the resistance training intervention (the literature review in Part One indicated that stretching and flexibility programmes showed no effect on

cognition). Each programme lasted 12 weeks and the two programmes were completed with a four-week washout period in between.

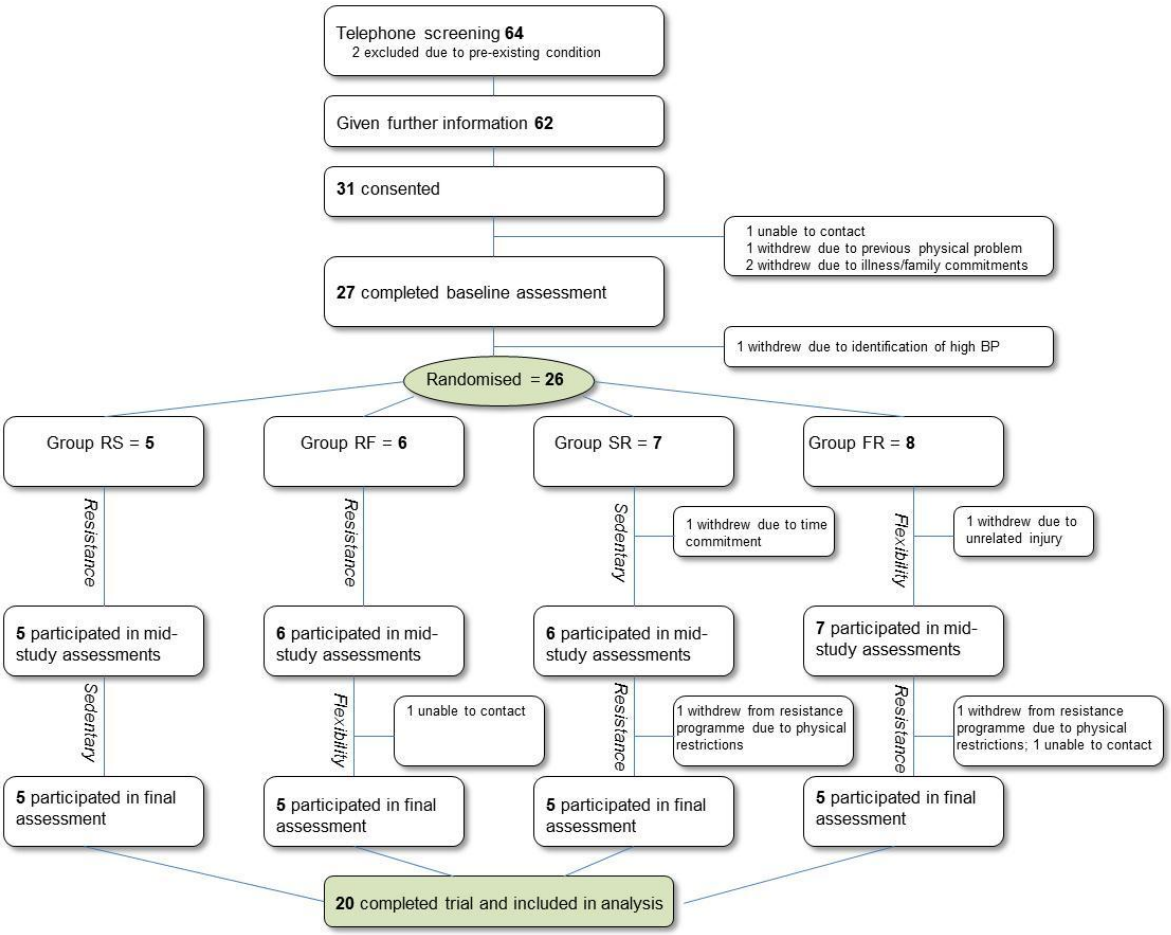


Figure 6
Flowchart of recruitment and participation

Nb: Group RS – Resistance/Sedentary; RF – Resistance Flexibility; SR – Sedentary/Resistance; FR – Flexibility/Sedentary.

7.2.2.1. Resistance programme

The resistance programme involved exercises with latex-free resistance bands. There were five bands of increasing resistance level and the programme was designed to increase muscle strength between baseline and post-intervention assessments by progressing through the resistance levels over the course of the programme. To reach an expected increase in muscle strength, the programme was to be performed three

times per week throughout the 12 weeks, and participants were encouraged to keep to this target wherever possible. Several muscle groups around the body were targeted by this intervention, namely the obliques, pectorals, gastrocnemius, quadriceps, biceps and deltoids (Figure 7). There were 6 different exercises, each targeting one of the different muscle groups (upper body rotation, arm extension, lunge, knee extension, arm curl and arm raise, respectively. Participants were given a set of written instructions and pictures to remind them how to complete each exercise when they were at home (see Appendix I).

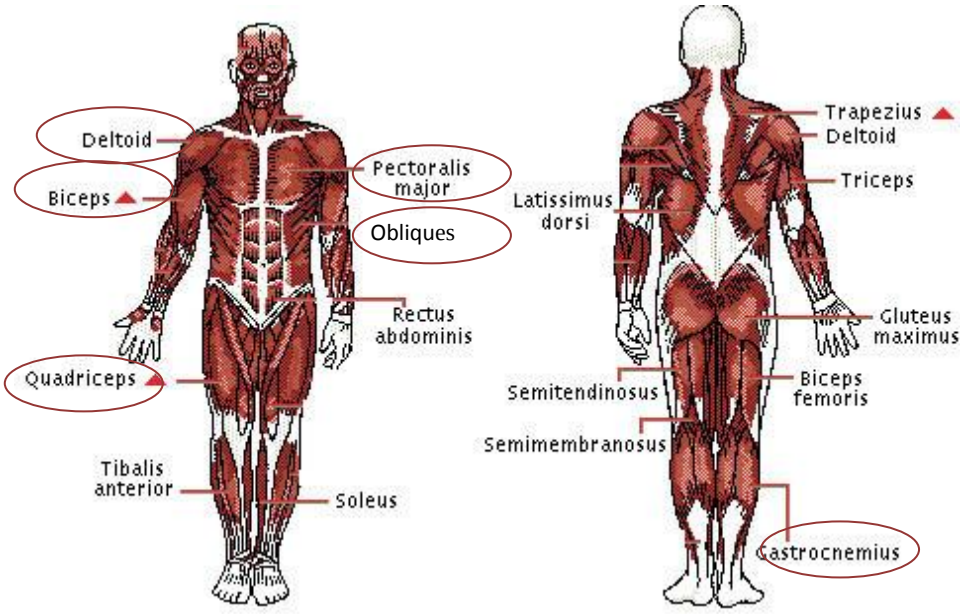


Figure 7
Location of the muscle groups targeted by the resistance training intervention

Picture adapted from: http://wserver.flc.losrios.edu/~willson/fitnessHandouts/muscleGroups.html

Each session consisted of a 5-minute warm-up, a 30-minute resistance section, and a 5-minute cool-down. Participants performed 3 sets of each exercise with 1-minute rests in between, and each set consisted of 12-15 repetitions. Once participants could perform 15 repetitions in all 3 sets comfortably without strain, they could move on to the next exercise band in their next exercise session. Each participant began the programme at the lightest resistance level for two weeks to get used to the movements of the exercises, and they could move on to the next band if they were ready. Participants could move on to a new exercise band for one muscle group (but not

others) if necessary to help optimise their training. Participants had an exercise diary in which they could note which resistance level they completed during their last session and how many repetitions they performed. They were therefore able to monitor their own progress through the study.

The bands were standardised to arm length to ensure that the amount of extension of each band was the same for all participants (bands were cut such that, when held out straight but not stretched, they reached from the individual's outstretched arm to the centre of their chest with extra length for wrapping around the hands, similar to the procedure used in Lachman et al., 2006). Resistance bands were chosen for this study as they are thought to provide similar strength training standards as weights in the early stages of training (e.g. Colado & Triplett, 2008). The investigators considered these bands to be safer and easier for participants to store in their homes as compared to free weights. They are also easily transportable (for example, if participants were going on holiday during the study), helping to promote adherence throughout the 12 weeks.

7.2.2.2. Flexibility programme

The flexibility programme involved Yoga-type stretching exercises. To match the resistance programme, the flexibility programme was performed 3 times per week for 12 weeks, and each session involved a 5-minute warm-up, a 30-minute flexibility exercise, and a 5-minute cool-down. The exercises stretched a range of muscle groups. However, they were not designed to increase strength in these muscles and the exercises did not change over the 12 weeks. Participants were again given a set of pictures and written instructions to remind them how to complete each exercise when they were at home (instructions taken from select parts of Currie, 2002[5]).

Past research has shown little evidence of a benefit of stretching alone on cognitive function (e.g. Colcombe et al., 2004) and this was therefore considered an appropriate control activity as the social and mental stimulation added by the resistance programme (visiting the lab, obtaining instructions etc.) could be matched as closely as possible with the flexibility group. The flexibility group met with the investigator at the same time points as the resistance group and also completed the same assessments. Participants were not told that this was a control programme but that the aim of the intervention was to assess the impact of different exercises on

[5] With thanks to Guy Hearn, photographer, for permissions to use his work for this purpose.

cognitive performance, thus treating the flexibility programme as a pseudo-intervention programme to remove participants' expectations regarding cognitive benefit or decline.

7.2.2.3. Sedentary programme

Although no benefits of stretching exercises have been seen previously, a sedentary control programme was used to control for any potential positive effects seen in the flexibility programme that may have masked benefits seen in the resistance group. Participants undertaking this programme were asked to maintain their normal lifestyle behaviour from before they enrolled on the study (including exercise, diet and social habits) for the 12 weeks. They completed the same cognitive and physical assessments as in the training programmes.

7.2.2.4. Exercise diaries

Participants received diaries (Appendix J) in which they were asked to log when they performed an exercise session as well as whether the session was completed. This was partly to help to encourage and remind them to perform the exercises, but it was also to help assess participants' adherence to the programme. Participants were strongly encouraged to perform the exercises three times per week but were also asked to complete the diaries honestly and accurately such that genuine adherence could be assessed and controlled for in the analysis. Participants were also asked to note the resistance level and the number of repetitions that they achieved during the resistance programme. This was to help them to monitor their own progress through the resistance bands and for the investigator to use as a measure of progression through the programme.

7.2.2.5. Encouraging adherence to the exercise and control programmes

One of the greatest challenges posed by intervention studies is that adherence rates can be quite varied, and Dishman and Buckworth (1997) suggest that attrition in exercise studies often exceeds 50%. This means that, in some cases, sample sizes are small and individuals placed in the exercise group may in fact have done very little exercise, leading to small differences between the exercise and control groups. Several strategies were therefore recruited in an attempt to encourage full and prolonged participation in the physical activity programmes:

(i) Education - Education about the benefits of the intervention and helpful advice on how to complete it have been found previously to help improve adherence

(e.g. Keele-Smith & Leon, 2003; Medina-Mirapeix et al., 2009). On their first visit to the university, volunteers were briefed on the challenges posed by dementia and the importance of the research to addressing those problems. Participants were promised a letter explaining the results of the study to help maintain their interest in the research, to help them feel as though they had played a central role in the study right until the end, and to encourage them against withdrawing.

(ii) Support to overcome perceived barriers - The investigator kept in regular contact with each participant throughout the study such that they could answer questions, give advice, discuss any perceived barriers to exercise and keep up to date with progression through the exercise programmes. Participants received exercise tips to help reduce perceived barriers to exercise and these were reviewed at the six-week follow-up meeting. Where necessary, participants were able to change individual exercises if they found them too difficult and thus impacted on their performance.

(iii) Goal setting - Goal setting and feedback during the programme appear to increase adherence (e.g. Duncan & Pozehl, 2002; Pinto, Rabin & Dunsiger, 2009; Chao, Foy & Farmer 2000), perhaps because it helps to increase the individual's confidence and/or motivation. The investigator was also able to give positive feedback concerning participants' adherence and muscle strength changes. Although participants were not set structured targets in this study, they were given individualised targets based on their previous adherence and performance at their 6-week review meeting.

7.2.2.6. Safety considerations for the exercise programmes

The training programmes were developed to be suitable for a sedentary, middle- to older-age participant group with adherence to guidelines from the American College of Sports Medicine (Whaley, Brubaker & Otto, 2005) on prescribing exercise programmes as well as with the guidance of a trained physiologist (Dr R Ferguson). All participants underwent a training session before beginning the exercises at home to ensure that they understood how to complete the exercises properly and safely, and this was reviewed at 6 weeks. The importance of performing a warm-up and cool-down during every exercise session was explained to participants during their training session, and participants were encouraged to give these sections priority over the resistance/flexibility section if they were short of time. Participants were instructed to cease exercising immediately if initial muscle ache persisted or if they became injured or ill at any time during the 12 weeks. No direct adverse effects were reported but four participants ceased exercising for up to one week due to unrelated illness or injury.

Participants were also encouraged to contact the investigator if they had any questions or concerns about the programme and the investigator remained in contact with all participants throughout the intervention. For the first two weeks of the resistance programme, participants were given the lightest resistance band only to get accustomed to the exercises and to avoid participants starting on too high a resistance level, reducing risk of adverse effects.

7.2.3. Cognitive outcome measures

Participants were assessed on the Hopkings Verbal Learning Test (HVLT; trial 1 and total), Verbal Fluency and Trail Making Test (TMT) as described in Chapter 4. Different versions of the HVLT were used on different occasions to avoid ceiling effects in the later sessions of the intervention. Version 2 and 4 were used during familiarisation, then the main assessments alternated between versions 1 and 5. The MMSE was also used as a screening tool for cognitive impairment at the start and finish of each intervention.

7.2.4. Physiological measures

Lachman et al. (2006) found that an increase in resistance level over the course of an exercise intervention predicted memory improvement. Therefore, in this study, muscle strength was measured before and after each of the exercise programmes to determine whether changes in strength drove any of the changes seen in cognitive scores. Lower body muscle strength was measured using a dynamometer on one muscle group only (quadriceps) so as to limit the demand on participants' time. However, this muscle group was one of those targeted by the main intervention so that changes in muscle strength due to the training programme could be estimated.

The strength test measured both isokinetic and isometric strength with participants in a seated position (see Figure 8a). The isokinetic strength involved kicks which pushed a bar (fixed at lower shin level) at varying resistance levels, namely 60°/s, 180°/s and 240°/s. The isometric strength involved maintaining a constant force for 3 seconds against the bar that did not move. The order of the different resistance levels was randomised for each participant. This testing took around 20-25 minutes for both legs. Grip strength in the right hand was also measured using a handheld dynamometer (see Figure 8b), as this has previously been shown to be related to cognition and risk of AD (Atkinson et al., 2010; Buchman, Wilson, Boyle, Bienias & Bennett, 2007).

Resting heart rate and BP were assessed at baseline and at the end of each training programme. Saliva samples were taken at the same time points and frozen at -20 degrees to analyse testosterone and cortisol levels at a later stage. Participants were given a salivette in which to dribble saliva immediately after waking in the morning of the meetings with the investigator. Height and weight were measured and BMI was calculated from these. Waist:hip ratio was also measured at baseline and 12-week follow-up sessions for each intervention.

A limitation of the observational study described in Chapter 5 is that the possible acute effects of physical activity were not controlled for, meaning that cognitive function scores may have been influenced in those who walked some distance to the testing centre compared to those who arrived by car. In this RCT, participants were asked not to walk to the University but instead to drive or take a taxi. They were also asked to avoid other moderate-intense physical activity, as well as to avoid consuming caffeine or alcohol, during the morning and/or afternoon prior to each session.

a) b)

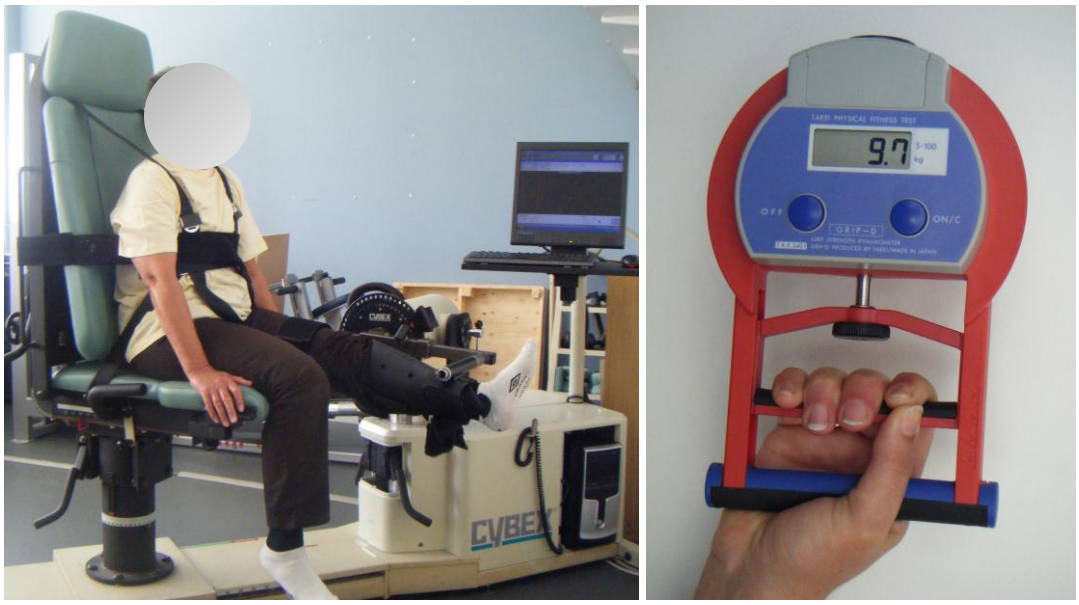


Figure 8.
Testing apparatus for a) lower body strength and b) grip strength

7.2.5. Lifestyle measures

A screening questionnaire (Appendix H) was completed at enrolment to assess demographic variables of interest (e.g. education and occupation) and general health (including details of any treatments and family history of memory problems). This health information was used to assess the risk of adverse effects for each participant and also to control in the analysis for medical conditions that have may put the participant at increased risk of cognitive impairment, such as stroke and diabetes.

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith,1983; Appendix K), a standardised measure of mood and anxiety, and a social support questionnaire (Appendix L) were used to assess relationships between these variables and changes in cognitive performance after physical activity.

Although asked to maintain their usual lifestyle outside of the study, previously sedentary participants may make multiple lifestyle changes, such as improved diet or more social contact, when they commence a physical activity programme in studies such as this. It is thus possible that it is these lifestyle changes that lead to cognitive changes rather than the participation in physical activity itself. A lifestyle questionnaire (Appendix M) designed specifically for this study was therefore given to ask about levels of physical activity, social activity, diet, smoking and alcohol and tea/coffee consumption over the previous two weeks. These questions were similar to those asked in the observational study described in Part Three. The data from these questionnaires were used to control for these variables in the analysis and to assess to what extent these variables may have acted as moderator variables.

7.2.6. Design

In this crossover study, the effect of treatment (resistance training v control) on cognitive performance was assessed. Random allocation to programme order was carried out by flipping a coin twice, firstly to determine whether the participant would perform the resistance or control programme first, and secondly to determine which control programme the participant would perform. Assignment did not occur until just before the participant received training. This meant that all of the information about the study was kept identical and the baseline measurement was not affected in any way by the investigator's knowledge about which type of exercise they would go on to perform next. Although the strength assessment and cognitive testing was not blinded at follow-up due to practical constraints, a script was adhered to for giving instructions to all participants for all cognitive and physiological tests.

The exercise programmes took place in the participants' homes rather than in an institutional setting. The exercises were deemed simple and safe enough for participants to do alone, and exercising at home allowed participants more flexibility in terms of when to exercise thus encouraging more participants to see the trial through to the end. It also allowed ongoing recruitment rather than requiring all participants to start at one time, which enabled larger group sizes at the end of the study, and this method removed the social component of group exercise. All meetings and assessments, however, took place at Loughborough University and participants were reimbursed for travel costs.

Hawkins, Capaldi and Kramer (1992) and Perrig-Chiello et al. (1998) found that improvements could be seen on cognitive tests after exercise programmes as short as 10 and 8 weeks, respectively. Thus, each programme ran for 12 weeks but measurements were done at 6 weeks also to assess if there were any early improvements. Two practise sessions were done before study onset that included muscle strength and cognitive testing to help reduce practice effects on these measurements after baseline.

7.2.7. Procedure (Figure 9)

7.2.7.1. Initial recruitment

The advertisements for this study asked volunteers to register their interest in the study by telephone or email. Some questions were asked for initial screening purposes (e.g. age and/or health conditions that may have put them at high risk of adverse effects to exercise, current activity levels) and contact details were taken. An information sheet was sent to volunteers explaining the study further and, if they were still interested, a meeting was arranged for the enrolment session. Participants were also advised to consult their GP before meeting for enrolment.

7.2.7.2. Enrolment

This was the first face-to-face contact that most volunteers had with the investigator and so involved a full explanation of the aims of the study, the procedures and how the results would be used. This was also an opportunity for volunteers to ask any questions they may have had. When the investigator and participant were both satisfied that the procedures had been fully explained and understood, informed written consent was obtained. The demographic/health screening questionnaire was completed.

7.2.7.3. Familiarisation sessions

Participants completed two familiarisation sessions at the University at least three days apart. This gave them familiarisation time with the muscle strength and cognitive measurements. During the first session, participants were also screened for cognitive impairment using the MMSE. Cognitive tasks during these and subsequent sessions were completed in a 5x6 foot research cubicle with controlled artificial lighting. This session lasted approximately 60 minutes.

7.2.7.4. Baseline session

Baseline measurements were obtained during this session, and participants were asked to bring a saliva sample from that morning. Upon arrival at the University, participants were asked to complete the lifestyle, social support and mood questionnaires while they sat quietly for 10-15 minutes, after which their BP and resting heart rate were taken. Participants then completed the muscle strength test on the dynamometer, followed by grip strength. Weight in kg, height in cm and waist:hip ratio were taken next. Then participants completed the cognitive tasks. Finally, participants were randomly assigned to an intervention group and were given training in the relevant exercise programme and keeping the exercise diaries (except for those completing the sedentary programme first). This session took approximately 90-120 minutes in total.

7.2.7.5. Continuation of programme at home

Participants began their assigned programme at home immediately after the familiarisation session. Participants met with the investigator after 6 weeks during which they completed the cognitive tests only. For the training groups, progress was reviewed and participants had the chance to discuss any problems they had with the programme since the last meeting. These meetings lasted approximately 30 minutes.

6.2.7.6. Cessation of the exercise programme

After 12 weeks, participants returned to the University (with a saliva sample taken in the morning) to complete the questionnaires and have their BP, heart rate and muscle strength measured. They also completed the cognitive tasks. They were instructed to continue their normal routine from before starting on the study for the next

four weeks. After the wash out period of four weeks, participants returned for their second baseline session. The procedure continued in the same way as described for their second programme.

Week: -2 Enrolment	-2 Familiarisation 1	-1 Familiarisation 2	0 Baseline 1	6 6 week follow up	12 12 week follow up	Wash out period	16 Baseline 1	22 6 week follow up	28 12 week follow up
Information and consent, demographic questionnaire	Strength testing and cognitive tasks	Strength testing and cognitive tasks	Questionnaires, BP, strength testing, physiological variables, cognitive tasks	Cognitive tasks	Questionnaires, BP, strength testing, physiological variables, cognitive tasks	Normal routine	Questionnaires, BP, strength testing, physiological variables, cognitive tasks	Cognitive tasks	Questionnaires, BP, strength testing, physiological variables, cognitive tasks

Figure 9.
Details of tasks completed in each session

7.2.8. Analysis

All analyses were conducted using SPSS v18.0. Demographic characteristics and mean cognitive scores were calculated using cross tabs and descriptive analyses for means. A repeated-measures ANOVA was conducted for each cognitive task to test the effect size and significance of time*treatment interactions for each cognitive test. To maintain power, only age and education were used as covariates in each model (no participants reported smoking). Analyses were also stratified by sex. No differences were seen in cognitive scores between sedentary and flexibility control groups (data not shown), and these groups were combined and analysed as one control group for comparison with resistance training. Visual assessment of histograms and normality tests revealed some violations of normality on some of the cognitive tests, which was expected in the smaller sample. In particular, TMT interference scores and HVLT total scores appeared not to be normally distributed. Transformations of the data did not improve estimates of normality and so the raw data was used in subsequent analysis. Maunchley's test of sphericity was applied to all ANOVAs and a correction was applied when necessary[6].

7.3. Results

7.3.1. Descriptive Statistics

Participant characteristics and baseline cognitive test scores are shown in Table 17, both total and split by control treatment group. Only data from participants who completed both the resistance training and a control programme (n=20) are shown here. Diet and physical activity outside of the intervention did not change significantly from baseline to follow up (data not shown).

[6] Greenhouse Geisser if estimate <.75 or Huynh-Feldt if estimate ≥.75

Table 17
Participant demographics at baseline

	Group 1 (Sedentary control group)	Group 2 (Flexibility control group)	Whole group
N	10	10	20
Mean age (*sd*)	58.3 (7.4)	60.1 (6.0)	59.2 (6.6)
Female; %	80	80	80
Education; %			
College or below	60	60	60
Degree or above	40	40	40
Mean MMSE score (*sd*)	29.1 (0.7)	28.6 (1.2)	28.9 (1.0)
Family history of dementia; %	50	40	45
Baseline Psychosocial factors			
Mean HADS score (*sd*)	9.9 (4.8)	7.3 (5.7)	8.6 (5.3)
Mean social support score (*sd*)	127.0 (24.7)	128.4 (23.5)	127.7 (23.5)
Mean alcohol units at baseline (*sd*)	5.1 (8.0)	11.7 (12.1)	8.4 (10.5)
Smoke; %	0	0	0
Baseline physiological factors			
Grip Strength; kg (*sd*)	29.5 (7.6)	31.0 (7.1)	30.3 (7.2)
Isometric Strength; kg (*sd*)	138.4 (65.9)	135.4 (32.7)	136.8 (48.1)
Isokinetic Strength; kg (*sd*)	66.4 (19.1)	83.2 (25.8)	75.3 (23.8)

Nb. There were no significant differences in baseline demographics between groups.

7.3.2. Learning effects

There were significant learning effects on the HVLT trial 1, HVLT total and Verbal Fluency scores over the two familiarisation and the baseline sessions. Although not significant, TMT interference effects also lessened during familiarisation. Significant differences were seen between familiarisation 1 and familiarisation 2, but learning effects were not seen between familiarisation 2 and baseline for all tasks (see Table 18). No correction for learning effects was therefore applied to the following analyses.

Table 18
T-tests between familiarisation and baseline sessions

Test	Familiarisation 1 – Familiarisation 2	Familiarisation 2 – Baseline
HVLT trial 1	$t(21)=-2.22$, $p=.038$	$t(17)=-0.62$, $p=.544$
HVLT total	$t(21)=-2.67$, $p=.014$	$t(17)=-0.77$, $p=.454$
TMT interference	$t(21)=1.23$, $p=.092$	$t(21)=0.23$, $p=.302$
Verbal Fluency	$t(21)=-2.42$, $p=.025$	$t(17)=-1.43$, $p=.170$

7.3.3. Whole sample

When analysed as a complete group, there were no significant effects of the resistance programme on performance on any of the cognitive tests. The data were thus stratified to assess whether any effect of the resistance training was influenced by sex, as seen in the observational study in Chapter 5. This left just 4 men in the sample, so the following analyses were conducted on women only.

7.3.4. Women only

No significant differences were seen on any of the cognitive tasks after 6 weeks. However, significant differences were seen between interventions on some of the cognitive tasks after 12 weeks (see Table 19), which are described below.

Table 19
Mean (s.d.) cognitive scores for control and resistance interventions (women only)

Group	Control		Resistance		Group*time interaction	
Time	Baseline	12 weeks	Baseline	12 weeks	*F*	*p*
HVLT trial 1	9.0 (2.2)	8.4 (1.5)	8.9 (1.4)	9.6 (2.0)	4.789	.047
HVLT total	31.1 (3.6)	30.6 (3.4)	31.3 (2.5)	32.6 (2.6)	4.155	.062
Verbal Fluency	29.8 (8.4)	30.8 (7.5)	32.3 (8.9)	32.1 (8.0)	5.035	.046[a]
TMT interference	21.5 (27.8)	16.3 (11.8)	14.4 (8.0)	18.4 (16.6)	1.545	.238

Abbreviations: HVLT – Hopkins Verbal Fluency Task; TMT – Trail Making Test
[a]Results shown for Group*time x Education interaction

7.3.4.1. Verbal Fluency

The number of words recalled on this task ranged from 17 to 50, with a mean of 31 words recalled at baseline and 31 words recalled at follow-up. There were no differences in baseline measurements between the resistance and control interventions ($t(15)=-1.257$, $p=.228$). Although participants showed some improvement after both interventions (see Figure 10), there was a larger increase in Verbal Fluency scores after 12 weeks of the resistance intervention compared to the control intervention. A 3-way interaction was seen between treatment, time and education level ($p<.05$). Post hoc comparisons did not reach significance but those with more

years of education appeared showed the greatest improvement after the resistance programme (Figure 11).

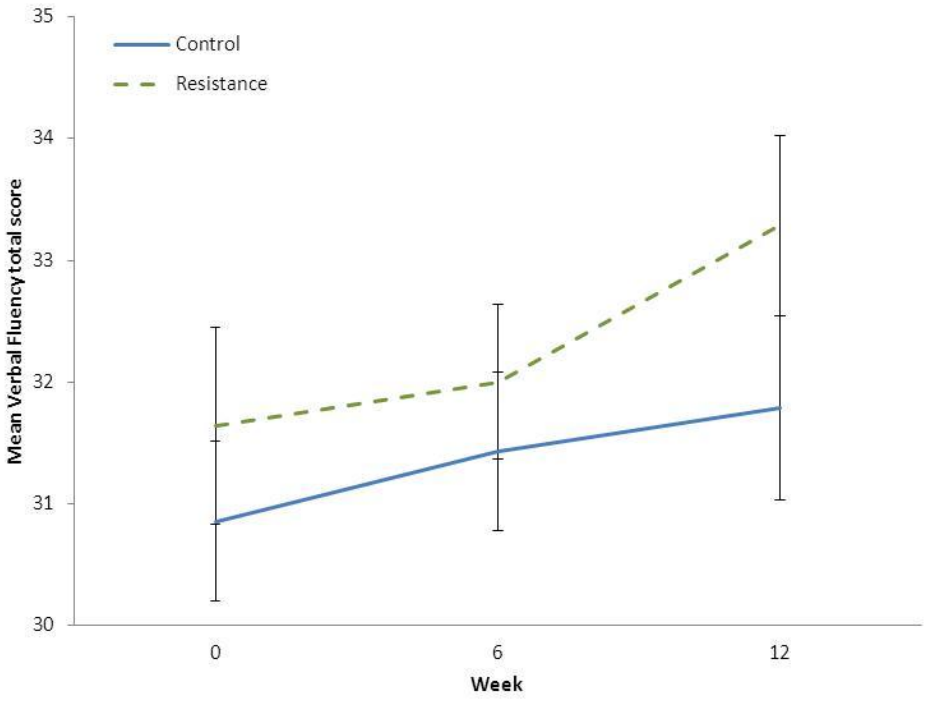
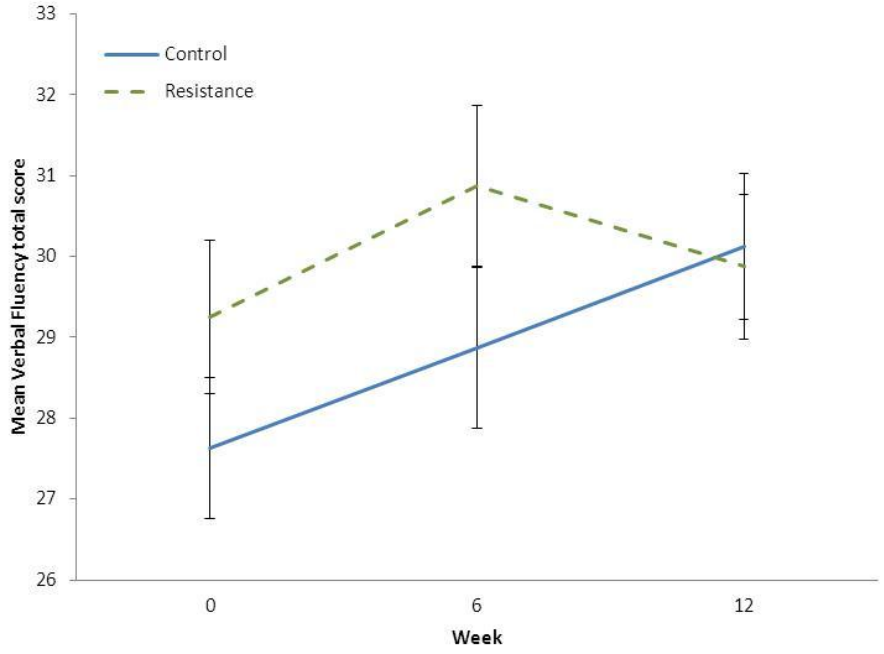


Figure 10
Verbal Fluency performance over 12 weeks of control and resistance interventions

Note: Error bars represent standard error

a)



b)

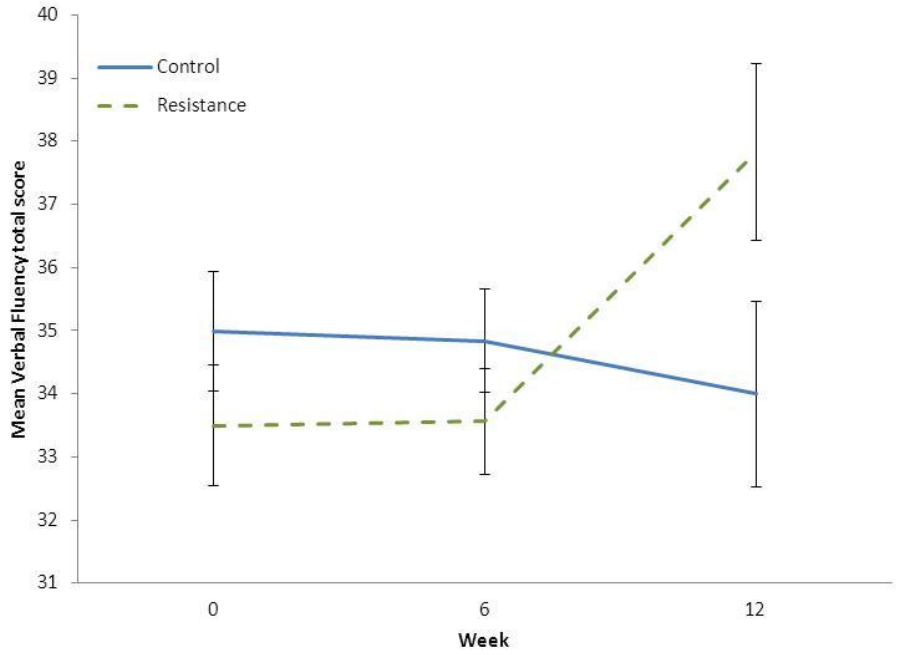


Figure 11

Change in Verbal Fluency performance over control and resistance interventions for (a) low education and (b) high education

Note: Error bars represent standard error

7.3.4.2. HVLT trial 1

The number of words recalled on this task ranged from 6-12, with a mean of 8.9 words recalled at baseline and 9.0 words recalled at follow-up. There were no baseline differences between resistance and control interventions on the HVLT trial 1 ($t(15)=0.12$, $p=.910$). There was a significant group by time interaction (see Figure 12) in which there was a significant improvement in scores after the resistance intervention, but not after the control intervention ($t(15)=-2.92$, $p=.011$).

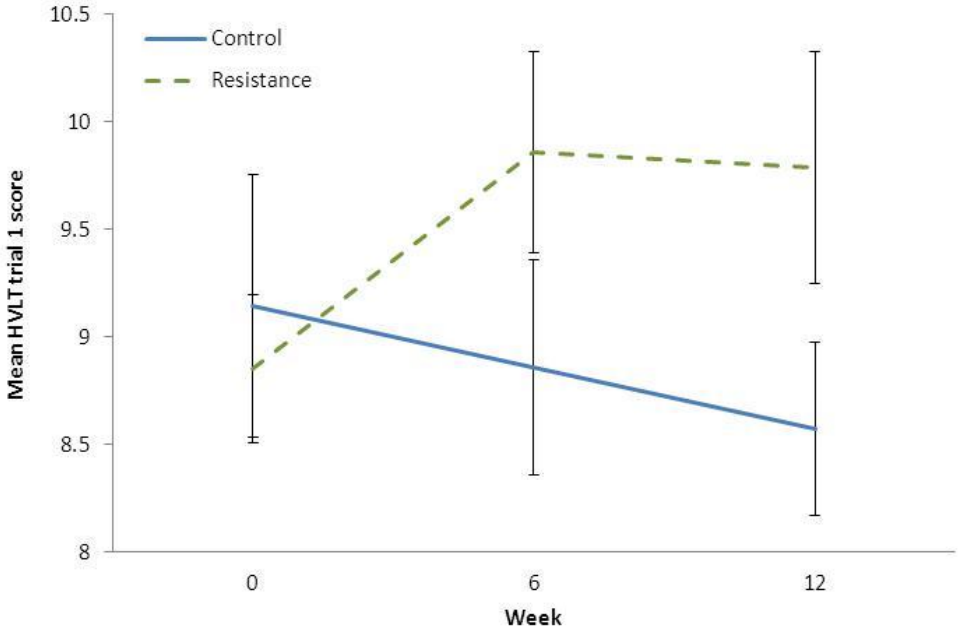


Figure 12
HVLT trial 1 performance over 12 weeks of control and resistance interventions

Note: Error bars represent standard error

7.3.4.3. HVLT total score

The number of words recalled on this task ranged from 24 to 36, with a mean of 31 words recalled at baseline and 32 words recalled at follow-up. There were no baseline differences between resistance and control interventions ($t(15)=-0.21$, $p=.838$). There was a group by time interaction (see Figure 13) for this task in which there was an improvement in scores after the resistance intervention, but not after the control intervention ($t(15)=-2.551$, $p=.022$).

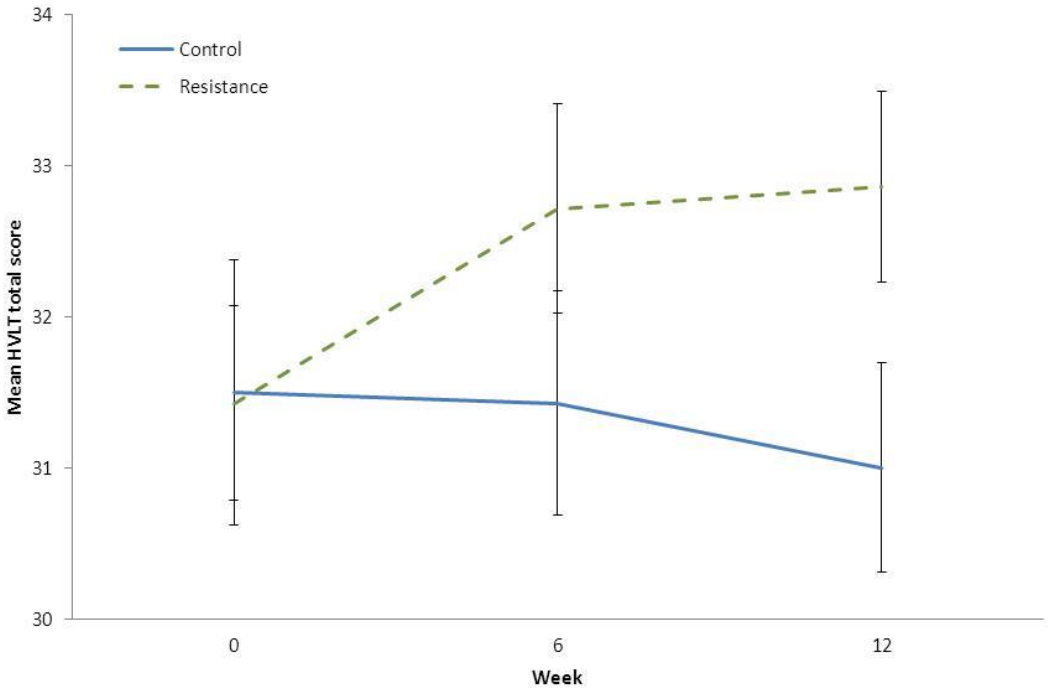


Figure 13
HVLT total performance over 12 weeks of control and resistance interventions

Note: Error bars represent standard error

7.3.4.4. TMT interference

There were no significant baseline differences between the control groups and resistance interventions ($t(15)=0.73$, $p=.478$). There was no significant treatment x time interaction on this task (Figure 14) and follow-up intervention scores were similar after both interventions ($t(15)=-0.536$, $p=.600$).

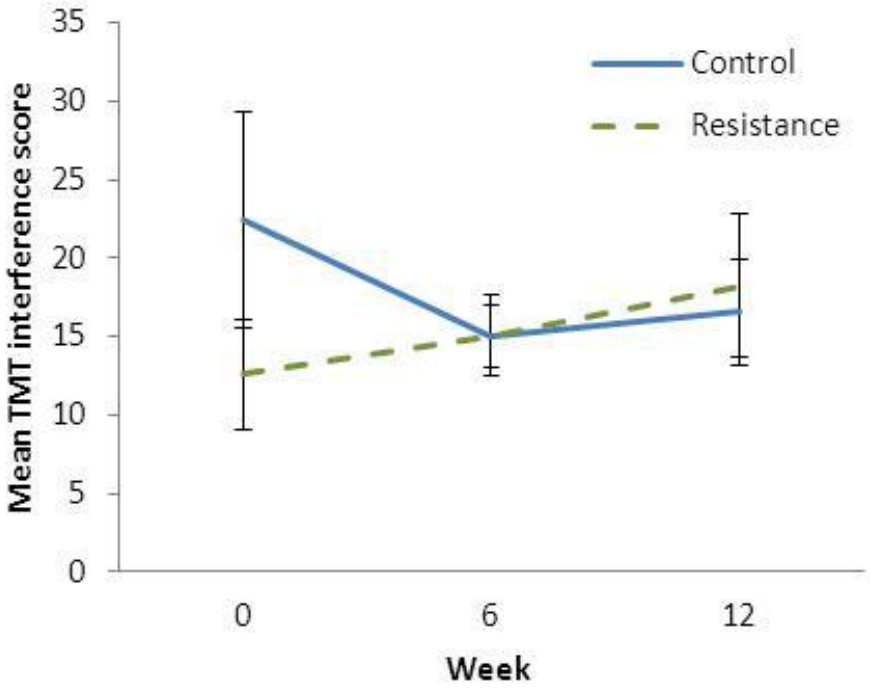


Figure 14
TMT interference scores over 12 weeks of control and resistance interventions

Note: Error bars represent standard error

7.3.5. Adherence to the resistance and flexibility programmes

Average reported adherence to the resistance programme was 84.6% (range 56-100%), compared to 87.2% (range 58-100%) for the flexibility programme ($p>.05$). The training order made no difference to adherence to the resistance programme ($t(15)=-.158$, $p=.876$) or the flexibility programme ($t(7)=.020$, $p=.984$). There were no significant correlations between adherence to the resistance programme and changes on any of the cognitive tasks (Table 20).

Table 20
Pearson correlations between adherence to the resistance programme and change scores on each of the cognitive tasks

Test	Pearson correlation	*p*
HVLT trial 1	.234	.321
HVLT total	.209	.377
Verbal Fluency	-.364	.115
TMT interference	-.089	.711
MMSE	.127	.593

N.b. *N*=20 for all correlations

7.3.6. Muscle strength

There were no group*time interactions for lower body strength (isometric or isokinetic), indicating that lower body strength did not change as a result of the resistance intervention. However, a repeated measures ANOVA found a group*time interaction for grip strength ($F(1,19)=3.01$, $p=.099$), where grip strength improved after the resistance intervention ($t(15)=-2.34$, $p=.030$) but remained stable over the control intervention ($t(15)=0.27$, $p=.791$) (Figure 15). There were moderate correlations between grip strength and TMT interference ($r=.445$), HVLT trial 1 ($r=.400$), HVLT total score ($r=.402$) and Verbal Fluency ($r=.689$), However, there were no significant correlations between changes in grip strength and changes in cognitive performance. No correlations were seen between lower body strength and cognitive performance at baseline.

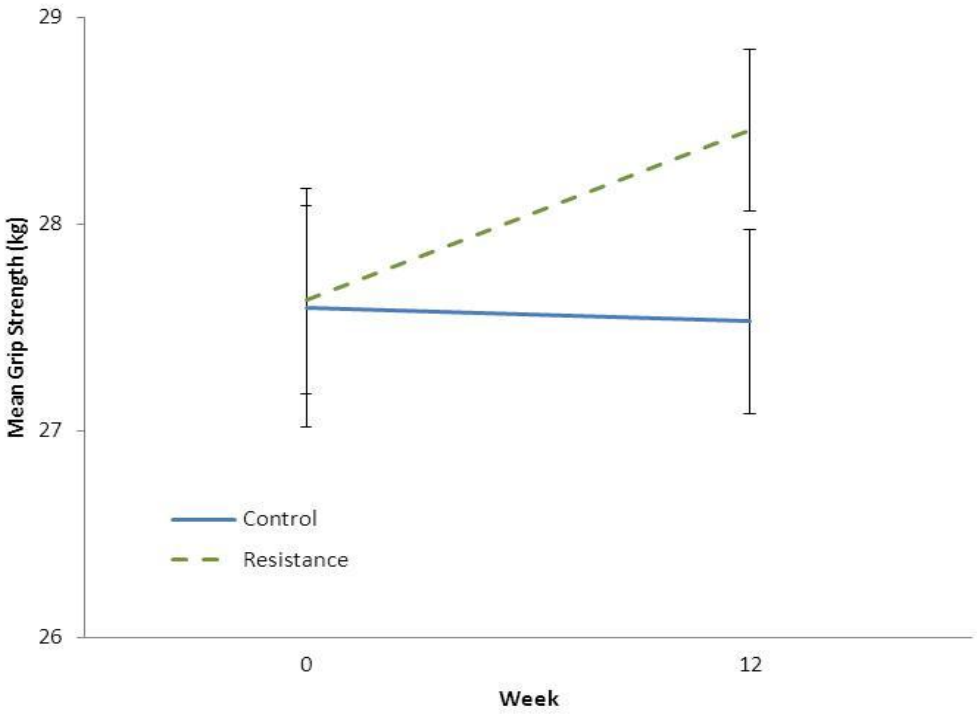


Figure 15
Change in grip strength (kg) after 12 weeks of the control and resistance interventions

7.3.7. Other variables

No significant changes were seen on BMI, weight, waist to hip ratio, BP or resting heart rate over any of the interventions. Responses on the HADS scale were counted to make three scores: depression, anxiety and total (depression + anxiety). There were no significant changes over the course of any of the interventions on any of the mood scores. Social support was counted to give a total score. There were no significant changes in social support over the course of any of the interventions. There were no correlations between any of these variables and changes in cognitive scores (data not shown).

7.3.8. Men only

As there were only four men in the sample, these data could not be analysed statistically. However, visual analysis of graphs (Figure 16) produced to show performance over 12 weeks of each of the interventions showed few differences between the interventions on any of the tasks. The inclusion of men in the sample therefore appeared to bias the findings towards the null.

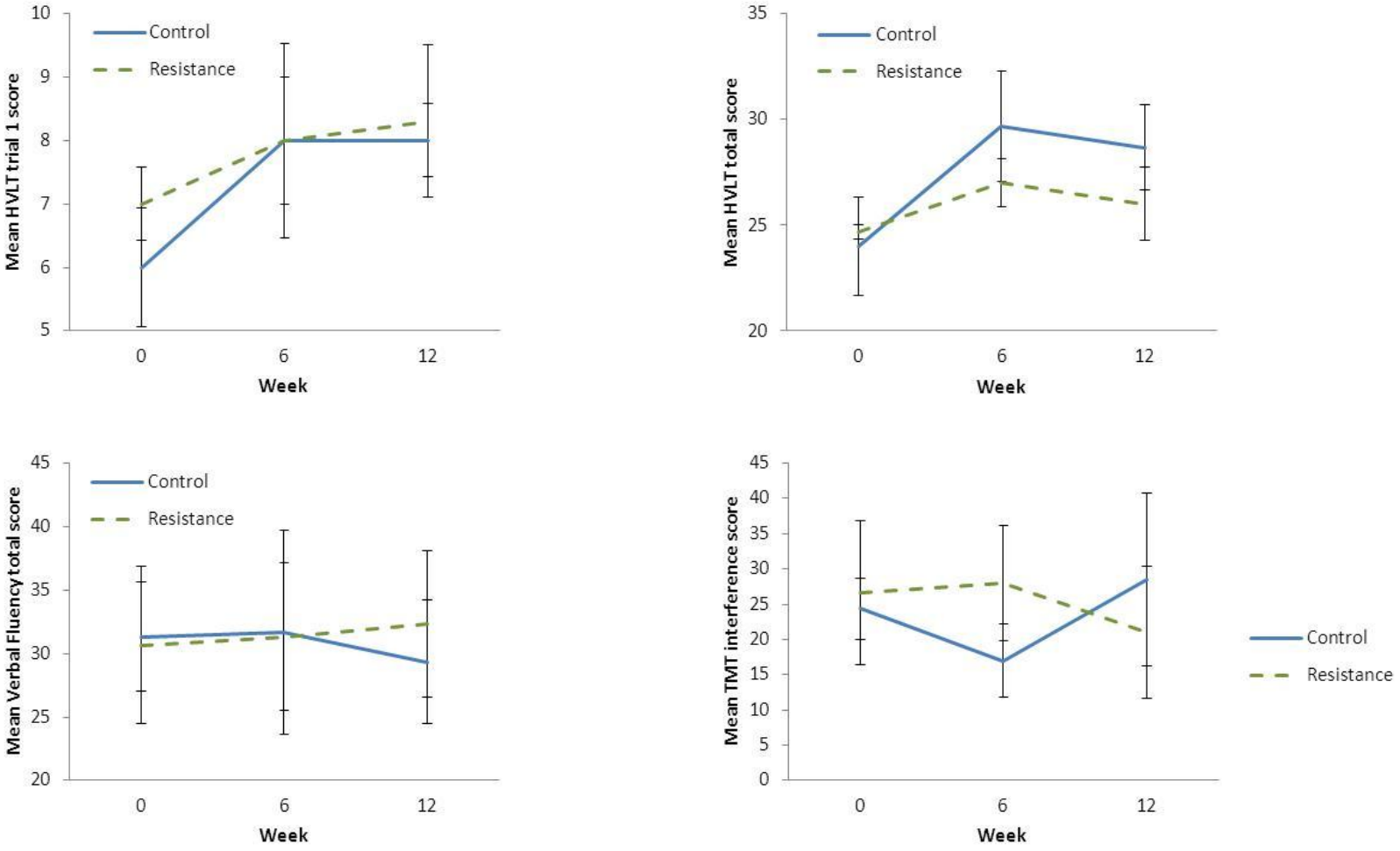


Figure 16

Performance on each cognitive task over 12 weeks of the control and resistance interventions in men only

7.3.9. Power calculation for future sample sizes

The interpretation of the null effect of intervention type on TMT interference scores is central to our research question. The power estimate given by the ANOVA was low (<.3) compared to in the models testing for differences in the memory tests (>.45). We therefore conducted a post hoc analysis using an online calculator[7] to determine the sample size required in future studies to rule out any effect of resistance training on TMT performance. Using a required Alpha Level of 5% and a required Beta Level of 10%, the calculator estimated a sample size of 85 would be required.

7.4. Discussion

This study aimed to investigate whether 12 weeks of non-aerobic activity with a strength training component impacted on different cognitive abilities compared to no activity or very light stretching exercise in healthy, middle-aged adults. Flexibility exercises had no effect on cognitive scores compared to no exercise. The resistance training intervention successfully improved memory performance, but not executive function, in women compared to the control intervention. The resistance intervention led to increases in grip strength, but the changes in memory were not associated with changes in grip strength after the intervention. These changes in memory were also not associated with other fitness variables (BP, BMI, resting heart rate), mood or social support. These differences were not seen in men for either memory or executive function, although there were few men in the sample.

Due to the lack of an association between strength and memory, it is unclear how this resistance intervention led to the improvements in memory. This programme was not designed to have an aerobic component, but there was no measure of aerobic fitness as part of this study, so it is not possible to exclude totally the possibility that these memory changes were driven by an aerobic change. These effects may be related to other physiological changes, such as Insulin-like Growth Factor (IGF-1) release, and/or changes in metabolism or release of testosterone (discussed in Chapter 1). These changes may also be a result of psychological mediators due to the expectation of strength improvements following the resistance intervention (Stock, Clifford and Hogervorst, 2012). Anecdotally, participants reported not enjoying the flexibility intervention due to not noticing any physical benefits. In contrast, the resistance training received positive feedback and participants reported feeling stronger (despite no measured strength changes). Further research should investigate

[7] http://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/samplesizecalculators.aspx

these physiological and psychological factors as possible mediators of the relationship between resistance training and cognitive functioning. However, the lack of an association between strength and memory may be due to low power and larger studies are therefore essential to determine the true extent of the association while controlling for other potential mediators.

The effects of resistance training appeared to be specific to memory and word generation (linked to semantic memory) with performance on the TMT, a measure of task switching, being unaffected. This was predicted from the literature review, with studies assessing memory finding more significant effects of physical activity than studies looking at executive function. Due to the small sample size combined with the high variance in scores on this task, the model had low power compared to the analyses of the memory tasks and we therefore cannot be certain that an effect of the resistance training would not have been seen had there been greater power in our study. However, Kimura et al. (2010) also found no effect of 12 weeks of resistance training on task switching compared to a health education class in 119 elderly men and women combined aged >65 years. In women only (*n*=33), Zlomanczuk et al. (2006) observed no effect of 3 months of resistance training with endurance on the SCWT compared to no exercise. In contrast, after 12 months of resistance training, Liu-Ambrose et al. (2010) found a significant effect on executive function in 135 women aged 65-75 years and Kwak, Um, Son and Kim (2008) showed a 30% improvement in general cognition in a parallel group study of 30 women with dementia after 12 months. This may indicate that longer interventions are needed for improvements in executive function to be seen, though again larger replications with the estimated sample size for the TMT (*n*=85) would be needed to ensure that these discrepancies are not simply due to low power.

In our study, associations between resistance training and memory were seen in women but not in men. The inclusion of men in the total sample appeared to remove the effect of resistance training and memory in women, although there were only four men included. Women may benefit more from resistance training due to the potential release of testosterone after resistance training (Kraemer et al., 1998; Marx et al., 2001), which itself can improve memory ability (Davison et al., 2011) although this association remains controversial in older adults (e.g. Kocoska-Maras et al., 2011; Hogervorst, Matthews & Brayne, 2010). Most other studies of resistance training that have shown an association with cognitive function also included a high proportion of women (Molloy, Delaquerriere-Richardson & Crilly, 1988; Zlomanczuk et al., 2006; Lachman et al., 2006). Further study with high numbers of men with a direct

comparison of effect size is therefore needed to fully determine whether they too experience improvements in memory after resistance training.

This pilot study allowed us to trial the methods used and found relative success with the resistance programme. Feedback from a questionnaire given to participants after the intervention suggested that the resistance bands were well tolerated by participants as a home-based intervention. They allowed individual progress to be monitored through the different resistance levels and many participants reported having taken the bands on holiday, meaning that they did not have to discontinue the programme while they were away from home. This helped to maintain reported adherence rates above 80% for the majority of participants. The feedback from this study can therefore recommend the use of resistance bands in future research of this nature, although modifications to the programme should be made in order to ensure higher strength increases at follow-up from baseline to allow the influence of strength changes can be fully determined.

Although general dietary habits by each participant were monitored over the course of the study, the effects of individual nutrients consumed immediately prior to testing were not controlled for. For example, glucose is important for cognitive function and those who missed breakfast or who had not eaten for several hours may have performed poorly on the cognitive tasks relative to their ability had they eaten. In addition, participants were tested at a time convenient to them; therefore, the effects of circadian rhythms could not be controlled. Especially given the small sample size, this may have had a confounding effect on our findings and these variables should be considered in future work.

In this pilot study, effects of resistance training were seen on memory compared to flexibility exercises and no physical activity in this sample of healthy, middle-aged women. This study thus adds to the evidence that resistance training, a relatively unexplored type of physical activity, is a potential alternative to aerobic activity as an intervention for improving memory in middle age and should be investigated thoroughly using larger scale studies. These associations in the absence of strength changes point towards previously unidentified mechanisms through which resistance training affects memory, and consideration of these factors in the future may lead to a better understanding of how to prevent cognitive decline in later life. These findings, though not conclusive, are consistent with previous studies and effects of cognitive domain and sex were also seen previously (Chapters 2 and 5), adding to the evidence that these factors act as moderators of the relationship between physical activity and cognitive functioning. This study could be expanded to assess whether resistance training can add to the benefits of aerobic training where the two are combined, or

whether resistance training can be considered an alternative for those who may find aerobic activity particularly difficult due to physical health concerns. In the following chapter we discuss the implications of these findings in combination with the results of the literature review in Chapter 2 and the observational study in Chapter 5.

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Part Five – General Discussion

Chapter 8 - Discussion

The aim of this thesis was to investigate the effectiveness of lifestyle changes for preventing or delaying the onset of AD. In particular, it aimed to explore the relationship between physical activity and cognitive functioning and the additional mediating and moderating factors that may be involved. Although our literature review in Chapter 2 found evidence of a relationship between physical activity and cognition/risk of dementia, these findings were not consistent. Chapters 3 and 4 identified the most optimal cognitive tests to use for AD and other types of age related cognitive impairments. These tests have even been shown to be sensitive to interventions in young healthy populations. The review in Chapter 2 had identified several variables that may explain conflicting results of previous studies investigating physical activity and cognitive function. Some of these variables were investigated through an observational study of Indonesian elderly and an RCT of resistance training in healthy middle-aged adults in the UK (Chapters 5, 6 and 7). The studies in this thesis showed consistent effects of sex, with women benefitting from physical activity more than men, and of the type of cognitive ability being measured, with stronger changes in memory than in executive function performance. Both aerobic and non-aerobic activity have been shown to benefit cognitive ability and while this may be partially through improving general health, other mechanisms also appear to be involved as health did not fully mediate effects of physical activity on cognition. There is also growing evidence that engaging in long-term physical activity behaviours in midlife are more effective than in older age when dementia pathology is increasingly present. These findings have theoretical implications for the field of dementia prevention and recommendations for future research are discussed in this chapter.

8.1. Moderators of effects of exercise on cognition: tests and functions

The type of cognitive measurement used in observational studies of healthy adults and in RCTs seems to have a strong effect on the findings of those studies. Although Hall, Smith and Keele (2001) and Colcombe and Kramer (2003) suggested that the benefits of physical activity were restricted to complex executive function

processes, this thesis has found that the benefits may be stronger for memory. Measures of memory such as digit span, word list learning and word generation were shown in Chapters 3 and 4 to be highly sensitive to AD. These studies may therefore have identified effects of physical activity in healthy middle- and older-age adults on cognitive tests that are relevant to AD, supported by previous studies that have found reduced risk of dementia in those who are physically active in midlife (Table 3). Although we found that some tests of executive function are sensitive to AD, performance on these tasks was less affected by physical activity and poor performance may be indicative of particularly severe pathology that is less responsive to treatment. However, the finding of a lack of an association between physical activity and executive function remains controversial (e.g. Eggermont, Milberg, Lipsitz, Scherder & Leveille, 2009; Abou-Dest, Albinet, Boucard & Audiffren, 2012). A longitudinal study showed that young-elderly with high fitness maintained executive function abilities over 6 years while those with low baseline fitness showed decline (Barnes, Yaffe, Satariano & Tager, 2003). Liu-Ambrose et al. (2010) observed reduced interference effects on executive function tasks among elderly women completing 12 months resistance training compared to balance training. Memory may therefore show immediate benefits of physical activity, while executive function may require longer-term interventions to show a robust effect.

The observed differences in exercise's effects between memory and executive function can possibly be explained by the neurogenesis hypothesis described in Chapter 1. Neurogenesis is currently accepted to occur mostly in the hippocampus (Zhao, Deng & Gage, 2008), an area that is important for memory function (Diana, Yonelinas & Ranganath, 2007). Since physical activity is thought to have an impact on neurogenesis, memory processes are therefore more likely to benefit compared to functions mediated by other cortical areas. However, the brain is highly interconnected and the prefrontal cortex has connections with many other regions including the medial temporal lobe which contains the hippocampus (Miller & Cohen, 2001). Prolonged physical activity over many years may thus impact on executive function abilities through knock-on effects from the hippocampus. Executive function may also benefit from improved angiogenesis after physical activity, possibly due to the increased availability of IGF-1 (Cotman, Berchtold & Christie, 2007; van Praag, Shubert, Zhao & Gage) or other direct vascular effects, such as enhanced perfusion leading to reduced risk for hypoxia (Querido & Sheel, 2007; Ogoh, 2008; Rhyu et al., 2010). Neuroimaging methods may help to sequence changes in these regions at various points through an exercise intervention to determine whether temporal differences are seen in the effect of physical activity on different cognitive abilities.

8.2. Moderators of effects of exercise on cognition: types of exercise

Different studies investigated the impact of different types of physical activity, which makes it difficult to determine which types of physical activity are most effective at improving cognitive functioning. Aerobic activity and resistance training both appear to have a strong effect on memory and our RCT showed that even low-intensity exercise can lead to improved memory performance (see also Tsutsumi, Don, Zaichkowsky & Delizonna, 1997; Cassilhas et al., 2007). These effects are likely to be due to the range of physiological effects that aerobic activity has on the body that are also implicated in cognitive performance, such as improved lung and vascular function. However, our randomised trial found that the effects of resistance training on cognitive performance were not associated with changes in strength (Chapter 7). In addition, the observational study found that associations between sport and memory were independent of physical health (Chapter 5). Further research should thus consider the influence of other neurophysiological factors, such as growth or sex hormones as well as psychological mediators (Stock, Clifford & Hogervorst, 2012) as possible pathways between physical activity and cognitive functioning. It is currently unclear whether the effects of aerobic and non-aerobic activity are additive or would interact to produce optimal benefits, and interventions using both, one and neither of the two types of activity should be trialled to investigate this.

In contrast, this thesis found little evidence that yoga and flexibility-type exercises have any benefit to cognition. It could be argued that participants may not enjoy a particular intervention, as was seen in our flexibility intervention, and so may not engage as strongly as they do with an intervention they enjoy. However, no effect of flexibility on cognition was seen throughout the literature (see Chapter 2) so it is unlikely to be due to participant preference. As the observed benefits of yoga often include improved mood, it suggests that mood is not a strong mediator of the association between physical activity and cognition. However, balance may benefit from yoga exercises, which could lead to reduced risk for falls in the elderly (Clemson et al., 2012; Li, Harmer, Fisher, & McAuley, 2004).

8.3. Moderators of effects of exercise on cognition: gender

This thesis suggests that certain groups may benefit more from physical activity than others. Most of the effects of physical activity are seen in women and a direct comparison of effect sizes showed a significant stronger effect of sport on memory and global cognition in women compared to in men (Chapter 5). In addition, the effect of

resistance training on memory in women was diminished when men were included in the analysis in our RCT (Chapter 7). These differences appear to be universal across cultures (Chapter 5) and are perhaps due to the range of physiological mechanisms through which physical activity affects cognitive functioning. Sex steroids affect brain function through multiple mechanisms and women show a sharp decline in both estrogens and testosterone after the menopause around the average age of 50 years (Hogervorst, Henderson, Gibbs & Brinton, 2009). For example, changes in testosterone following resistance training may benefit women more so than men who already have optimal levels of testosterone. In addition, there is evidence that estrogen increases BDNF, as does physical activity as described in Part One (Zhao, Deng & Gage, 2008). When relatively high levels of estrogen and physical activity co-occur, they may interact such that the benefit on cognition is increased compared to when they occur alone (Berchtold, Kesslak, Pike, Adlard & Cotman, 2001). Due to the range of physiological and psychological mechanisms possible, different types of physical activity may be beneficial to men and women separately.

Studies of men did show some benefit of physical activity (Cassilhas et al., 2007; Shay & Roth, 1992; Abbott et al., 2004) and so it should not be considered a female-only intervention. However, it is clear that sex should be considered as a moderating factor rather than a covariate in this relationship. In addition, studies in this field should always compare the effect size between men and women to determine the true effect of the intervention in both groups.

8.4. Moderators of effects of exercise on cognition: genetics

The literature review suggested that baseline risk of AD, as indicated by genetic status, might mediate the relationship between physical activity and cognitive ability (Rovio et al., 2005; Podewils et al., 2005). However, as few studies had looked at this it was not clear whether the benefit was greatest in those who were ApoE4 positive or negative, or whether this was simply a chance finding from repeated analysis. Unfortunately this factor could not be investigated in this thesis. However, our randomised trial found a possible effect of education, with those with more years of education showing a faster cognitive improvement with physical activity (Chapter 7). As discussed previously, low education level is a risk factor for AD and is associated with lower cognitive scores, as seen in our observational study (Chapter 5). These observations may suggest that groups with additional risk factors for AD and cognitive decline may be less responsive to short-term treatment interventions. However, it is at present unclear whether they may benefit from longer term interventions. Any risk

factors for AD should therefore be considered as moderating factors and interactions between risk factors and intervention group should be analysed to determine their impact on the intervention's effectiveness.

8.5. Moderators of effects of exercise on cognition: mental activity

Ultimately, the discrepancies in previous research may be due to physical activity alone not being sufficient to maintain cognitive health. Physical activity is known to promote the release of neural stem cells (Schaeffer, Novaes, da Silva, Skaf & Mendes-Neto, 2009) but there is little evidence that it promotes the survival of these cells. Instead, it may be that mental stimulation and learning is required to integrate these cells into existing networks; if they are not recruited into existing networks and used, they might not offer benefit to cognitive performance. This would also indicate that physical activity with a mental or social component will be more beneficial compared to physical activity that occurs alone. Indeed, completing both physical and mental activities has been shown to create a bigger improvement in memory performance compared to completing only one or neither activity over 8 weeks (Fabre, Masse-Biron, Chamari, Varray et al., 1999). Rather than being seen as two different interventions, physical and mental stimulation may be considered as complementary; the success of a physical activity intervention against cognitive decline may depend upon the mental stimulation that participants receive outside of the study, while research into the benefits of mental stimulation may be most successful if participants are also physically active. Therefore, physical activity may be important but not sufficient for prolonged cognitive health. Future research is investigating these aspects of activity in more depth at Loughborough University and elsewhere.

8.6. Strengths and limitations of our work including future directions

This thesis adds to the current knowledge regarding factors that may influence the relationship between physical activity and age-associated cognitive impairment and dementia. The development of these studies and their hypotheses has been evidence-based, guided by the findings of our literature review. Taking this into consideration, this thesis supports future research into the possibilities of using physical activity as a lifestyle intervention for age-related cognitive decline with consideration of the aforementioned moderating variables. Physical activity should not be considered a possible cure for Alzheimer's disease or a solution to extinguish the presence of dementia. Not only is there currently little evidence that physical activity influences memory in those already afflicted with cognitive impairment (Chapter 2), the theory

presented in this thesis proposes that the effects of physical activity work on an individual level, lessening risk rather than preventing completely. Thus, physical activity is likely to have its limitations (especially counteracting the impact of genetics) if used independently without consideration of other risk factors. Prevention should focus on additional lifestyle change including smoking cessation, dietary alterations etc.

One hypothesis that may explain the discrepancies between the findings of previous studies is that, although we predict that physical activity in midlife before pathology begins is most important, it may not be possible to measure the true effect size using cognitive tasks in healthy adults. Although previous observations suggest that physical activity leads to short-term improvements in cognitive function (Chapter 7), the ultimate effect of long-term physical activity on reduced risk of dementia may be maintenance of function. Giving the brain the resources to adapt to pathology does not mean that performance will increase when little pathology exists. Healthy, high functioning middle-aged adults may therefore not show much benefit of most physical activity until they reach older age.

Although prospective studies are useful for assessing the risk of developing AD over a given timescale based on a set of baseline predictors, these studies take a long time to conduct and it is difficult to control for variables such as type of activity, intensity and mental stimulation. One way to get around this problem is to use MRI in healthy middle-aged adults during an RCT. This type of study would be able to assess hippocampal changes that may occur after long-term physical activity, even if these changes do not show up on tests of memory. Another option is to study MCI patients as part of an RCT. Although MCI patients may already show dementia pathology, their brains might still have the capacity to adapt and show improvements on cognitive tasks after an intervention. Although not all MCI patients go on to develop AD, a physical activity intervention may reduce the conversion rate to AD. A future study at Loughborough University investigates our resistance training programme in older institutionalised elderly to determine whether effects are larger in those with more cognitive and/or functional impairment. Studies including participants with dementia have shown large effect sizes if they included women in the sample (Hogervorst et al., 2012) but methodological limitations (e.g. sample size) mean that replication of these findings is required.

Another limitation of our observational work is the lack of objective physical and fitness assessment as well as morbidity. Studies at Loughborough University in combination with the Shanghai Mental Health Center and the Center for Aging Studies Indonesia have collected data on these variables and analyses are now underway. Our physical markers did not totally mediate effects in the observational study or RCT but

future studies will hopefully include biochemical assessments to investigate physiological mechanisms associated with change (including testosterone, collected as part of the RCT). Power of the study or the intervention itself may have been insufficient in terms of intensity or duration to reflect physiological mechanisms. We did not analyse psychological mediators of the effect other than mood which was not seen to affect cognitive change in this group without depression. Future work at Loughborough University will investigate mediating effects of empowerment and self-efficacy.

8.7. Conclusions

AD and other types of age related cognitive impairment is a growing problem around the world but there is evidence that physical activity is a potential lifestyle intervention that can help to lower an individual's risk of developing symptoms of the disease. However, various factors appear to mediate or moderate these findings and it is thus important to consider their influence when evaluating the effectiveness of physical activity as an intervention against AD and other age-related cognitive impairments. If our findings can be replicated in larger controlled studies then they would support government-funded exercise programmes for the elderly and suggest that a simple home-based, affordable resistance exercise programme should be further developed to enable the full benefits and participation in those who find aerobic activity especially difficult (e.g. those with asthma, Chronic Obstructive Pulmonary Disease etc).

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Appendix A

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Maintaining cognitive health in elderly women

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Abstract

This review indicates that possible preventative activities and lifestyle changes to maintain cognitive health and prevent dementia in old age may be particularly important in middle-age. Cardiovascular disease risk factors are the same as those for dementia including its most common form, Alzheimer's disease. Treating high blood pressure, high cholesterol and thyroid hormone deficiency, maintaining a normal weight having a healthy diet, and engaging in resistance or aerobic exercise can all possibly help sustain cognitive health.

Long-term treatment with estrogenic compounds (> 1 year) does not seem to be indicated and may actually confer risks for dementia in older women over the age of 65 years. The same may be the case for phytoestrogens. The possibility that folate can off-set some of the negative effects of (phyto)estrogens merits more research in this area. Whether there is an optimum age to engage with these types of life style behaviours is currently unclear and also requires additional research.

1. Introduction

1.1 Focus and aims of this review of dementia and mid-life risk factors

There is substantial variation in the rate at which we cognitively age, ranging from successful aging with sometimes even superior performance to that of some younger people, to that of the severe and devastating cognitive decline seen in dementia [1, 2]. Dementia is a pathological condition characterized by brain pathology (e.g. plaques and tangles in Alzheimer's disease (AD), vascular pathology in vascular dementia (VaD), Lewy Bodies in LBD etc.) and cognitive impairment impacting on activities of daily life [3, 2]. Of the dementias, Alzheimer's disease (AD) is probably the most common form and is characterized by gradual progressive loss of memory functions, followed by more widespread cognitive dysfunction impacting on the activities of daily living, such as shopping, conducting bank transactions and engaging in social interactions [3]. The human and economic costs of dementia are high [4] and, with an

increasing aging population worldwide, there is a clear necessity of research into preventative measures.

The age group identified to target potential interventions towards prevention of cognitive decline and dementia has important implications for governmental policy and the content of public health messages. Most of the studies reviewed in this article suggest that interventions in middle-age, before major irreversible damage to the brain is done, may be most successful to prevent dementia. When dementia becomes apparent, in most cases after the age of 65 years, the brain will usually show extensive pathology, such as neurofibrillary tangles and plaques in AD [5] and it may be too late to reverse this process.

In this article we will review various potential preventative activities to be carried out in mid-life and beyond to prevent the development of dementia, such as reducing cardiovascular risk, engaging in physical exercise and other life style alterations, including the intake of caffeine, soy products and hormones. This is not a comprehensive review, but uses examples of studies to illustrate that some preventative interventions to maintain cognitive health may be most appropriate in middle-age rather than old age. Data on intellectual stimulation, the role of education, and other demographic and non-modifiable factors, such as genetics, are therefore not included in this review as for these data, to our knowledge, no specific focus on middle-age interventions and risk is given in the literature. In addition, it would be impossible to generate any reasonable review including all these factors within the limitations of one article. The focus is therefore on cardiovascular disease, exercise and (phyto)hormone related interventions as illustrations of the importance of treating people in middle-age rather than beyond that when it may be too late for effective interventions. Where that is appropriate, given the scope of the journal, we will focus on particular treatments pertaining to women (e.g. in the hormone section).

Several cohort studies have shown that AD prevalence is higher in women than it is in men (e.g. [6]). While this might be the case because women reach an older age than men and age is a risk factor for dementia [6], the age-specific incidence of AD is also higher in women than it is in men [7]. This suggests that perhaps gender-related lifestyle variables (e.g. fewer women used to smoke than men, differences in activity levels) and/or hormone differences could play a role in the development of AD.

1.2. Dementia, mild cognitive impairment and age-related cognitive decline

It should be noted that the distinction between 'normal'[8] age-related cognitive decline and dementia is often difficult to establish in observational research, even when that includes post-mortem confirmation of dementia pathology. Firstly, some elderly with brain pathology and lesions will show no cognitive impairment; and overlap of different dementia pathology within individuals is more common than finding pure forms (e.g. of VaD or AD) [8, 9, 10]). Specificity of the differential dementia diagnosis is thus low and data indicate the absence of a linear association between markers of dementia, such as brain pathology, and their symptomatic clinical counterparts. In addition, those with mild cognitive impairment (MCI [11]), who are thought to be at risk for dementia, can show reversal to normal function, remain in that stage or show decline at follow-up [12] and are thus a heterogeneous group. Furthermore, 'dementia' assessment shows variation in that some studies have used the required multidisciplinary assessments [3], whereas others only used the non specific MMSE cut-offs or related screening tests to establish this. Lastly, risk factors for accelerated cognitive decline and dementia are often the same (e.g. an older age, low levels of education, high blood pressure, diabetes, smoking etc.). Therefore in this review, the distinction between cognitive decline (which may be within normal age-adjusted limits) and dementia is highlighted for individual studies, but it should be noted that this is a difficult area which warrants extensive review in its own right.

2. Cardiovascular risk in mid-life and later life risk of dementia

2.1. Associations of obesity, blood pressure and cholesterol with dementia risk

Several large cohort studies which have followed their participants over a period of time have suggested that cardiovascular risk factors are also risk factors for AD and other types of dementia. These risk factors may be particularly important in mid-life, which is when preventative actions should probably take place. The Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study followed their 1449 participants from middle-age, beginning at around the mid 40th decade of their lives [13]. They found that being obese (body mass index or BMI over 30), having a high blood pressure and high total cholesterol in mid-life increased the risk for AD 18 years later by a factor 1.5 to 2; these factors individually thus doubled the risk of AD. When the 3 factors were presented together, the risk for AD was increased by a factor 6. This was independent of reported fat intake or physical activity, age and education. Similarly, in the Honolulu-Asia Aging Study [14], increased blood pressure in mid-life, in the 5th decade of life,

[8] Indeed some elderly are better at some cognitive tests than some younger participants and ageing is characterized by a huge variation of performance within and between subjects and is further test dependent (i.e. not all cognitive tests show a decline with age)

was associated with an increased risk of AD after 25 years in non-treated individuals. In the Kaiser Permanente of Northern California Medical Group study elevated levels of cholesterol at 40-45 years of age were associated with a doubled risk of AD and VaD after a 30 year follow-up [15] and being overweight or obese in the early 40s was also associated with a 2 to 3 fold increase in risk of AD in later life [16]. The Swedish Adoption/Twin Study Aging study similarly suggested that higher BMI in mid-life , in the 4th decade of life, was associated with lower global cognitive ability 25 years later and faster cognitive decline [17].

However, these cardiovascular risk factors have been shown to change in the years before dementia becomes clinically apparent, with a subsequent lowering of BMI, cholesterol levels and blood pressure. This is possibly related to dysfunctional regulation at the central nervous system level, which could be a by-effect of the pathological changes in the brain seen in the different types of dementia. For instance, a meta-review of the literature [18] showed that high blood pressure in mid-life is associated with AD, whereas low blood pressure in older age is associated with AD. In cross-sectional case control studies, in those with established dementia, blood pressure is often found to be lower [19]. In addition, in a longitudinal study, high blood pressure was found to be a risk factor in mid-life for later life dementia [20], but was seen to drop in the years preceding the clinical onset of dementia. Similarly, being overweight or obese in later life (>60 years of age) has been associated with a decreased risk of dementia [21], despite mid-life obesity being associated with increased risk as mentioned previously.

This has important implications for treatment. For instance, a recent Cochrane review [22] found no evidence that reducing cholesterol through the use of statins lowered risk of AD and dementia in individuals above the age of 70 years. It may be the case, however, that treatment when initiated at mid-life would have preventative actions. A similar pattern was found with anti-hypertensive medications, with a review suggesting that such medications did not lower risk of cognitive impairment or dementia in participants with a mean age of 72.8 years [23]. These data could reflect the need for early mid-life, rather than later life interventions, as in later life changes in regulatory mechanisms may have become impaired.

2.2. Life style behaviours, such as mid-life smoking and coffee drinking, and dementia risk

There may be additional mid-life style changes that can affect the risk for both cardiovascular disease and dementia, such as smoking or drinking coffee. The CAIDE study mentioned earlier found that alcohol drinking, smoking, physical inactivity, a low-moderate intake of polyunsaturated fats, and moderate-high intake of saturated fats at mid-life all increased the risk of dementia at an older age (>65 years), particularly among those who were genetically at risk for AD and carried the apoE epsilon4 allele [24]. Similarly, the Rotterdam Study found that smoking in mid-life (in the 5th decade of life) increased the risk for dementia and AD by around 50% at a follow-up 7 years later [25]. Smoking cessation in mid-life or before is advised as past smoking in mid-life did not confer significant risk.

The relationship between alcohol use and dementia is complicated as dose dependent associations (similar to caffeine, see below) may exist (e.g. [26]) and hence is not further discussed in this review. We will, however, briefly review some of the literature on caffeine which could again suggest the importance of mid-life interventions for this factor.

Coffee intake may be an important confound in the relationship described between cardiovascular risk factors and cognitive decline due to the impact that caffeine has on blood pressure. Despite many GPs advising their older patients to reduce caffeine intake because of its suspected effects on blood pressure, a recent review suggested that there may actually be protective effects of drinking more than 4 cups of coffee per day against hypertension (particularly in women), although this reduced risk of hypertension was also seen in coffee abstainers [27]. These data suggest optimal inverted U-curve related associations between caffeine intake and blood pressure which may also impact on cognitive function and dementia risk. Coffee drinking in the CAIDE cohort in mid-life was indeed shown to have protective effects on the later development of dementia. Here, however, the lowest risk for dementia (with a more than 50% risk reduction) was found in people who drank 3-5 cups of coffee per day in mid-life. The cross-sectional data from the Maastricht Aging Study suggested a similar coffee intake optimum related to optimal performance on a reading test, although there were linear associations for memory and psychomotor speed, and no interactions with age [28]. In this cohort, however, there was evidence of decreased caffeine consumption with age [28]. This may indicate that different optimal caffeine levels exist for each age group (e.g. elderly needing less caffeine for optimal effects on cognitive function). Some experimental studies indeed suggest that optimal levels may be

dependent upon age, habitual consumption, and cognitive test type. A treatment study comparing different age groups found that the positive effect of 250 mg of caffeine on short term memory tests was particularly significant in those of middle-age [29], but not in those who were older or younger and who were negatively affected by this dose. Middle-aged participants were found to habitually drink more caffeine and withdrawal effects may thus have explained some of these results. In another study, only including 30 very healthy middle-aged and old subjects, 100 mg of caffeine was found to positively affect colour naming, but not to have any effects on focused attention or (short term) memory tests [30] and there was little difference between those of middle-age and those who were elderly. These data suggest that the higher dosage effect in the middle-aged reported by [29] was not explained by withdrawal effects, as these would have normally been alleviated by a 100 mg intake in habitual caffeine consumers.

We recently also found positive associations between daily coffee consumption and memory recall in a cross-sectional large Indonesian cohort of elderly (n=719), but here effects were mainly significant for those older than 68 years of age. How much caffeine was ingested by this age group in total and strength of the coffee was not investigated. However, these data indicate that effects of coffee are not only explained through its potential preventive actions in middle-age, as by the age of 68 years, brain pathology in some form or another will probably be present. Caffeine can act directly on neurotransmitters activity necessary for concentration and memory functions, which are affected with age and which could explain its potentially direct positive effects on cognition in the old [28]. In our Indonesian study (unpublished data, for description of the cohort and methods, see [31]), for global cognition, as measured with the Mini-Mental Status Examination (MMSE), effects of daily caffeine consumption were also most apparent in women, perhaps reflecting gender differences in mechanisms underlying cognitive aging (see also sex hormones section).

How these findings taken together translate to advice for the general public is at present not clear. However, it can be concluded from this brief review that lifestyle behaviours in mid-life may have important effects on cognitive functions in later life. Interventions to reduce dementia risk could thus focus on reduction of cardiovascular risk, such as cessation of smoking. Whether caffeine, statins and antihypertensive medications should be prescribed in mid-life to prevent later life dementia is currently not clear. Those who habitually consume coffee should probably continue to do so, but whether positive effects of caffeine consumption will be seen in older caffeine naive

subjects (and at which dose) remains to be seen. However, it is also possible to reduce obesity and lower levels of LDL cholesterol, triglycerides and blood pressure through exercise. Associations of exercise and cognition are discussed in the next section.

3. Does exercise protect against dementia and cognitive decline?

3.1. Biological plausibility for the relationship between physical activity and cognitive health

Physical activity has long been considered important to maintain health but also optimal cognitive function. As vascular risk factors are associated with an increased risk of dementia, the reduction of body fat mass (particularly around the abdomen) and blood pressure [13] through exercise may explain the indirect effects of exercise on improving cognitive function and reducing dementia risk. However, there is an increasing body of evidence to suggest that physical activity can also directly benefit cognitive health and protect the aging brain and several biological mechanisms pertaining to the direct protective effects of exercise have been suggested. Exercise may encourage prolonged neurogenesis, particularly in the hippocampus [32], an area affected in AD [33] and which is thought to crucial play a role in memory processes [34]. Other theories suggest that synthesis of neurotransmitters, such as norepinephrine, dopamine and serotonin, may be affected by physical activity thus assisting in the maintenance of cognitive function [35]. Exercise increases blood flow, improving oxygen and glucose deliverance to the body and the brain [36]. Exercise could thus reduce the risk of hypoxia, which can lead to the loss of brain tissue [37] and is thought to play an important role in age-related cognitive decline. These potential mechanisms are discussed in more detail elsewhere (e.g. [38, 39]) but they do give theoretical grounding to the premise that cognition can be directly influenced and maintained by engaging in physical activity, in middle-age possibly through its reduction of cardiovascular risk and in later life possibly through its effects on cerebral perfusion, neurogenesis and neurotransmitter synthesis as described above.

3.2. Is exercise particularly important in middle-age and is there a gender difference ?

The CAIDE study mentioned earlier indeed found that the risk of dementia and AD 21 years later could be dramatically decreased by engaging in leisure time activity at least twice a week in mid-life (around the 5^{th} decade of life),, with a risk reduction for dementia reported to be 52% and for AD 62% [40] . The Swedish Twin study also mentioned earlier showed a similar risk reduction with regular exercise in midlife for

dementia and AD after a 31 year follow-up of around 66% [41]. As stated earlier, [13] suggested that activity is especially important in middle-age for maintenance of long-term cognitive health, which may be mediated by reducing blood cholesterol, weight and blood pressure.

While exercise in middle-age may have the largest benefits to cognitive health, preservation of cognitive functioning in the elderly may also help to resist the onset of serious cognitive impairment. There is some evidence, however, that the benefit seen on cognition is more pronounced in older women than in older men. For instance, one observational study [42] found that risk of AD in women over 65 years of age was reduced by around 50% for those who had exercised intensely and frequently in the five years previous to assessment, compared to those who were less active. However, there was no such reduction for active over less-active men of the same age. Another relatively observational small study [43] found an 88% reduced risk of cognitive impairment after an average follow-up of 5 years in very old women (of an average age 88.5 years) who exercised more than 4 hours per week compared to those who exercised less. In this study, less active women had 2 times the incidence rate of CI compared to less active men and almost 5 times the rate compared to active women These findings were independent of co-morbidities and presence of the apoE epsilon4 allele. Another longitudinal Chinese study [44] found that women over the age of 70 years had a 2.5 higher risk of cognitive impairment (CI) than men at a 3 year follow-up. However, women -but not men- had a doubled risk of CI when they had been sedentary at baseline versus those who had been active. This is not to say that men do not benefit from exercise, as significant risk reductions have also been seen in studies that have used men only [45]. However, the effect in women appears to perhaps be exaggerated compared to that in men and there are no studies to our knowledge that have found the reverse. The reason for this difference is unclear, but could reflect the social influence of the specific exercises that the two groups choose to participate in that has an additional beneficial effect on cognition. For example, women may participate more in activities that have a social support component, such as exercise classes or walking with friends, while men may participate in more activities alone, such as jogging and gym workouts (NB: it is interesting to note that this gender bias is not reported in intervention studies, where the type of activity and program is controlled). Indeed, regular social activity has been shown to reduce risk of dementia by 42% [46], so this factor may mediate the magnitude of the effect of engaging in exercise and cognitive improvement seen in women. Alternatively, exercise may affect sex steroid metabolism and synthesis which could affect cognitive function. This

association is described in more detail in section 4. An example of how an exercise intervention can affect and interact with various aspects of cognition and dementia risk is given in figure 1.

3.2. Exercise treatment for dementia and cognitive impairment and the role of fitness

Relatively few treatment studies have investigated the effects of exercise in individuals who had already been diagnosed with dementia or memory impairments. A recent study found modest cognitive improvements on cognitive tests after a 24-week aerobic and strength training programme among individuals who had memory impairments (but not dementia) [47]. However, other randomised controlled trials have found no benefit of physical activity on those afflicted with MCI or AD. For example, a one-year walking programme was found to have no benefit on memory or executive function in participants with MCI [48]. A six-month programme of activity compared to rest was also found to have no benefit on MMSE scores in AD patients [49]. It is therefore perhaps less likely that exercise can benefit cognitive ability once decline has begun. Thus, if uptake of physical activity is left until older age, when brain pathology is more likely to be established, there may be less benefit to cognitive health as compared to when it has been taken up during middle-age. However, more research needs to be done to establish the age at which exercise interventions are most successful at preventing the onset of dementia in the future.

It should be noted, however, that the lack of change may be partly due to individuals with existing cognitive impairment not being able to benefit from feed-back and encouragement (perhaps because of their cognitive impairments) to participate in activity that is intense enough to cause physiological changes that may be necessary for a benefit to be seen. Previous studies suggest that the benefit of exercise does not necessarily increase with length of an exercise session or frequency per week [50]. Rather, an increase in objective fitness measures, such as VO_{2max} or caloric expenditure, may be more important for predicting an improvement in cognitive functioning in mid-life (<60 years old) [51, 52], although some studies (e.g. [53, 54, 55]) reporting a positive effect of either aerobic or strength training exercises also showed a concomitant increase in objective fitness measures for the exercise groups in slightly older participants (around 65 years old). To improve VO_{2max} or muscle strength, participants need to fully engage with the exercises to ensure that they are reaching a certain level of intensity. Many studies suffered from attrition and/or low compliance to exercise regimes and this may help to explain some of the variation seen in past

research when no benefits have been seen [50]. Some participants may thus have not engaged in exercise of a high enough intensity to actually improve their physical fitness. Importantly, the effects of exercise can also be seen very quickly, with some studies showing benefits to cognition after just 2 months [56]. This is long enough for an improvement in fitness to be detected, so this again supports the notion that relative fitness (as improvement from baseline) affects cognition, rather than the exercise activity itself. It may be that this problem of adherence is more so the case for studies with elderly rather then relatively younger participants but these data need to be further investigated. In addition, not all previous studies have reported objective measures of fitness, so there is not as yet a wealth of evidence to substantiate this point.

3.3. Which cognitive domains are particularly affected by exercise interventions and are these relevant for dementia?

Numerous cross-sectional studies and controlled treatment trials have shown that individuals who participate in exercise and sports show better performance on tests of memory, executive function and language compared to those who are mostly sedentary (for review see [50]). Following a recent review of the literature [50], however, it appears that the relationship between exercise and cognitive function is complex and may be affected by mediating variables such as type of exercise and cognitive domain being tested. It is at present not clear whether exercise affects specific cognitive domains or whether it has a more general effect on cognition, and/or whether there is an age-specific effect. While some past studies have found benefits on all tests administered, many have found that only some tests show a positive effect. This could be due to methodological issues, but it could also indicate that distinct processes in the brain are affected differently. It has been suggested previously that exercise benefits ability on complex tasks more than on simple tasks, as more automatic processes are less liable to decline with age [57]. Other reviews have also suggested that physical activity affects primarily executive control processes over more simple processes (e.g. [58, 59, 60]) For example, in a treatment study, complex reaction time on a dual task specifically - but not the simple tasks- improved in an older group attending a 10 week water aerobics class [58]. However, a recent review [50] revealed that the more simple memory tasks (e.g. Digit Span) were more consistently affected by exercise across most studies. As these tests are not affected by age or dementia processes in the early stages of the disease [61], it is not clear what the relevance of exercise for prevention of dementia is, as different functional areas may be affected by the intervention but not in dementia per se. This area of research is further complicated as some studies have used their own versions of tests or tests that

are not used in other research of this type, interfering with a direct comparison of results. A set of standardised tests should thus be agreed upon by the research community, such that future research can be compared to establish which cognitive domains may be most affected by exercise and whether this pertains to processes implicated in dementia.

3.4. Which types of exercise are most beneficial to maintain cognitive health ?

Overall, however, the literature suggests that some types of exercise may be more beneficial to cognitive function than others. Treatment studies including elderly participants that have investigated the effects of aerobic activity, such as running and cycling, seem to show the most consistent benefits on cognition [62, 58]. While there is no evidence to suggest that stretching exercises, such as Yoga, improve cognitive functioning [63], some studies have found that resistance exercise, which increases muscle strength, may also help to improve cognitive ability. For example, one study [64] found that an increase in resistance level over a 6 month training program predicted improved scores on the more complex Digit Span backwards test. In addition, [56] found that 8 weeks of resistance exercises lead to significant increases in immediate and delayed recall and recognition, as compared to no exercise. These findings may have relevance to dementia, in which these functions were to be particularly affected.

As mentioned, improvements in fitness may be particularly important for benefits in cognition; therefore, any type of exercise that increase aerobic fitness or muscle strength may be effective. Some benefits of exercise were seen in the elderly, but once cognitive impairment has set in, it seems that this intervention is no longer effective. It may be that a lack of improvement in fitness in this group is related to this, and/or alternatively the advanced brain pathology, which can no longer be reversed. From observational data it thus seems that exercise interventions focused on reducing cardiovascular risk should be initiated in middle-age. One of the mediating mechanisms responsible for improvements could be concomitant changes in sex steroid levels affecting both cardiovascular risk and dementia, particularly in middle-age. However, sex steroids such as estrogens have also been found to negatively affect the brain cells once dementia-related pathology has set in [65]. This literature is described in more detail in the following section.

4. Sex hormones and cognitive function

4.1. Biological plausibility of exercise and sex hormones affecting the brain

Some but not all studies suggest that testosterone levels increase after exercise (e.g. [66]). After the menopause, women have much lower levels of sex steroids (such as testosterone and estrogens) than men and this has been mentioned as a possible reason for the observed increased risk for dementia (see introduction and paragraph 4). There is abundant evidence from animal and cell culture studies to suggest that sex steroid hormones such as estrogens and testosterone can protect brain. Estrogen's biological plausibility to protect the aging brain was once called 'its strongest suit' [67]. It is possible that some of the effect of exercise is thus mediated by the promotional activity from increased levels of sex steroid hormones, such as testosterone and estradiol, which can be converted from testosterone in the brain. In addition, studies [68] have suggested that the synergistic interaction between estrogens and physical exercise may further increase hippocampal Brain-Derived Neurotrophic Factors (BDNF) levels. BDNF is important for memory and neuronal survival. Possibly in line with this, one observational study [69] reported that women who took hormone therapy for less than 10 years had better cognitive function when they also had high fitness levels, than compared to those women with low fitness levels.

4.2. Menopause and cognitive function

Up to the turn of the century, estrogen research would be mentioned in review articles as one of the more promising lines of research leading to potentially successful AD treatment options and prevention. This was based on the basic sciences data, the observational studies showing a 30-45% lower risk of dementia in women who used estrogen therapy and several relatively small treatment trials (e.g. [70, 71]).

Women would take estrogen replacement therapy to alleviate menopausal symptoms, such as hot flushes and night sweats, typically occurring in the 5^{th} decade of their lives. Because of estrogens biological plausibility to protect the aging brain, one would expect that estrogen deprivation after the menopause (which occurs because of depletion of ova, which produce estrogens) would dramatically accelerate cognitive decline. However, studies investigating the natural menopausal transition actually show few cognitive changes [72, 73, 74, 75].

4.3. Surgical menopause and cognitive function

On the other hand, small prospective studies of women who underwent surgical menopause by removal of the ovaries (which leads to an abrupt drop in estrogen

levels) showed a rapid drop in cognitive functions sensitive to dementia [76, 77]. One large prospective study found that women who had undergone surgical menopause in mid-life had an almost doubled risk for dementia, particularly if they had not been treated with replacement estrogens up to the age of menopause (at approximately 50 years of age). This study also showed that the younger the age at surgical menopause without hormone replacement treatment, the higher the risk for dementia [78]. In addition, meta-analyses of hormone treatment studies found the most significant positive effects of estrogens (and testosterone) on cognition in middle-aged recently surgically induced menopausal women and/or those who were highly symptomatic [70, 71]. Effects were most apparent on those tests that are sensitive to dementia and age-related cognitive decline, such as some memory functions, executive functions and attention tests

4.4. Surgical menopause, symptoms, BMI and cognitive function

A caveat here may be that women who undergo surgical menopause usually report a higher frequency (and distress) associated with menopausal symptoms, such as forgetfulness, hot flushes and night sweats. It is not clear whether the positive effect that estradiol (the most potent estrogen) seemed to have on cognitive functions was mediated by alleviation of menopausal symptoms in the earlier studies mentioned which showed a positive effect of treatment on cognition. By reducing flushes and sweats, estrogens could improve sleep, concentration and mood, each of which could have a subsequent positive indirect effect on memory and other cognitive functions [79]. Several studies controlling for symptom relief [80, 81] found that symptoms did not statistically mediate the association between treatment and improvement in cognition. However, as all of the studies which did report a positive effect of estradiol on cognition in recently menopausal women had included women who were highly symptomatic, whether symptom relief can be entirely eliminated as a mediating factor remains a question to be answered. One study with asymptomatic women [82] found no effects on cognition, but had also used tests which were earlier not found to be affected by estrogens and which are also not sensitive to dementia. Estrogens seem to exert sex sensitive specific tests (e.g. on verbal memory and verbal fluency), targeting those functions and brain areas, such as the hippocampus [83] and prefrontal brain areas [84] which are also affected in dementia and age-related cognitive decline.

The role of BMI and fat mass in the mediation of symptoms and cognitive function is also not entirely elucidated. BMI is important as estradiol conversions occur in fatty tissue, so a high fat mass should thus theoretically protect against cognitive decline.

This was indeed found in one longitudinal study, where overweight women show less cognitive decline on specific tests (Fluency, verbal memory) after menopausal transition than normal weight women [74]. On the other hand, women with high body fat usually complain more of menopausal symptoms, possibly because they are more insulated and flushes and sweats thus have a higher impact [85]. Depending on the degree of obesity in the cohort, this could perhaps explain why many studies found no effects of menopausal transition on most cognitive tests, because a) studies controlling for BMI would eliminate the variance related to this factor as described above and would thus not be expected to find any associations between menopausal transition; and b) beneficial effects of estrogen conversion in fat tissue would probably be cancelled out by independent effects of a higher frequency of menopausal symptoms in women with a higher fat mass impacting on cognitive function. Importantly, earlier reviews show no consistent association between high estrogen levels and cognitive function or decline [86]. In fact, high estrogen levels in older women over the age of 65 years were associated with an increased risk of AD [87]. In addition, the study that found less cognitive decline in women with a higher BMI had perhaps not controlled for all potential (subclinical) morbidity associated with weight loss and a low BMI, such as cancers or other wasting syndrome morbidity, which could impact on cognitive decline. Lastly, as discussed, in the longer term, a high BMI in mid-life independently predicts both cardiovascular disease and dementia (see section 2), so any small surplus positive effect of endogenous estrogens in women with high fat mass in mid-life would probably be cancelled out by these negative longer-term effects. Related to this, estrogens have been hypothesized to exert their protective effects via their positive effects on the cardiovascular system [88] or via protective actions on insulin resistance and the development of diabetes mellitus which may detrimentally affect cognitive function. However, again the current hypothesis is that for estrogen treatment to have beneficial effects on, for instance, cardiovascular disease, this should be initiated in middle-age [89, 90].

4.5. Long term treatment with estrogens and cognitive function

It has now also become clear that longer term estrogen treatment (e.g. > 1 year) has no beneficial effects on cognition and that it should not be prescribed for long-term maintenance of cognitive function and prevention of dementia. In fact, the initial benefits seen after 2-3 months on cognition may start to reverse after one year of treatment [70]. For instance, in one observational study (where incidentally undergoing surgical menopause was not associated with worse cognitive function in older women [91]), those women with a mean age of 74 years who had undergone surgical

menopause many years before, but were still using hormone treatment at the time of testing, actually had worse cognitive function than those who did not take hormones. This was also found in another study which had tested women who had undergone surgical menopause 10 years before and who, when still taking hormones at the time of testing, had worse cognition then those who did not take estradiol [92]. The study which showed that hormone treatment could protect surgically menopausal women against dementia [78] had only investigated effects of treatment up to the natural age of menopause and not beyond. In another observational study [73], when hormone treatment was given before the menopause, when some aspects of memory were affected, it was shown to improve cognition. However, when hormone treatment was initiated after menopause, cognitive decline accelerated. Similarly in the before mentioned study [69] investigating fitness and hormone treatment, when hormone treatment was given for longer than 10 years, brain scans showed more gray matter decline and a concomitant faster decline in cognitive function than in women who did not receive such long term treatment. However, in women who were physically fit, this decline was less pronounced, again suggesting an interaction between exercise and hormone treatment.

4.6. Age and estrogen treatment

Negative effects of estrogens may thus be more likely to occur in women who are far beyond the natural age of menopause (e.g. after age 65 years) and who may already show pathological changes in the brain. Several large well controlled trials indicated that estrogens treatment do not improve dementia symptoms in women with AD for more than 2-3 months [93, 94, 95] and may even worsen their dementia severity [96]. The Women's Health Initiative Memory Study (WHIMS) also showed a doubled risk for AD in older women (> 65 years of age) who had been allocated to conjugated equine estrogens treatment, particularly when this was combined with medroxy progesterone acetate [97, 98].

The current hypothesis among many scientists in this particular field is that, similar to its indications for cardiovascular disease interventions [89], hormone treatment – when given for menopausal symptoms- should be initiated close to the age of menopause, but probably also stopped before the sixth decade. This regime would also reduce the increased breast cancer risk, which has been shown to occur with hormone treatment, particularly after longer duration treatment (e.g. 5 years) in women over the age of 60 years [99].

Testosterone has been found to have similar effects as estrogens in recently menopausal women (e.g. [76]) and can be converted to estrogens in the brain. However, similar to estrogens, testosterone does not seem to lower risks for cardiovascular disease and breast cancer in women over 65 years of age [87] and more trials would need to be done to further elucidate its potential role as an alternative for estrogens.

4.7. Other hormones

Older women after the menopause also have a higher risk of thyroid disease than men [100]. Hypofunction of the thyroid is a known risk factor for dementia [101]. We [100] found that half of healthy elderly who had thyroid disease (as established by using their serum thyroid hormones and comparing these against established laboratory cut-offs for thyroid disease) to be unaware of their condition. Even in these preselected relatively healthy elderly cohort, hypofunction of the thyroid was shown to significantly affect their cognitive function. However, in those without thyroid disease, having high-normal thyroid hormone and/or lower thyroid stimulating hormone (TSH, as seen in subclinical hyperthyroidism) was also found to be associated with a higher risk of AD [102] and a more rapid cognitive decline in healthy elderly [100]. This may indicate that thyroid hormone treatment, when given for hypofunction of the thyroid, needs to be carefully monitored. In addition, thyroid hormone and estrogen both increase sex-binding globulin, thereby decreasing free and bioavailable sex steroid hormones [103] Interactions of sex steroids further exist with Growth Hormone (GH) and Insulin-like Growth Factor (IGF-1) which both decline with age [103] and which can also positively affect the brain [104]. However, GH treatment, which like thyroid hormone treatment is sometimes prescribed by anti-aging practitioners for those without related morbidity, is not without risk (e.g. affecting insulin resistance [104]) and should be carefully considered.

5. Micronutrients and dementia risk: a focus on phytoestrogens and folate

5.1. Is soy the solution?

Because of the negative publicity surrounding the WHIMS, many women stopped taking estrogens for menopausal complaints and some switched to what they perceived as more natural alternatives for menopausal symptoms and to maintain health, such as phytoestrogens. Phytoestrogens are plant hormones with estrogenic activity; they can act like estrogens, binding to the estrogen receptor with about half the activity of estradiol [105]. Recent years have seen soy, which contains high levels of phytoestrogens, to be promoted as a superfood in protecting against cardiovascular

disease, cancer, dementia etc. Indeed, in countries such as Japan, where consumption of soy products is high, AD risk is lower [106]. While several treatment studies have found positive short term effects on cognition in middle-aged women, this was not the case for older women [95], although a recent treatment study did show a positive effect of phytoestrogen treatment in both older men and women (> age 62 years) who had been treated up to 6 months. However, placebo was also shown to have an advantage on some of the executive function tests [95, 107]. In addition, several observational studies reported, also similar to estrogen treatment (see above), an increased risk for dementia and dementia markers with high habitual tofu intake. In an Indonesian sample of elderly men and women we found [31], consistent with findings of the Honolulu Asia Aging Study (HAAS) [108] and the Kame project [109], that high tofu consumption in older participants (> 68 years of age) was associated with worse cognitive function and a higher risk of possible dementia. Tempe, a fermented soy bean product, in these analyses was found to off-set the negative association of tofu, but it had no significant associations with cognition by itself. Genistein (the most potent phytoestrogen in soy) had an optimal level relationship with memory performance, particularly in women younger than 68 years of age and in older men. In line with the data on tofu, in older participants there was a trend negative association for genistein with global cognitive function, as measured with the MMSE. In analyses stratified for sex, associations were strongest in women, but there were fewer men in this cohort and power issues could have potentially explained these results [110]. The HAAS similarly found that elderly (>71 years of age) men and their wives who had reported consuming tofu more than twice a week in mid-life had a higher risk of dementia, more brain atrophy and lower cognitive function than those who consumed less tofu. The Kame project also found negative associations of high tofu consumption (more than 3 times a week) with cognitive decline over a 2 year period in Japanese American elderly over age 65 years. In stratified analyses this remained significant only for women who were hormone replacement users, but not for those who were not hormone users, elderly men or those who consumed moderate (twice a week) to low amounts of tofu. These data again suggest that there may be optimal levels of phytoestrogens, perhaps interacting with age, sex and estrogen levels. On the other hand, the Study of Women's Health Across the Nation (SWAN) data did not find optimal calculated (from Food Frequency Questionnaires, so not measured) levels of genistein and daidizein in their middle-aged women [111]. The SWAN analyses included 195 Japanese and 185 Chinese women between 42 to 52 years of age and found no association between calculated phytoestrogen intake and cognitive function (memory, processing speed and executive function). The authors surmised that the effects might only be present in

women who are in low-estrogen (post-menopausal) state, although that contradicts with the other observational studies mentioned above. The authors used tertiles to investigate optimal genistein and daidizein levels, rather than report weekly soy intake as was done in the other studies so results are difficult to compare. The cognitive tests used in this study were also not affected by soy treatments in our studies and perhaps more difficult memory tests (word list free recall) would have shown significant differences. Other cohorts including elderly women with Western diets with general low soy intakes [112] have generally not found any associations with cognition, possibly again indicating optimal levels, which are perhaps also age-dependent.

A novel findings in our Indonesian study was the different associations found for different types of soy processed foods. Tofu is processed soy curd, whereas tempe is made of the whole soy bean which undergoes fermentation. Tempe has higher genistein levels than tofu [113] which would not explain why tempe might off-set negative effects of tofu, unless the curvilinear term would follow a U curve, instead of the inverted U curve, which gave a better fit for the data. However fermentation using molds increases folate levels in tempe [114]. Our earlier work in Oxford indicated that a) women with dementia had higher levels of endogenous estrogens than controls when sensitive assays were used and b) that women who had high endogenous estrogens, but who also had high levels of serum folate, did not perform below the 25 points performance cut-off score of the MMSE [115]. Future studies need to investigate the interaction between serum (phyto)estrogens and folate levels in determining dementia risk.

5.2. Folate and other dietary components

Folate has protective effects on brain function and been associated with lower levels of homocysteine, an important modifiable risk factor for cardiovascular disease, dementia and AD [116]. A randomised controlled study of participants aged 50-70 years without dementia but with raised plasma total homocysteine who were treated with 800 mug daily oral folic acid (the supplement form of folate) for 3 years showed improved cognitive function on those tests sensitive to aging and dementia compared to those taking placebo [117]. However, folic acid has again not been shown to be effective in those who already had developed dementia or who had significant cognitive impairment [118] possibly again indicating the importance of early interventions, before major damage to the brain has occurred.

Lastly, other supplements such as anti-oxidant vitamins (E, C, A) may protect against cognitive decline, but their use is controversial [119] and the current discussion seems to have shifted towards the use of whole foods (e.g. adherence to a Mediterranean diet is associated with lower MMSE decline [120] and lower AD risk [121] rather than prescribing supplements. Reviews also suggest that lower cognitive decline is associated with low intake of foods such as vegetables, fruits and cereals (e.g. [122]). Whether these types of diet should be initiated in mid-life or before that for maximum benefit remains to be further investigated.

6. Conclusion

This review has discussed several possible options for maintaining cognitive health in women. The interventions discussed should probably take place in mid-life (or even before) for maximum benefits, before extensive brain pathology has occurred. This pathology, only when it has spread substantially much later in life, can lead to the appearance of clinical dementia symptoms, which at present are untreatable. Risk factors for cardiovascular disease, such as obesity, high total cholesterol and high blood pressure increase dementia risk and the risk for accelerated cognitive decline. This risk should thus probably be reduced in mid-life, as these factors have been seen to change in the years before dementia onset, probably related to the pathological changes in the brain, leading to loss of body mass and a lowering of blood pressure.

Aerobic and resistance exercise will help reduce these risk factors. Whether these benefit cognition once dementia has become apparent, however, is unclear. So far studies suggest that low level exercise, such as yoga or stretching, is perhaps of less value in preventing dementia and improving cognitive function. Improvement in physical function (e.g. strength, VO2max) is needed for cognitive benefits, but adherence to regimes was often found to be low in treatment studies. It may be that some of the benefits of exercise are through its effect on sex steroid metabolism and synthesis. Sex hormone treatment may interact with fitness levels, but on the basis of the current data is not indicated to maintain longer term cognitive health in women. There is in all likelihood an increased risk of cognitive impairment with longer duration hormone treatment, particularly in women over the age of 65 years. In addition, some studies have shown a reversal of its positive effects already after one year of treatment in both middle-aged and old women, so at present this avenue seems of limited value. Alternative products, such as soy containing phytoestrogens, should also be regarded with caution in the elderly, although an intake of less than twice a week should not pose any risks based on current data from treatment and observational studies.

Whether estrogenic compounds positively interact with folate remains to be further investigated. More research is now focused on whole foods, rather than supplements to maintain health.

Future perspectives

This review has indicated that relatively cheap possible preventative activities to maintain cognitive health may exist and these seem to have a particular value for women. Visiting the GP to treat high blood pressure and assessment of cholesterol and thyroid hormone levels, and maintaining healthy diets, cessation of smoking and exercise can possibly help sustain successful cognitive aging and maybe delay dementia onset, particularly when this is done at middle-age.

Well controlled large studies are currently taking place to investigate optimal exercise regimes to maintain cognitive health, taking into account limitations (e.g. frailty, risk of fractures etc) associated with aging. Long term treatment with estrogenic compounds does not seem to be indicated at this stage and may actually confer risks, unless alternative regimes (e.g. intermittent treatments) offer safe and effective alternatives. Limited data suggest that phytoestrogens are not such an alternative. However, the possibility that folate can off-set some of the negative effects of (phyto)estrogens merits more research in this area.

Research has moved from supplements to whole foods containing folate and anti-oxidants within a varied diet including plenty of vegetables, fruits and polyunsaturated fats to maintain both physical and cognitive health. Whether optimal intakes of caffeine and alcohol exist to help prevent dementia is unclear, how these interact with cardiovascular risk and whether there is an optimum age to engage with these types of life style behaviours is currently unclear and also requires additional research. Future research should focus on combinations of life style interventions, such as diet, exercise etc and the off-setting of particular behaviours, the optimum levels of interventions and the optimal age of initiation of interventions.

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Appendix B

Validation Study Participant Questionnaire

Questionnaire

Participant Number…….
Date ……

F2.1 Respondent Characteristics and Demographics

F2.1a What was your age at your last birthday?

Age	……. years old	
Not sure		98
No answer		99

F2.1b1 Are you:

Man		1
Woman		2
No answer		99

F2.1b2 What is your marital status:

Married		1
Unmarried living together		2
Widow		3
Divorced/separated		4
Single		5
No answer		99

F2.1c What is the highest education level that you have obtained?

No formal education		1
Elementary or primary school (unfinished)		2
Elementary or primary school (finished)		3
Secondary school (unfinished)		4
Secondary school (finished)		5
College (finished)		6
Academy/University at least one year finished or more Other (please specify)…….		7
No answer		99

F What is your profession?

Higher – manager, admin or professional		6
Intermediate – manager, admin or professional		5
Supervisory or clerical, junior manager, admin or professional		4
Skilled manual		3
Semi or unskilled manual		2
State pensioner, not working		1

F2.1e What is your ethnic origin?

	F2.1e1 My father was/is		F2.1e2 My mother was/is	
White British		1		1
South Asian (Indian/British Indian/Pakistani, Bangladeshi		2		2
Caribbean/British Caribbean		3		3
White other (European, USA etc)		4		4
East Asian (Chinese/Japanese)		5		5
Other, please specify		97		97
No answer		99		99

F What is your religion? ……

F2.1h With whom do you live at this moment?

Alone		1
Wife/husband/partner		2
Wife/husband/partner and child		3
Child (without wife/husband)		4
Relatives		5
Institution		6
Other…….		97
No answer		99

F2.1i The house you live in:

Do you own it?		1
Do you rent it?		2
Do you live in other people's house (family etc)?		3
Do you live in a social institution/care home?		4
Other…….		97
No answer		99

F Do you have any children?

No		0
Yes		1
No answer		99
If yes, how many?	……..	

Health Survey

F7.1 In general, how would you say your health is?

Excellent		5
Very good		4

Good		3
Fair		2
Poor		1

F What is your:

Height	……ft……..inches
Weight	……st……..ibs

(a) Do you smoke? (circle) Yes No (b) If yes, how many a day? Cigarettes 40 or more 20-39 10-19 1-9 Cigars or pipes 5 or more inhaled Less than 5 or non-inhaled
(c) Do you exercise regularly? (circle) Yes No (d) How many days per week do you spend at least 20 minutes in moderate to strenuous exercise? 0 1 2 3 4 5 6 7 days per week (e) Can you walk 4 miles briskly without fatigue? (circle) Yes No
(f) Units of alcohol consumed per week…… (1= glass beer, 1= glass wine, 1= unit of spirit) (g) Number of cups tea/coffee consumed per week ……

F2.2 Health

At present, do you have any health problems for which you are:		Yes (1)	No (0)
a	Using prescribed medication?		
b	Attending your doctor?		
c	On a hospital waiting list?		
In the past two years, have you had any illness which required you to:			
d	Consult your doctor/GP?		
e	Attend a hospital outpatient department?		
f	Be admitted to hospital?		

If ‘no’ to above questions, please skip next section (F2.3) and continue with F2.4 Family history

F2.3 Medical examination and history based on Cambridge Mental Disorders of the Elderly Examination (Roth, 1984)

Have you been told by a doctor that you have (had):		Yes (1)	No (0)
1	High blood pressure		
2	A heart attack or other heart problem		
3,4	Stroke or TIA		
5a	Diabetes		
5b	If diabetes, do you take medication (insulin)?		
6a	Dementia or other neurological problem		
6b	If yes, what……		
7	Problems with alcohol or drugs		
8	Asthma or other lung disease		
9	Thrombosis or other blood disorder		
10	Digestive/gastrointestinal disorder		
11	Epilepsy		
12	Intolerance to goods containing soya		
13	Cancer or benign growths		

14	Vision or hearing problems		
		Yes (1)	No (0)
15	Kidney or liver problems		
16	Allergies……		
17a	Do you use hormone therapy?		
17b	If yes, which of the following:		
	Estrogens		
	Thyroid		
	Testosterone		
	Soy/phytoestrogens		
	Viagra		
	Are you using medication prescribed by a doctor:		
18a	To be calm, to be able to sleep		
18b	To not be depressed		

F2.4 Family history

Has any member of your family had any of the above diseases, please state **which disease** and **age** at onset:

Whom:

(a) Father…….

(b) Mother……

(c) Sibling…….

F.2.5 Do you eat?

	Times per day (0-4)	Days per week (1-7)	Days per month (1-31)
(a) White rice			
(b) Brown rice			
(c) Fruit			
(d) Orange/red veg			
(e) Green veg			
(f) Fish			
(g) Tofu (tofu products)			
(h) Tempe			
(g) Tahoe			
(i) Soy milk (soy products)			
(j) Tumeric			
(k) Miso soup			

Appendix C

Geriatric Depression Scale

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

1.	Are you basically satisfied with your life?	yes	no
2.	Have you dropped many of your activities and interests?	yes	no
3.	Do you feel that your life is empty?	yes	no
4.	Do you often get bored?	yes	no
5.	Are you in good spirits most of the time?	yes	no
6.	Are you afraid that something bad is going to happen to you?	yes	no
7.	Do you feel happy most of the time?	yes	no
8.	Do you often feel helpless?	yes	no
9.	Do you prefer to stay at home, rather than going out and doing things?	yes	no
10.	Do you feel that you have more problems with memory than most?	yes	no
11.	Do you think it is wonderful to be alive now?	yes	no
12.	Do you feel worthless the way you are now?	yes	no
13.	Do you feel full of energy?	yes	no
14.	Do you feel that your situation is hopeless?	yes	no
15.	Do you think that most people are better off than you are?	yes	no

Total Score _____

Appendix D

Observational Study Participant Questionnaire

Questionnaire

SEMAR
2006

I. Local Orientation

1. District / City :

Jakarta	1
Sumedang	2
Yogyakarta	3
How long have you lived here…yrs Where did you live before rural/urban	

2. Subdistrict :

3. Village

RT : _____ RW : _____

How long have you lived here……. Where did you live before…….

4. Location

Institution	1
Community	2
Other place, please specify ……..	3

5. Interviewer

6. Interviewer No.:

7. Respondent Name

8. Respondent No. :

II. Interviewer Visit and Recapitulation

9. Interview date : date _ _ / month _ _ / 2006

10. Interview time:

Start	hour _____ minute ____
Finish	hour _____ minute____

11. Carer present:

Spouse	1
Child	2
Relative	3
Caregiver	4
Other, please specify ……	5

12. Visit result ***:***

Rejection	1 →		Reason for ***rejection***:	
Completion	2		No reason	1

Incomplete	3		Weak condition	2
Delayed	4		Serious illness	3
Respondent not present	5		Other	4
Other, please specify	6		Please specify…….	5
……			……..	

13. Completion and consistency of answers to this questionnaire is inspected by:

Name	Status	Examination Date	Signature
	Interviewer I		
	Interviewer II		
	Supervisor		

F1

Informed Consent

Consent from Study Respondent of the influence of phytoestrogen levels on memory in men and women in Indonesia

The purpose and details of this study have been explained to me. I understand that this study is designed to further scientific knowledge and that all procedures have been approved by the Faculty of Medicine University of Indonesia Ethical Advisory Committee.

I have read and understood the information sheet and this consent form.

I have had an opportunity to ask questions about my participation.

I understand that I am under no obligation to take part in the study.

I understand that I have the right to withdraw from this study at any stage for any reason, and that I will not be required to explain my reasons for withdrawing.

I agree that a saliva sample will be taken and used to assess the level of plant hormones in my body.

I understand that all the information I provide will be treated in strict confidence.

I am happy to provide a saliva sample for testing of plant hormones.

I agree to participate in this study.

Your Name : ……

Your Signature : ……

Caregiver Name : ……

Caregiver Signature : …….....

Name of Investigator : ……

Signature of Investigator : ……

Date : ____ / _____ / 2006

F2.1 Respondent Characteristics

F2.1a How old are you (**age from your last birthday**) ?

Age *(if any doubt about the answer/doesn't remember/doestn't know, check respondent's ID card)*	…. Yrs old
Doesn't know/ doesn't remember	98
No answer	99

F2.1b Sex:

Male	1
Female	2

F2.1c What was the highest education level you graduated from?

No formal education	1
Elementary school (unfinished)	2
Elementary school/Hollands Inlandische School/equivalent	3
Primary school/ Middelbaar Uitgebreid Lagere Onderwijs/domestic girls school/equivalent	4
High school/ Hoge Burgerlijke School/equivalent	5
Academy/ University	6
Other, please specify…….	97
No answer	99

F2.1d What's your **profession** before retire?

Not working	1
Civil servant (teacher/lecturer/government employee)	2
Entrepreneur (businessman/trader)	3
Employee in private company	4
Army/police	5
Doctor/Lawyer	6
Farmer	7
Fisherman	8
Labour/ no permanent job	9
Other, please specify	97

F2.1e What is your parents race?

	F2.1e1 Father	F2.1e2 Mother
Javanese	1	1
Sundanese	2	2
Malayan	3	3
Batak	4	4
Minang	5	5
Other, please specify	97 ……	97 ……

F2.1f Your religion/faith:

Islam	1
Protestant	2
Catholic	3
Hinduism	4
Buddha	5
Confucianism	6
Other, ……..……..	97
No answer	99

F2.1g Living area:

Urban	1
Rural	2

F2.1h With whom do you live at this moment?

Alone	1
Wife/husband	2
Wife/husband and child	3
Child (without wife/husband)	4
Relatives	5
Institution	6
Others.....	97

F2.1i House ownership :

Own house	1
Renting	2
Live in other's house	3
Social institution	4
Others.....	97

F2.1j Children :

How many children do you have (including the one(s) who passed away)	..... persons
How many children are still alive	..... persons
How many children live nearby (easy to visit)	..... persons

F2

HEALTH STATUS

Important for respondent is they are healthy and never experienced serious illness in the past. This is to confirm (i) their own health, and (ii) to avoid possibility of health problems as confounding factor in study result. Complete this questionnaire fully and clearly to assert the ability to become a participant. Explain clearly and comprehensively whether you have health problems, no serious problems, or in good maintenance (controlled).

F2.2 Health Complaint

		Participant		Caregiver	
<u>At present</u>, do you have any health problem for which you are:		Yes **(1)**	No **(2)**	Yes **(1)**	No **(2)**
a	On medication, prescribed or otherwise (traditional medicine: ask to see boxes etc., write down names of drugs and number)	1	2	1	2
b	Attending your doctor, health provider or traditional healer (and for what)	1	2	1	2
<u>In the past two years</u>, have you had any illness which require you to:					
c	Consult your doctor health provider or traditional healer	1	2	1	2
d	Attend a hospital outpatient department or health centre	1	2	1	2
E	Be admitted to hospital	1	2	1	2

F2.3 Tobacco, Alcohol Consumption and Other Risk Factor for Dementia

F2.3a Have you EVER smoke?

Yes	1
No (**continue to F2.3e**)	2

F2.3b Are you a REGULAR smoker ?

Yes	1
No (**continue to F2.3e**)	2

F2.3c How much do you smoke? (*choose amount of cigarettes and one time frame which respondent remember easily*)

	Yes	Amount
Amount per day	1	..... cigarettes
Amount per week	1	..... cigarettes
Amount per month	1	..... cigarettes

F2.3d Cigarettes type:

Kretek	1
White	2

F2.3e Have you EVER drink alcoholic beverages?

Yes	1
No (**continue to F2.3h**)	2

F2.3f Do you ROUTINELY/ALL THE TIME/OFTEN drink alcoholic beverages?

Yes	1
No (**continue to F2.3h**)	2

F2.3g How much alcohol consumptions you have each week?

1 glass of beer	1
1 glass of wine	2
1 unit of spirits	3
Other, please specify	97

F2.3h Do you drink tea?

GREEN TEA	
Yes	1
No (**continue to F2.3j**)	2
BLACK TEA	
Yes	
No (**continue to F2.3j**)	

F2.3i How much tea you drink? (*conform the answer to glass amount/time frame which respondent remember easily*)

	Yes	Amount
Amount per day	1	..... glass
Amount per week	1	..... glass
Amount per month	1	..... glass

F2.3j Do you drink coffee?

Yes	1
No (**continue to F2.4**)	2

F2.3k How much coffee you drink? (*conform respondent's answer to glass amount/time frame which respondent remember easily*)

	Yes	Amount
Amount per day	1	..... glass
Amount per week	1	..... glass
Amount per month	1	..... glass

F2.4 Are you on hormone therapy in the past 6 months? (e.g. use of hormone (for men), viagra, plants) **circle**

Yes	1
No	2

F2.5 Compare to others:

	More	The same	Less
a. Do you feel happy?	1	2	3
b. Do you feel secure?	1	2	3
c. Do you in stress or anxious?	1	2	3

F2.6 Food Consumption

How much do you consume the following food item		Do you eat it daily? *If yes, ask how many times a day and continue to the next food item*			Days in a week	Days in a month
		Yes, how many times a day		No		
a	Rice	1	.....	2		
b	Fruit/juice	1	.....	2		
c	Orange/red colored vegetables	1	.....	2		
d	Green vegetables	1	.....	2		
e	Fish	1	.....	2		
f	Tempe	1	.....	2		
g	Tahu/Tofu	1	.....	2		
h	Soy milk, other soy product	1	.....	2		
i	Tumeric as jamu (herbal medicine)	1	.....	2		
j	Tumeric as spices	1	.....	2		
k	Tumeric as raw vegetables	1	.....	2		
l	White meat (chicken)	1		2		
m	Red meat (beef/lamb/veal)	1		2		

F2.7 Physical, Mental and Social Activities

F2.7a Your position during activities

Position		Never **(1)**	Seldom **(2)**	Sometimes **(3)**	Often **(4)**	Very often **(5)**
	Sit	1	2	3	4	5
	Stand	1	2	3	4	5
	Walk	1	2	3	4	5
	Lift heavy things	1	2	3	4	5
	Feel tired afterwards	1	2	3	4	5
	Sweat afterwards	1	2	3	4	5

F2

F2.7b Compared to people of you own age, how do you rate your physical activity:

Lighter	1
As heavy	2
Heavier	3

F2.7c Do you play sport regularly:

Yes	1
No **continue to F2.8**	2

F2.7d What kind of sport:

Kind of sport played	Frequency (how often)	Time frame		
		Day	Week	Month
1.	..... times	1	2	3
2.	..... times	1	2	3
3.	..... times	1	2	3
4.	..... times	1	2	3
5.	..... times	1	2	3

F2.8 Mental/Social Activities

F2.8a Do you engaged in the following activities :

	Activities:	Never (1)	Seldom (2)	Sometimes (3)	Often (4)	Very often (5)
a	Read	1	2	3	4	5
b	Write letters	1	2	3	4	5
c	Watch TV	1	2	3	4	5
d	Talk to friends, neighbours or family	1	2	3	4	5
e	Go to gatherings (social)	1	2	3	4	5
f	Pray together	1	2	3	4	5
g	Have dinners with friends/family	1	2	3	4	5
h	Go to theatre /film (ketoprak, ludruk, reog, topeng, lenong)	1	2	3	4	5
i	Go to musical gathering (jaipongan,gending)	1	2	3	4	5
j	Involved in community social activities	1	2	3	4	5

F2.13 INFORMATION FROM CAREGIVER

THE FOLLOWING QUESTIONS ABOUT THE ELDERLY IN LAST COUPLE OF YEARS IS DIRECTED ONLY TO CAREGIVER

F2.13a Does the elderly you care for (the one concerned with this questionnaire) have memory problems :

Yes	1
If yes which? explain	
No, **please continue to F2.13**	2

F2.13b If yes, does it happen consistently

Yes	1
No	2

Appendix E

Activities of Daily Living Questionnaire

No	Function	Points	Criteria
F5.1	Defecation control	0	Irregular/incontinence
		1	Incontinence sometimes (once a week)
		2	Continence
F5.2	Urinate control	0	Incontinence or using catheter and uncontrolled
		1	Incontinence sometimes (max. 1x24 hour)
		2	Independent
F5.3	Ability to clean themselves (wash the face, to comb, brush the teeth)	0	Need help
		1	Independent
F5.4	Toilet use. To go to and from toilet (take off and wear trousers, wipe, flush)	0	Dependent
		1	Need help in some activites but independent in others.
		2	Independent
F5.5	Eat	0	Unable
		1	Need someone to cut the food
		2	Independent
F5.6	Change position from lie down to sit up	0	Unable
		1	Need help to sit (2 persons)
		2	Help from 1 person
		3	Independent
F5.7	Mobility/walking	0	Unable
		1	Use wheel chair
		2	Walk with help from 1 person/walker
		3	Independent
F5.8	Get dressed (put clothes on)	0	Dependent
		1	Partly dependent (e.g. buttoning shirt)
		2	Independent
F5.9	Climb up and down stairs	0	Unable
		1	Need help from others
		2	Independent (climb up and down)
F5.10	Take a bath	0	Dependent
		1	Independent
	Total score		Criteria

ADL Score:
20 : Independent
12-19 : Lightly dependent
9 – 11 : Moderately dependent
5 – 8 : Heavily dependent
0 – 4 : Totally dependent

Appendix F

Instrumental Activities of Daily Living Questionnaire

Activities		Criteria		
F6.1	Extending message/using the telephone	0	I am unable to use the phone	
		1	I am capable of answering phone but unable to operate it	
		2	I am able to operate the phone	
F6.2	Shopping	0	I am unable to do any shopping	
		1	I am capable of purchasing up to 3 items, otherwise I need help	
		2	I do my shopping independently	
F6.3	Preparing meal	0	I am unable to cook	
		1	I am able to cook if the ingredients are ready or to warm cooked food	
		2	I cook independently	
F6.4	Housekeeping	0	I am unable to do the housekeeping	
		1	I am able to do light tasks (sweeping, make the bed) only, but otherwise I need help	
		2	I do the housekeeping independently (capable to do all household tasks including mopping and washing clothes)	
F6.5	Washing clothes	0	I am unable to wash my clothes	
		1	I am able to wash light clothes or ironing, but otherwise need help	
		2	I do my washing independently (using washing machine included)	
F6.6	Utilisation of transportation means	0	I am unable to travel with any transportation means	
		1	I travel on public transport/taxi or private car if I am helped/accompanied by another	
		2	I travel independently	
F6.7	Responsibility of own medication/ preparing own medication	0	I need help from others to prepare and consume my medication	
		1	I am able to take it if medication is previously prepared	
		2	I take my medication independently (I am able to prepared my own medication according to prescribed dose and time)	
F6.8	Ability to handle finances	0	I am incapable at handling my own finances	
		1	I am able to arrange my daily purchases but need help with banking/major purchasing	
		2	I am able to manage financial problems (household budget, pay the rent, receipts, bank matters) or to monitor my income	

Appendix G

SF-36 Questionnaire (Health-related Quality of Life)

1. In general, would you say your health is:	
Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
2. Compared to one year ago, how would your rate your health in general now?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(Circle One Number)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

21. How much **bodily** pain have you had during the **past 4 weeks**?

(Circle One Number)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** . . .

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

How TRUE or FALSE is each of the following statements for you.

(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Appendix H

Randomised Controlled Trial Participant Questionnaire

Participant ID: ……

1. Date of Birth: ……./……./19……

2. Gender (please circle): male / female

3. What is your occupation? (please tick):
Higher manager, admin or professional …
Intermediate manager, admin or professional …
Supervisory or clerical, junior manager, admin or professional …
Skilled manual …
Semi or unskilled manual …
Retired …

4. What is the highest level of education you have completed? (please tick):
Primary …
Secondary …
College, diploma or equivalent …
University Degree (undergraduate) …
University Degree (postgraduate) …

5. What is your marital status? (please tick):
Single…
Married…
Separated…
Widowed…

6. Do you have children? (please circle): yes / no
If yes, how many? ……..

7. Do you or have you in the past suffered from any of the listed medical conditions? (please tick)

- Diabetes mellitus …
- Endocrine problems (prostate/testicular) or hypofunction of the thyroid …
- Coronary heart disease/arrhythmia/ myocardial infarct/stroke …
- Asthma or other lung disease …
- Thrombosis or other blood (clotting) disorder …
- Digestive, gastrointestinal problems …
- Dementia (e.g. Alzheimer's disease) …
- Cancer or benign growths (polyps etc.) …
- Vision / ear / hearing problems …
- Kidney or liver problems …
- Allergies (please state) ……
- Other (please circle): lung or kidney disease, neurological (e.g. epilepsy, or mental health disorders e.g. depression for which you are receiving medical treatment) or (please state)
  ……
  ……

Are you still receiving medical treatment for these conditions now? (please circle) yes / no

8. Do you have any memory complaints? (please circle): yes / no

9. Has anyone in your direct family (e.g. parent, sibling) suffered from dementia or memory problems? (please circle): yes / no

10. Do you have a physically demanding job? (please circle): yes / no

Appendix I

Resistance training exercises

Sit on the floor or mat with your back straight. Wrap your band across the ends of your feet and pull the band towards you. Rotate the top half of your body pulling the band keeping your abdominals pulled in tight. Repeat to the opposite side.

Stand with your feet shoulder width apart and your back almost straight. Wrap your band round the top of your back with either end in your hands. Start with your elbows slightly bent and push your hands out in front of you until your elbows are almost straight.

Stand with a split stance with your front foot over the middle of your band holding either end in your hands by your side. Raise both your arms up to shoulder height and slightly tilt them forwards then slowly back down. Repeat with the other side.

Stand with a split stance with your front foot supporting the middle of your band holding both ends by your side. Curl your arms up to the point of tension bending at the elbows and slowly back down again.

Sit with your knees bent and your back tilted slightly back, wrap your band round one foot holding each end at your knees. Push your leg out straight keeping your grip at your knees and bring back in slowly. Repeat on the other leg.

Stand with a split stance and place your band under your front foot holding either end at the side of your body and bend your legs down into a lunge position. Pull your band tight and push up through your feet to a standing position and slowly back down.

Appendix J

Exercise diaries

Resistance intervention:

Participant ID……..

Week	Date	AM or PM	Resistance level used / # reps	Completed? (tick)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

Flexibility intervention:

Participant ID……..

Week	Date	Time (AM/PM)	Completed?
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			

Appendix K

Hospital Anxiety and Depression Scale

HADS scale

Participant ID: .....

Read each item and place a tick in the box opposite the reply which comes closest to how you have been feeling ***in the past week***. Please don't take too long thinking about your answer.

Tick only one box ☒ in each section

1. I feel tense or wound up:
- Most of the time ☐
- A lot of the time ☐
- Time to time ☐
- Not at all ☐

2. I feel as if I am slowed down:
- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

3. I still enjoy the things I used to enjoy:
- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

4. I get a sort of frightened feeling like butterflies in the stomach:
- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

5. I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

6. I have lost interest in my appearance:
- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

7. I can laugh and see the funny side of things:
- As much as I always could ☐
- Not quite as much now ☐
- Definitely not so much now ☐
- Not at all ☐

8. I feel restless as if I have to be on the move:
- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

9. Worrying thoughts go through my mind:
- A great deal of the time ☐
- A lot of the time ☐
- From time to time but not too often ☐
- Only occasionally ☐

10. I look forward with enjoyment to things:
- As much as ever I did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

11. I feel cheerful:
- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

12. I get sudden feelings of panic:
- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

13. I can sit at ease and feel relaxed:
- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

14. I can enjoy a good book or radio or TV programme:
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

A _____ D _____

Appendix L

Social Support Questionnaire

Please rate on a scale of 1-7 how well your social networks provide the type of support or help that is listed in the left hand column as follows.

1 2 3 4 5 6 7
Never Sometimes Always

To what extent can you:	Friends / Family/ Colleagues		
Trust, talk frankly and share feelings with?	…..	…..	…..
Lean on and turn to in times of difficulty?	…..	…..	…..
Get interest, reassurance and a good feeling about you?	…..	…..	…..
Get physical comfort?	…..	…..	…..
Resolve unpleasant disagreements if they occurred?	…..	…..	…..
Get financial and practical help?	…..	…..	…..
Get suggestions, advice and feedback?	…..	…..	…..
Visit them or spend time with them socially?	…..	…..	…..
Get help in an emergency?	…..	…..	…..
Share interests and hobbies and have fun with?	…..	…..	…..

Appendix M

Lifestyle Questionnaire

Lifestyle Questionnaire

Participant ID: Date: Week:

1. Please state how often **over the past 2 weeks** you have eaten the following foods:

	Every day	More than 4 times per week	1-3 times per week	Once per fortnight	Not at all
Fish	☐	☐	☐	☐	☐
Red meat	☐	☐	☐	☐	☐
White meat	☐	☐	☐	☐	☐
Green vegetables	☐	☐	☐	☐	☐
Red vegetables	☐	☐	☐	☐	☐
Fruit	☐	☐	☐	☐	☐
Rice	☐	☐	☐	☐	☐
Soy product	☐	☐	☐	☐	☐

2. Please state how often **over the past 2 weeks** you have engaged in the following physical activities:

	Every day	More than 4 times per week	1-3 times per week	Once per fortnight	Not at all
Brisk walking	☐	☐	☐	☐	☐
Running	☐	☐	☐	☐	☐
Gardening	☐	☐	☐	☐	☐
Housework	☐	☐	☐	☐	☐
Hiking	☐	☐	☐	☐	☐
Swimming	☐	☐	☐	☐	☐
Sport	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

If 'sport' or 'other', please specify:

3. Please state how often over the past 2 weeks you have engaged in the following social activities:

	Every day	More than 4 times per week	1-3 times per week	Once per fortnight	Not at all
Visit from another	☐	☐	☐	☐	☐
Visit to another's home	☐	☐	☐	☐	☐
Lunch in café, restaurant etc	☐	☐	☐	☐	☐
Evening meal at restaurant etc	☐	☐	☐	☐	☐
Shopping	☐	☐	☐	☐	☐
Social club	☐	☐	☐	☐	☐
Day trip	☐	☐	☐	☐	☐
Phone call for social purpose	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

If other, please specify:

Do you smoke? Yes ☐ No ☐
If yes, how many cigarettes on average have you smoked per day over the past 2 weeks?

Do you drink alcohol? Yes ☐ No ☐
If yes, please state approximately how many units have you consumed over the past 2 weeks?

Do you drink tea or coffee? Yes No
If yes, please state approximately how many cups you have consumed per day over the past 2 weeks?
Tea
Coffee