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Lifestyle factors and Alzheimer-type dementia: The link between exercise and cognitive change.

Nicolas Farina

Statement

I hereby declare that this thesis has not been and will not be, submitted in whole or in part to another University for the award of any other degree.

Nicolas Farina

Acknowledgements

UNIVERSITY OF SUSSEX

Nicolas Farina

Thesis submitted for the degree of Doctor of Philosophy

Lifestyle factors and Alzheimer-type dementia: The link between exercise and cognitive change.

Summary

Alzheimer's disease (AD) is a neurodegenerative disorder that results in cognitive and functional impairment. Current pharmacological treatments have limited effect on correcting cognitive deficits. However, there is a growing amount of literature to suggest that lifestyle factors, such as physical activity, may have a positive effect on cognitive function for people with AD. Through a series of four articles I have addressed methodological short-comings in the existing literature, and determined, through collection and analysis of data in a longitudinal cohort study, the impact of lifestyle factors on cognitive performance in AD.

Article I systematically reviews previous physical activity intervention trials and their effects on cognition in an AD population. Physical activity interventions were found to have a moderately positive effect on global cognition. However, the review highlights the apparent heterogeneity between intervention trials as well as the lack of domain specific cognitive outcome measures.

Article II focuses on the importance of sensitive measures of cognition in an AD population. Comparing people with AD and age-matched control volunteers, measures of prospective memory were shown to decline with age in the AD volunteers. Significantly, the cost of carrying a PM intention, a measure of working memory, did not exhibit an age related decline and did not differ compared to cognitively healthy controls.

Article III explores whether habitual physical activity, is significantly associated with cognitive outcome on a composite measures of executive function. Habitual physical activity significantly accounted for variance (8%) on executive function even after controlling for covariates.

Article IV investigates the contribution of habitual physical activity to executive function change in AD over a year. Habitual physical activity was found to be associated with executive function change.

These articles contribute in the understanding of the association between habitual physical activity and cognitive function in an AD population.

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A Introduction and Overview

A.1 Outline of Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that results in cognitive and functional decline. In 2010 it was estimated that there were 35.6 million individuals diagnosed with dementia, and this number is expected to increase to 115.4 million by 2050. The concern is that at present there are no effective pharmacological treatments for AD. Therefore there is need to explore alternative interventions to sustain cognitive function or slow down decline.

Lifestyle factors such as physical activity, diet, cognitive activities and social network size have all been implicated in affecting cognitive function in healthy older adults. The primary concerns presented in this thesis address whether lifestyle factors such as physical activity affect cognitive function in an AD population. Therefore I will begin by reviewing literature that has previously explored the effects of lifestyle factors on cognition in AD. I will then further explore the importance of measuring specific cognitive measures and the association between habitual physical activity and executive function. Finally, I will explore the role of habitual physical activity in sustaining cognitive performance in an AD population.

A.2. Assessing Cognitive Performance in Ageing and Dementia

As cognitive decline is the primary symptom of AD, it is important to establish the common methods by which cognitive impairment is assessed in an elderly population. In this section, the most popular cognitive assessment tools used to measure and screen for cognitive impairment will be reviewed.

The mini-mental state examination (MMSE; Folstein, Folstein, & McHugh, 1975) is the most widely used cognitive screening tool (Shulman et al., 2006). The MMSE assesses orientation, memory, attention and calculation, language and visual construction. Participants are able to score a minimum of 0 and maximum of 30. A cut-off score of 24-25 on the MMSE provides a reliable diagnosis of dementia with high sensitivity, specificity and diagnostic value (Stuss, Meiran, Guzman, Lafleche, & Willmer, 1996). The tool's popularity is in part due to its ease of administration without the need for

extensive training, and as a consequence the MMSE has been validated in many languages (e.g. Beaman et al., 2004; Foroughan, Jafari, Shirin, Ghaem Magham Faraahani, & Rahgozar, 2008; Rakuša, Granda, Kogoj, Mlakar, & Vodušek, 2006). However, there are several weaknesses of the MMSE. Age and education alone accounts for 12% of the variance of MMSE scores (Bravo & Hébert, 1997) and as such ideal cut-offs to screen for cognitive impairment vary according to the populations demographics (Bertolucci, Brucki, Campacci, & Juliano, 1994; Crum, Anthony, Bassett, & Folstein, 1993; Lourenço & Veras, 2006; Uhlmann & Larson, 1991). Other demographic factors such as being a non-native English speaker and being from certain ethnicities have been implicated in influencing the performance on the MMSE (Escobar et al., 1986; Ng, Niti, Chiam, & Kua, 2007; Vertesi et al., 2001). In addition, the MMSE suffers from floor effects in advanced dementia and ceiling effects in very mild dementia (for review see Simard, 1998). The MMSE also does not contain much capacity to test certain cognitive domains such as executive or visuospatial functions (Woodford & George, 2007).

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was initially designed to screen for cognitive impairment. Similar to the MMSE, the MoCA is a relatively short tool scored out of 30. In fact, there are many similar item themes between the two tasks, including: attention, language, memory and orientation. However, the MoCA improves upon the MMSE by including a measure of executive function. Such an inclusion provides a more 'complete picture' of cognitive impairment exhibited in dementia, particularly as executive dysfunction is present from very early on in the disease process (Binetti et al., 1996; Collette, Van der Linden, & Salmon, 1999). MoCA though more sensitive than the MMSE (0.97 vs 0.65) is less specific (0.60 vs 0.89; Larner, 2012).

The Alzheimer's Disease Assessment Scale-Cognitive subsection (ADAS-Cog; Rosen, Mohs, & Davis, 1984) is one of the most administered cognitive outcomes in AD clinical trials. The ADAS-Cog includes seven items and four clinician-rated items assessing memory, language, praxis and orientation. Compared to the MMSE and MoCA, the ADAS-Cog measures a broader range of cognitive domains, however, the tool still under-evaluates executive function, attention and semantic memory (Simard & van Reekum, 1999). Participants can score from 0 to 70, with higher scores (>18)

indicating greater cognitive impairment. The availability of alternative forms is also advantageous for longitudinal studies that require repeat testing, as it reduces the chance of practise effects. Another strength of the ADAS-Cog is that the demographic variables such as age and education do not seem to significantly affect ADAS-Cog performance (Pyo, Elble, Ala, & Markwell, 2006).

The Addenbrooke's Cognitive Examination-Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) was designed as a brief bedside cognitive screening instrument. The ACE-R is scored out of 100 and consists of six cognitive components including; orientation, attention, memory, verbal fluency, language and visuospatial ability. One of the key strengths of ACE-R is the ability to extract subscale information about the six cognitive components (Crawford, Whitnall, Robertson, & Evans, 2012). The ACE-R can be completed in around 10-15 minutes (Larner, 2007) and has an excellent sensitivity and specificity for the diagnosis of dementia at a cut-off of 88/100 (Mioshi et al., 2006).

A.3. Current Treatments

At present there are four drugs licensed to treat AD in the UK for the management of AD; Donepezil, Galantamine, Rivastigmine and Memantine (NICE, 2011).

A.3.1. Acetylcholinesterase inhibitors (AChEIs)

Neurochemical studies of those with AD have found that there is a decreased production of acetylcholine and cortical cholinergic dysfunction (for a review see Francis, Palmer, Snape, & Wilcock, 1999). This has led to the research into therapies that are able to increase levels of acetylcholine in AD. AChEIs sustain acetylcholine in the synaptic cleft by reducing the enzymatic breakdown of acetylcholine, thereby enhancing signalling between neurons (for a review see Benzi & Moretti, 1998). Donepezil, Gelantamine and Rivastigmine are the only licenced AChEIs for the treatment of AD in the UK (NICE, 2011).

Evidence suggests that these AChEIs have positive effects on cognitive function in AD. A meta-analysis of the literature has found that the mean proportion of cognitive responders (as defined a 4-point or greater improvement on the ADAS-cog) to AChEI treatment in excess of placebo treatment

was 10% (Lanctôt et al., 2003). In a more recent systematic review, Birks (2006) confirms that AChEIs do have a beneficial effect on cognition compared to placebo, though the treatment effect is not large. However, some researchers still criticise the use of AChEIs as they tend to only have minimal beneficial effects (Kaduszkiewicz, Zimmermann, Beck-Bornholdt, & Bussche, 2005).

In addition to the limited benefits on cognition, the AChEIs are also associated with adverse events which typically are a result of increased central and peripheral concentrations of acetylcholine. In a meta-analysis of the safety of Donepezil, Galantamine and Rivastigmine found that 76% of participants reported at least one adverse event (Hansen et al., 2008). With nausea (19%), vomiting (13%), diarrhoea (11%), dizziness (10%) and weight loss (9%) being the most common adverse events. Another meta-analysis of studies also found that patients on AChEIs were more likely to withdraw from the drug than from placebo (OR 2.32, 95% CI 1.95-2.76, p <.00001) (Birks, 2006).

A.3.2. Memantine

Memantine is the only medication currently licenced for treatment in those with moderate to severe dementia and for those who are unable to take AChEIs (NICE, 2011). Memantine is a partial *N-methyl-D-aspartate* (NMDA) receptor antagonist. In doing so it prevents the excess stimulation of the glutamate system, reducing glutamate mediated neurotoxicity, which is associated with the pathogenesis of AD (Parsons, Danysz, & Quack, 1999).

Systematic reviews of the RCT literature reveal that in moderate to severe AD, memantine showed statistically significant benefits versus placebo on measures of cognition (McShane, Areosa Sastre, & Minakaran, 2006; Winblad, Jones, Wirth, Stöffler, & Möbius, 2007). More recent reviews of the literature support the notion that memantine has a positive effect on cognition in an AD population compared to placebo (Van Marum, 2009; Wilkinson, 2012). Although not the primary population for prescription, some studies have also found that memantine has a positive effect on cognition in a mild to moderate AD population (Bakchine & Loft, 2008; Peskind et al., 2006). However, a review of the literature has concluded that the evidence is still lacking in this population (Schneider, Dagerman, Higgins, & McShane, 2011).

In previous trials memantine has consistently been found to be well tolerated and safe (Ditzler, 1991; Reisberg et al., 2006; Rossom & Dysken, 2004). A systematic review of adverse events revealed that patients taking memantine experienced nausea, dizziness, diarrhea and agitation (Raina, 2008). However, it has been found that the number of adverse events reported in memantine treatment does not significantly differ to those receiving a placebo (e.g. Orgogozo, Rigaud, Stöffler, Möbius, & Forette, 2002).

A.4 Lifestyle factors and cognitive performance in AD

There is growing evidence to suggest that lifestyle factors may be beneficial to cognitive outcome in an AD population. In this section the current state of literature surrounding some key lifestyle factors (diet, cognitive activities, social network and physical activity) will be reviewed. Although there is a wealth of literature on the effects of these lifestyle factors on cognitive performance in healthy older adults, the focus will primarily be the effects on reducing the risk of disease onset and disease progression. This was decided because age related cognitive decline pathologically differs to cognitive decline associated with the onset and subsequent progression of AD (Ghosh, Agarwal, & Haggerty, 2011), and consequently mechanisms of effect may also differ.

A.4.1 Mediterranean Diet

The Mediterranean diet (MeDi) has been associated with a reduced risk of a range of age-related conditions, including; stroke, type 2 diabetes and coronary heart disease (Willett, 2007). As a result it is considered one of the healthiest dietary patterns worldwide. Traditionally, MeDi refers to a diet profile characterized by a high intake of fruit, vegetables, cereals, legumes and nuts, a high intake of olive oil but a low level of saturated fats, a low intake of meat and poultry, moderately high intake of fish, a low-to-moderate intake of dairy products, and a moderate intake of alcohol (Trichopoulou, Costacou, Bamia, Trichopoulou, & Trichopoulos, 2003).

In an AD population adherence to a MeDi is significantly lower compared to healthy controls (Gardener et al., 2012). Compared to the lowest tertile, adhering to the highest tertile of MeDi have been found to reduce to reduce the risk of developing AD by 34-40% (Gu, Luchsinger, Stern, & Scarmeas, 2010; Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006). Scarmeas and colleagues specifically noted that each additional unit of the MeDi score was associated with 9-10% less risk of developing AD. Such beneficial effects are in line with other research which has found that each unit score for adherence to a MeDi was associated with a 19-26% reduced odds of having AD (Gardener et al., 2012). However, not all literature supports the beneficial effects of adhering to a MeDi on AD outcome. Féart and colleagues determined that adhering to a MeDi is not associated with incident dementia (Féart et al., 2009), though the study did not distinguish between dementia subtypes. A meta-analysis of the literature found that a 2-point increase in score for adherence to a MeDi reduced the risk of AD and Parkinson's Disease by 13% (Sofi, Cesari, Abbate, Gensini, & Casini, 2008). An updated review of the literature by the same group had similar findings, with a 2-point increase in score for adherence to a MeDi reducing the risk of neurodegenerative disease by 13% (Sofi, Abbate, Gensini, & Casini, 2010).

To date, no literature has explored the association between adherence to a MeDi and cognitive decline in an AD population.

A.4.2. Social Network

Social network is defined as the structure comprising an individual's social ties and the ties among them (Gottlieb & Bergen, 2010), but also provides information about social integration and social support. In older adults (65+) never being married resulted in having 2.68 times the risk of developing AD compared to individuals who were married or cohabiting (Helmer et al., 1999). Apart from one notable exception (Yoshitake et al., 1995), not being married has repeatedly been shown to increase the risk of dementia (Bickel &

Cooper, 1994; Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Van Gelder et al., 2006). However, social network extends greater than marriage alone. Older adults that report that they are lonely have also been found to have twice the risk of developing AD compared to those that were not lonely over 4 years (Wilson, Krueger, et al., 2007). A poor or limited social network has also been found to increase the risk of dementia by 60% over a 3 year period (Fratiglioni et al., 2000). Having a larger social network also appears to have a protective effect against AD and dementia. Crooks and colleagues found that those that report a larger social network, in a population of 2259 elderly women, had a decreased incidence of dementia development (HR, 0.74; 95% CI, 0.57-0.97) (Crooks, Lubben, Petitti, Little, & Chiu, 2008). It has also been found that compared to individuals that do not participate in any social activity, socialising occasionally (less than weekly; RR=0.92) and frequently (RR=0.58) was associated with a reduced risk of developing dementia (Wang, Karp, Winblad, & Fratiglioni, 2002). However, Amieva and colleagues have argued that social network size alone is insufficient to protect against dementia (Amieva et al., 2010). The authors found that individuals that were very satisfied in the quality of the support their social network provided had a 23% reduced risk of developing dementia compared to those that perceived there social support as poor or not satisfied (Amieva et al., 2010). Caution should be taken when interpreting these findings as the majority of studies do not differentiate between dementia subtypes.

Regardless of the evidence to suggest that social network may have a protective role (for a review see Fratiglioni, Paillard-Borg, & Winblad, 2004), to my knowledge there is currently no published research within an AD population about the potential effects of social network on trajectory of cognitive outcome. However, current research is taking place in Sussex to assess the impact of social network on rate of cognitive decline in AD patients (Personal Communications- Dr Tabet).

A.4.3 Cognitive Activity

It has been found that people participating in cognitive activities in older age have reduced risk of AD (Wilson et al., 2002). Wilson et al. (2002) found that after controlling for age, sex and education, a 1 point increase in cognitive activity was associated with a 33% decrease risk of AD (HR, 0.67; 95% CI, 0.49-0.92). More recently, Wilson and colleagues supported their initial findings by determining that more frequent participation in cognitive activities again was associated with a reduced incidence of AD (HR=0.58; 95% CI: 0.44-0.77) after controlling for age, sex and education (Wilson, Scherr, Schneider, Tang, & Bennett, 2007). Stern and Munn (2010) in a systematic review of the literature found that participating in cognitive activities throughout adulthood is beneficial in reducing the risk of AD, although the evidence is not strong enough to infer causality.

Helzner and colleagues measured participation in various leisure activities prior to diagnosis of AD and followed participants up for an average of 5.8 years (Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007). It was found that more time spent participating in intellectual activities prediagnosis increased the rate of cognitive decline over the course of the study, specifically an additional decline of 0.03 of a z-score unit per activity per year. The authors argued that these intellectual activities acted as a proxy for cognitive reserve and as a result individuals are able to compensate the effects of AD pathology for longer. Hence, by the time of diagnosis individuals with greater cognitive reserve are relatively more advanced in AD neuropathology and may have a faster subsequent rate of decline. A similar finding by Wilson and colleagues noted that a one point increase in premorbid cognitive activity levels was associated with a 42% increase in mean rate of global cognitive decline per year in AD (Wilson et al., 2010). Even on the basis of retrospective reports of reading activity, increased premorbid reading levels have been found to be associated with a rapid global cognitive decline in AD population (Wilson et al., 2000). Evidence that premorbid cognitive activities

cause a greater cognitive decline post diagnosis supports the notion that cognitive activities may combat the initial symptoms of cognitive decline in AD. There is also evidence to suggest that participating in cognitive activities post diagnosis may combat cognitive decline. Treiber and colleagues found that engaging in cognitive activities early in the course of the disease (mean CDR = 1.4) was associated with a slower cognitive decline (Treiber et al., 2011).

A variety of cognitive-based interventions, referred to as cognitive training, have also been developed in the effort to combat the onset of AD and subsequent progression of the disease. Cognitive training typically is an intervention technique that teaches theory-based skills and strategies that are aimed at specific or multiple cognitive domains (Belleville, 2008). A systematic review of controlled studies of cognitive training (as defined as "any non-pharmacologic intervention designed to improve cognitive functioning, regardless of mechanism") in an AD population revealed that cognitive training had a positive effect (0.38) on general cognitive function (Sitzer, Twamley, & Jeste, 2006). A critical analysis of the literature also supports the beneficial effect of cognitive training in AD (Yu et al., 2009). However, a more recent systematic review of RCTs determined that there was no positive or negative effect of cognitive training on global cognition (Bahar-Fuchs, Clare, & Woods, 2013). It should be noted that the latter systematic review limited the study population to mild to moderate AD and vascular dementia, whilst cognitive training was defined as structured tasks and environments focussed in isolated cognitive abilities and processes. Such discrepancies and make comparisons between the two reviews more difficult.

A.4.4 Physical Activity

In older adults (65 years old +), adhering to higher levels of physical activity (as defined as engaging in exercise 3 or more times a week at an intensity more than walking) was associated with a reduced risk of AD (OR, 0.50; 95% CI, 0.28-0.90; Laurin, Verreault,

Lindsay, MacPherson, & Rockwood, 2001). Similar protective effects have been found in older adults that adhere to some physical activity (0.1 hours of vigorous, 0.8 hours of moderate, or 1.3 hours of light, or a combination) compared to those that do not adhere to any physical activity (HR, 0.75; 95% CI, 0.54-1.04; Scarmeas et al., 2009). A systematic review of the prospective literature found that healthy elderly participants that adhered to the highest physical activity category compared to the lowest had a significantly reduced risk of developing AD (RR, 0.55; 95% CI, 0.36–0.84; Hamer & Chida, 2009).

In an AD population a range of studies have investigated the effects of physical activity interventions on cognition, in a single cohort design. Some of the research have reported a significant improvement on cognitive measures between baseline and following intervention (Palleschi et al., 1996; Rolland et al., 2000), whilst others found no difference in cognitive performance (Frederiksen et al., 2012; Hokkanen et al., 2003; Yu, Leon, et al., 2011). As these studies did not have any control groups, it is difficult to ascertain whether physical activity interventions combatted cognitive decline in these studies. The small sample size of the studies, ranging from 4 participants (Hokkanen et al., 2003) to 23 participants (Rolland et al., 2000), also means that caution should be taken with regards to the over interpretation of this literature due to publication bias.

A series of RCTs, a methodologically stronger intervention design type, have also been conducted in an AD population and *Article I* in this thesis reports a systematic review of the literature.

Several studies have also sought to investigate the association between physical activity and cognition in an AD population using measures of habitual physical activity. Burns and colleagues investigated the effects of cardiovascular fitness, a proxy measure of aerobic physical activity, on a series of cognitive measures in an early AD population (mean MMSE

= 26.2) (Burns et al., 2008). After controlling for age, cardiorespiratory fitness did not significantly correlate with any cognitive measure. However, when explored longitudinally for 2 years there was an association between baseline cardiorespiratory fitness and change in dementia severity (Vidoni, Van Sciver, et al., 2012). The positive effects of physical activity on cognition in AD can also be observed in studies that use subjective reports of physical activity. For example, Winchester and colleagues measures informant based reports of walking activities in a mild to moderate AD population (MMSE > 18; Winchester et al., 2013).

A.4.4.1 Summary of Article I

When reading through the literature, it was apparent that there was a lot of potential for physical activity to have a positive effect on cognition in an AD population. However, I did notice that reviews conducted in the area were not specific enough to allow for the best interpretation. Most notably previous reviews have neglected to 1) differentiate between AD and other dementias; 2) differentiate between purely physical interventions and those that incorporated cognitive stimulation too. As outlined in *Article I* (Chapter B) a systematic review was conducted on RCTs that explored the effects of physical activity on cognitive outcome in an AD population. I was able to conclude that physical activity interventions had a positive effect on global cognitive function, though heterogeneity between study designs prevented specific conclusions to be made about specific intervention types and durations. In addition, the use of global cognitive measures prevented conclusions to be made on domain specific outcomes.

A.5. Domain specific effects

Many authors have previously attempted to measure cognition as a single term. However, this has led to an oversimplification of a very complex process and as a result some researchers

have opted to use a single test as an absolute outcome. In reality cognition is an umbrella term for a whole host of domains which can be individually defined and measured. In addition, individuals with AD show different levels of impairments in different domains through the course of the disease.

A.5.1. Domain specific deficits in Alzheimer's disease

Whilst cognitive decline is symptomatic of AD, deficits do not occur in all cognitive domains, with some domains remaining relatively intact. In this section I will focus on two particular domains memory (episodic memory, semantic memory and prospective memory) and executive processes (executive function, working memory and attention).

Episodic memory loss is one of the defining features of AD. Episodic memory deficits occur very early in the course of the disease with impairment being observed in preclinical AD several years prior to diagnosis (Bäckman, Small, & Fratiglioni, 2001). Compared to an older healthy population (> 75 years old), patients with mild AD (< 75 years old) were significantly impaired (Cullum, Filley, & Kozora, 1995). The ability to retain new information after a delay has consistently been shown to be a sensitive measure of early AD (e.g. Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Greene, Baddeley, & Hodges, 1996; Locascio, Growdon, & Corkin, 1995; Perry & Hodges, 2000)

Prospective memory has been defined as the act of "remembering to do things in the future". Individuals with AD have subjectively reported more PM failures compared to both age-matched healthy controls and those with MCI (Eschen, Martin, Schreiter-Gasser, & Kliegel, 2009). Such subjective reports have been confirmed through objective measures. PM impairment has been reported in mild AD (MMSE= 15-24) using a range of tasks (e.g. Martins & Damasceno, 2008, 2012).

Semantic memory is defined as our permanent store of representational knowledge, including facts and the meaning of words (Chertkow & Bub, 1990). Like episodic memory and prospective memory, semantic memory also shows deficits in an AD population (Salmon, Butters, & Chan, 1999). Using a range of semantic memory measures 'very minimal' AD patients (MMSE > 23) were found to be impaired on four out of six semantic memory measures compared to healthy controls (Hodges & Patterson, 1995). As semantic deficits do not always exist across all semantic tasks, it has been proposed by several authors that the deficits occur in a hierarchical fashion (Hodges, Salmon, & Butters, 1992; Martin & Fedio, 1983; Salmon et al., 1999), primarily affecting subordinate information (e.g. *the cat meows*) first and superordinate knowledge (e.g. *the cat is a mammal*) later on in the disease. Regardless of the specific dysfunction within semantic memory, deficits have been found to be present very early in the course of the disease and even during MCI stages (e.g. Adlam, Bozeat, Arnold, Watson, & Hodges, 2004).

During clinical observations of dementia patients it has been noted that individuals have difficulty concentrating and fatigue easily (Lezak, 2004). In part this can be attributed to deficits of attention. A range of attentional deficits have been reported in an AD population (e.g. Filoteo et al., 1992; Levinoff, Saumier, & Chertkow, 2005; Nebes & Brady, 1989). Specifically mild AD patients (mean CDR = 0.68) have been reported to have significantly impaired performance compared to controls on measures of sustained attention, divided attention, selective attention and visual processing speed (Rizzo, Anderson, Dawson, Myers, & Ball, 2000). Deficits in attention are particularly important in AD as it influences other domains such as memory (Simone & Baylis, 1997).

Executive control is involved in the planning, initiation and regulation of behaviour (Lezak, 2004). Often the terms executive function and attention are used in conjunction, with reviews noting that attention and executive processes are substantially and broadly impaired in an AD

population (Perry & Hodges, 1999). Research indicates that executive deficits occur relatively early in the disease course (Binetti et al., 1996; Collette et al., 1999). Other studies have determined that even prior to the clinical diagnosis of AD executive deficits have been reported, with executive tasks being useful in discriminating those who will convert into AD (Albert, Moss, Tanzi, & Jones, 2001). Executive deficits have been reported in those who went on to develop AD 6 months after testing compared to participants that did not develop the disease (Sgaramella et al., 2001). Executive dysfunction has also been found to be associated with dementia severity and worse overall cognitive status in an AD population (MMSE > 10; Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004). However, it has been argued that some individuals with AD who exhibit very prominent executive dysfunction may have a frontal variant of AD, with those with frontal variant having significantly higher neurofibrillary tangle load in the frontal cortex compared to those with typical AD (Johnson, Head, Kim, Starr, & Cotman, 1999).

Working memory (WM) is the temporary storage of information required for performance of other cognitive tasks (Baddeley, 1992) or the ability to maintain information in a quickly retrievable state (Engle, 2002). Digit and word span task performance is a common measure of WM, which has often been found to be impaired in early AD compared to healthy older adult controls (e.g. Becker, 1988; Cherry, Buckwalter, & Henderson, 1996). Whilst some studies have reported no difference in performance between the two groups (e.g. Lines et al., 1991; Orsini, Trojano, Chiacchio, & Grossi, 1988; Perry, Watson, & Hodges, 2000), this is likely to reflect the different definitions of disease severities (Huntley & Howard, 2010). Huntely and Howard also highlight that during the very earliest stages of the disease WM remains intact but subsequently significantly declines in the mild to moderate stages of the disease.

A temporal order of cognitive deficits has been identified in AD for some of the more prominent cognitive domains with deficits occurring in episodic memory first, followed by semantic memory, and then attention and executive dysfunction (Carter, Caine, Burns, Herholz, & Ralph, 2012).

A.5.1.1 Summary of Article II

It was made evident from *Article I* that there is an over-reliance on measuring global cognitive outcomes, though as stated previously (A.5.1), individual cognitive domains are differentially affected by AD. In *Article II* (Chapter C) I highlight the importance of testing domain specific measures in an AD population in order to support the focus on a specific cognitive domain rather than global cognition. The study was composed of three groups; younger older adults, younger AD and older AD. All participants were given a battery of PM tasks. In all measures of objective and subjective PM the younger older adults performed significantly better compared to both AD groups. One PM task, the card sort task, involved participants to sort cards into the appropriate suits in the first trial, and in the second trial participants identify the number '7' cards (PM target) in addition to sorting the cards into the appropriate suits (ongoing task). Through the subtraction of reaction times between the two trials cost of carrying a PM intention can be calculated. The cost of carrying a PM intention did not differ between the young older adults and the AD groups, highlighting a unique dissociation. In addition, only the subjective measures of PM declined between younger AD and older AD groups.

The findings indicate that although PM is impaired in AD, this is not due to the PM intention not being held. As a result future studies should ensure that cost of carrying a PM intention is measured alongside PM accuracy measures in an AD population.

A.5.2 Evidence of selective effects on cognition of physical activity

As previously mentioned (A.3.4) there is substantial evidence to suggest that being physically active can delay the onset and positively affect cognition in AD. It was initially noted by Kramer and colleagues that aerobic physical activity in healthy older adults selectively affects tasks requiring executive control (Kramer et al., 1999). Smiley-Oyen and colleagues more recently confirmed that a 10 month aerobic intervention had the greatest effect on the cognitive tasks that required the greatest executive control (Smiley-Oyen, Lowry, Kohut, & Ekkekakis, 2008). A series of meta-analyses have been conducted that have investigated whether physical activity RCTs have a selective effect on cognition in healthy older adults. An earlier meta-analysis of the literature found that physical activity had the greatest effect on executive function (Colcombe & Kramer, 2003). However, more recent meta-analyses have not supported such findings. Angevaren and colleagues found that motor function and auditory attention were the most greatly affected by physical activity (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008), whilst Smith and colleagues found that alongside executive function, memory and attention/processing speed also benefited from physical activity interventions (Smith et al., 2010).

Literature from a MCI population can also provide an insight into the selective effects of physical activity. In the same meta-analysis by Smith and colleagues the authors found that compared to healthy older adults, physical activity has a greater positive effect on memory in those with MCI (Smith et al., 2010). Physical activity also had a positive effect on executive function and attention/processing speed in the MCI population; however compared to a healthy population the improvements in executive function were smaller. In another meta-analysis of the MCI literature, Gates and colleagues separated executive outcomes based on task (Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013). The study found that physical activity only had a significant positive effect on verbal fluency.

Unfortunately, as noted in *Article I* (Chapter B) research within an AD population tends to measure global cognitive function rather than considering specific cognitive domains. Preliminary evidence at least can confirm that a physical activity intervention can sustain executive function in an AD population (Yu et al., 2013), however further research is needed to determine whether habitual physical activity is associated with executive function using a range of measures.

A.5.2.1 Summary of Article III

In this study, the aim was to determine whether habitual physical activity was significantly associated with executive function in an AD population (Chapter D). A single composite measure of executive function was created. A multistage multiple regression model was conducted with the composite measure of executive function as the dependent variable. After controlling for disease severity, cognitive reserve, cognitive stimulation and neuropsychiatric symptoms habitual physical activity significantly accounted for variance (8%) of executive function. The findings show that habitual physical activity status is associated with sustained executive function.

A.6. Effects of habitual physical activity on cognitive change over time

Whilst single time-point snapshots are important in determining associations between variables, it is important to determine whether the habitual physical activity is able to sustain cognitive processes over time. This is primarily for two reasons. First, as AD is a neurodegenerative disease, cognitive performance is set to decline over time. Therefore establishing whether habitual physical activity can combat this decline is an important question. Second, as habitual physical activity is tied to an individual's physical capability and motivation it is susceptible to be affected by many factors, particularly related to age. It is therefore important to establish whether habitual physical activity is able to combat cognitive

decline in the knowledge that the level of activity is also likely to decline as the disease progresses.

A.6.1 Defining the Trajectory of Change

An important consideration when investigating cognition in an AD population longitudinally is trajectory of the disease. In an AD population there have been varying reported rates of global cognitive decline. Over an average of 2.4 years, individuals with mild to moderate AD (MMSE >10) show an annual MMSE decline of 3.4 points (Clark et al., 1999). Xie and colleagues found similar rates of decline in mild to moderate AD group (Mean MMSE = 18), with an annual decline of 2.15 points over two years (Xie et al., 2009). Similar rates of decline have been reported in severe AD patients (Mean baseline MMSE = 9.9) with an average annual decline of 2.2 points during a 3 year period (Holmes & Lovestone, 2003).

However, some authors have found that the rate of decline is not always linear throughout the course of the disease. For example, Holmes & Lovestone (2003) found that cognitive decline was greatest in the first year of testing (annual MMSE decline of 2.4 points) but then only declined 1.9 points during the second year and 1.4 points during the third year. Xie et al. (2009) found an average annual decline of 2.15 points in the first two years, then subsequently increased to 3.83 points per year for the next 3 years and then changed to 1.63 points during the last 2 years of the study. Cortes and colleagues also noted that their AD population (Mean MMSE = 20.01) on average declined 4.57 MMSE points over a 2 year period (Cortes et al., 2008). However, the authors noted that participants could be categorised into different rates of cognitive decline. Just over 10% of patients declined more than 9 points over the 2 years, 56.89% reported a loss of 3 to 9 points, whilst 23.32% were stable or improved. Wilkosz et al. (2010), in support for different disease paths, identified six separate disease trajectories of MMSE decline over 13.5 years in an AD population. The authors also determined that age, initial MMSE and psychotic symptoms best defined cognitive trajectory.

Evidence of varying and non-linear cognitive trajectories was supported by the presence of cognitive plateaus in which cognitive performance remained relatively stable (Bozoki, An, Bozoki, & Little, 2009; Haxby, Raffaele, Gillette, Schapiro, & Rapoport, 1992; Piccini, Bracco, Falcini, Pracucci, & Amaducci, 1995). In a sample of 243 moderately severe AD patients (mean MMSE = 17.0), 22% of individuals exhibited a cognitive plateau, of which half lasted as long as the patient was enrolled in the study (average 4.3 years) (Bozoki et al., 2009). In addition, the authors also noted that those that did not exhibit a plateau in cognition had a slightly higher dementia severity at baseline compared to those who did, with the highest cases of plateaus occurring at the mild stages (CDR=1).

Notably very little research has investigated the rate of decline for individual cognitive domains in an AD population.

A.6.2 Physical activity and trajectory

Very limited research exists in an AD population about the effects of habitual physical activity on cognitive change over time. Initial evidence determines that habitual physical activity level measured prior to the onset of AD does not predict rate of cognitive decline following onset (Scarmeas et al., 2011). Winchester et al. (2013) determined that AD patients who were doing 2+ hours of walking per week significantly improved in cognitive performance over a year, whilst those that did no walking showed a significant decline in cognition. Whilst such findings are positive there are notably several shortcomings to the research; 1) MMSE was the only measure of cognitive outcome; 2) habitual physical activity only considered walking habits; 3) at baseline MMSE differentiated the sedentary and the walking groups. Vidoni et al. (2012) also found that there was an association between baseline cardiorespiratory fitness and dementia severity change over 2 years. The use of cardiorespiratory fitness provides a broader insight into the physical habits of the AD

population compared to walking alone (as measured by Winchester et al., 2013), however such a measure is only provides an insight into aerobic physical activity.

A.6.2.1. Summary of Article IV

In *Article IV,* the same AD cohort as reported in *Article III* was followed up one year later (Chapter E). Structural equation modelling (SEM) was utilised to determine whether habitual physical activity was associated with executive function change over the year. In the final model a significant path was found between habitual physical activity status and executive function change even after controlling for key confounding variables. A subsequent cross-lagged panel analysis supported the findings from the SEM.

B. **Article I:** The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review[1]

C. **Article II:** Prospective Memory in Alzheimer-type dementia: Exploring prospective memory performance in an age-stratified sample [2]

D. **Article III:** Habitual physical activity (HPA) as a factor in sustained executive function in Alzheimer-type dementia: A cohort study.[3]

E. **Article IV**: The relationship between habitual physical activity and executive function in an Alzheimer's Population: A longitudinal, cross-lagged panel analysis.

Abstract

Background: In Alzheimer's disease (AD) it is important to understand which factors can alter the trajectory of cognitive decline. Evidence suggests that physical activity levels are associated with global cognitive change in AD (Winchester et al., 2013). The aim of this study was to determine whether habitual physical activity specifically influences executive function change in AD over 1 year.

Methods: Eighty-five participants were recruited at baseline and 45 participants were followed up 1 year later. Executive function measures (map search task, digit symbol substitution task, controlled oral word association task, verbal fluency task) and habitual physical activity measures (physical activity scale in the elderly (PASE) and handgrip strength) were taken at baseline and follow up. Individual composites were subsequently created. Additional demographic, lifestyle and neuropsychiatric measures were also taken.

Results: In a structural equation model (χ^2 (26) = 9.84, p = .998, CFI = 1.00, RMSEA = .00) a significant association was found between habitual physical activity and executive function change (β= .27, p = .04). In a cross-lagged panel analysis a significant path was found between the PASE score and executive change (β=.22, p= .01).

Discussion: Habitual physical activity was associated with reduced executive function change. Whilst specific recommendations cannot be made about of the best type of physical activity to effect a reduction in executive function change, interrogation of data shows that

the habitual physical activity conducted may not need to be muscle building to elicit an effect.

E.1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that results in the progressive decline of cognitive performance. A meta-analysis of the literature has reported that individuals with AD decline on average a 3.3 MMSE points annually (Han, Cole, Bellavance, McCusker, & Primeau, 2000). However, it is important to note that the rate of cognitive decline substantially varies in individuals with a diagnosis of AD (Hui et al., 2003). There is also evidence that in AD there are stages in which global cognitive decline plateaus (Bozoki et al., 2009; Haxby et al., 1992; Piccini et al., 1995). Variations in cognitive trajectory can be attributed to a multitude of factors including age, severity and years of education (e.g. Scarmeas, Albert, Manly, & Stern, 2006; Teri, Mccurry, Edland, Kukull, & Larson, 1995).

Executive function is the cognitive process involved in the planning, initiation and regulation of behaviour (Lezak, 2004). Executive function has consistently been found to be impaired early in the disease course (Binetti et al., 1996; Collette et al., 1999; Lafleche & Albert, 1995). Even prior to the clinical diagnosis of AD, executive deficits can differentiate between those who go onto develop the disease and those that do not (Albert et al., 2001; Sgaramella et al., 2001). However, the majority of literature is cross-sectional in design and therefore little is known about the trajectory of executive function change within an AD population. Understanding more about the rate of executive decline in AD is a prerequisite for identifying factors that can alter executive trajectory, allowing a more direct approach to maintaining functionality, where executive function plays a vital role (Martyr & Clare, 2012).

One potential factor that could affect the executive trajectory in AD is physical activity. A systematic review of published randomised control trials (RCTs) on this topic found that physical activity interventions have a positive effect on cognitive function in AD (Farina, Rusted, & Tabet, 2013). Whilst this highlights the potential of physical activity to positively affect cognition, limited conclusions could be drawn about how it specifically affects the

trajectory of executive decline. In part this was due to the majority of RCTs measuring global cognitive function rather than domain specific outcomes. In addition, physical activity interventions in AD have been relatively short lived and can span anywhere between 4 weeks (Rolland et al., 2000) to 24 weeks (Hernandez et al., 2010; Venturelli et al., 2011; Yu et al., 2013). The length of the intervention may not be sufficient to cause a sustained shift in the trajectory of executive function decline in AD.

A particular area of interest is the impact of habitual physical activity. Habitual physical activity is defined here as the physical activity conducted by individuals in everyday life, and reflects both an individual's ability and their motivation. As such, habitual physical activity encompasses leisure activities (e.g. walking, group sports) but also can include activities that are conducted in the home (e.g. gardening, cleaning) and at work. Evidence for positive effects of habitual physical activity on cognition in an AD population is mixed. Burns et al. (2008) measured an extensive battery of cognitive measures but only found two of the tasks (Trails B and logical memory) in the AD sample (mean MMSE= 26.2) to be associated with cardiorespiratory fitness, their proxy measure of aerobic habitual physical activity. After controlling for participants' age the association was no longer significant. Preliminary data from the present authors have also determined that there is an association between habitual physical activity, as measured by the Physical Activity Scale in the Elderly (PASE), and selective executive tasks in an AD population (mean MMSE = 23.61) (*Article III*). Notably, as this research is conducted at a single time point, conclusions about the effects on trajectory or even the direction of the effect are limited.

Only a few studies have explored the effects of habitual physical activity on cognitive change in AD longitudinally. Vidoni and colleagues found that that baseline cardiorespiratory fitness was positively associated with dementia severity change in AD patients (CDR = 0.5 and 1)

that were followed up over 2 years (Vidoni, Honea, et al., 2012). Winchester and colleagues explored the effects of habitual physical activity on cognitive change over a 1-year period in 104 AD patients (MMSE>18; Winchester et al., 2013). Based upon walking habits alone, participants were split into an active (engaged in more than 2 hours of walking per week) and a sedentary group (did not engage in any walking). It was found that those that were in the active group at baseline showed a significant improvement in MMSE over 1 year, whilst the MMSE of the sedentary group significantly declined. Both studies implicate habitual physical activity as a factor in the rate of global cognitive change in AD. However, to the authors' knowledge no research exists on the effects of habitual physical activity on the trajectory of executive function decline.

To date, the majority of studies that have explored the association between habitual physical activity and cognition in AD have only focussed on select components of habitual physical activity. For example, Burns et al (2008) and Vidoni et al. (2012) measured cardiorespiratory fitness which is only reflective of aerobic physical activity. Winchester et al. (2013) measured a variety of physical activities, but only investigated the relationship between walking and cognition. This is problematic as it makes that assumption that only aerobic activities are able to positively affect cognition. Limited literature exists in an AD population regarding the best type of physical activity to elicit an effect, with heterogeneity of intervention types existing in the reported RCTs (Farina et al., 2013). In a meta-analysis of the healthy older adult literature it was reported that aerobic exercise interventions have a greater effect on cognitive speed and visual attention compared to any other intervention type (Angevaren et al., 2008). However, the positive effects of specific physical activity types on cognition are still under debate. A more recent review reported that aerobic activity and strength training have a positive effect on cognition in healthy older adults, whilst stretching

and flexibility activities do not (Clifford et al., 2009). It has also been suggested that no specific physical activity type has consistently been found to have a particular benefit to cognition, and that participating in novel and multiple physical activities is more important (Bielak, 2010).

The present study focus is on disentangling the longitudinal relationship between physical activity and executive function in an AD population. This will be achieved by exploring whether levels of habitual physical activity over a twelve month period have an effect on executive function decline.

Based upon previous research suggesting that habitual physical activity can combat global cognitive decline in AD (Vidoni, Honea, et al., 2012; Winchester et al., 2013) it is hypothesised that habitual physical activity will be significantly associated with trajectory of change. It is also hypothesised that this will be a causal relationship as inferred from a cross-lagged panel analysis, with habitual physical activity being able to predict executive function decline even after controlling for potential confounding effects of other physiological indices of physical status. By determining whether habitual physical activity can affect the trajectory of executive function decline it will better allow clinicians to recommend to patients and their carers the benefits of an active lifestyle.

E.2. Methods

E.2.1. Participants

Ethical approval was obtained from the National Research Ethics Service Committee London – Camberwell St Giles.

The AD patients were aged between 65-90 and had an English proficiency equivalent that of a native speaker. Eligible participants had previously been clinically assessed using the International Statistical Classification of Diseases, 10th revision (ICD-10; World Health Organization, 1992), and received a diagnosis of probable dementia of Alzheimer's type or atypical AD with a mild to moderate severity (MMSE>12). AD patients were excluded if they had a major depressive disorder (Cornell Scale of Depression in Dementia >10). AD patients were recruited through Sussex Partnership NHS Trust. AD patients all had a personal consultee (relative or friend), and were either clinically or self-referred.

Of the AD patients included in the study ($n = 85$) a subset of the AD population ($n = 25$) were selected to compare to an opportunistic sample of healthy elderly volunteers ($n = 18$). The primary purpose of the comparison was to determine how lifestyle behaviours differed between a healthy elderly population and an AD population so that inferences could be made on the potential to alter lifestyle behaviours in an AD group. The AD subset represented the entire AD sample whose ages fell within the same age range as the opportunistic sample of healthy older adults. These volunteers were all aged 67-77 years old and had an English proficiency equivalent to that of a native speaker. Healthy elderly participants were recruited from various groups (e.g. churches and clubs) and through word of mouth in and around Brighton, Sussex.

E.2.2. Materials

A MMSE score was derived from the Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) to provide a standardised measure of global cognitive status. The Cornell Scale of Depression in Dementia (CSDD; Alexopoulos, Abrams, Young, & Shamoian, 1988) was used to screen the presence of major depression. The Neuropsychiatric inventory (NPI; Cummings et al., 1994) was used to assess the presence of psychiatric and behavioural disturbances.

E.2.2.1. Executive measures

A series of executive function measures were selected:

For the Trail Making Task (TMT; Army Individual Test Battery, 1944), participants were required (Trails A) to connect numbers distributed on the page in ascending order, and then (Trails B) to connect, alternately, sequential numerical and alphabetical stimuli. Participants were instructed to complete the tasks as quickly and accurately as possible. Both parts of the TMT were scored in time to completion (seconds). Through the subtraction of Trails A from Trails B a measure of executive control is created independent of motor and visual scan speed.

The Controlled Oral Word Association Test (COWAT; Spreen & Strauss, 1998) required participants to verbally list words beginning with the letters F, A and S in a fixed time limit of 60 seconds for each letter. Following standard instructions, participants were instructed that they should not list proper nouns or supply the same words but with a different ending. The COWAT was scored as the total number of allowable words generated across the three letters.

The verbal fluency subscale of the ACE-R (Mioshi et al., 2006) composed of two tasks. In the first task participants verbally listed words beginning with the letter P in a fixed time limit

of 60 seconds. In the second task participants had to list as many animals as possible within 60 seconds.

The Map Search Task (Robertson et al., 1994) is a component of the Test of Everyday Attention. Participants were required to identify target symbols (e.g. restaurant) on a city map. Participants have a total of 2 minutes to circle as many target symbols as possible. The Map Search Task is scored on the total number of target symbols accurately identified during the time limit.

The Digit Symbol Substitution Test (DSST) (Wecshler, 1981) is a pen and paper task. The task is composed of two phases. In the first phase, participants were provided with a sequence of symbols and required to copy as many symbols as possible in 30 seconds. In the second phase, participants were given a code table displaying the correspondence between digits (from 1 to 9) and symbols. Participants were required to fill in blank squares with the symbol paired to the digit displayed above the square. The mean time per item was calculated for each phase. Subtracting the DSST copy score from phase two of the DSST provided the time required per symbol for higher mental functions (Glosser et al., 1977; Storandt, 1976).

E.2.2.2. Lifestyle measures

A series of lifestyle measures were administered by questionnaires to the carer of the participant.

Physical activity was measured using the Physical Activity Scale for the Elderly (PASE; Washburn, Smith, Jette, & Janney, 1993). The PASE comprises 12 items addressing the leisure, household and work over the past week. The PASE has previously been validated against physiological measures of physical activity including accelerometer (Washburn & Ficker, 1999), mini-logger (Harada et al., 2001), peak oxygen uptake and balance score

(Washburn et al., 1999). The questionnaire is validated for completion by carers of dementia patients (Burns et al., 2008, 2010; Honea et al., 2009).

Cognitive activities were measured using the Florida Cognitive Activities Scale (FCAS; Schinka et al., 2005). The scale consists of 25-items using a 5-point Likert response format based on activity frequency. The FCAS has with a reasonably high level of internal consistency (α= .65) for an elderly Caucasian sample. The FCAS has also been validated for use with people with AD (Schinka et al., 2010).

Social network was assessed using the Lubben Social Network Scale – 6 (LSNS-6; Lubben, 1988). The LSNS-6 is a 6 item scale, 3 items concerning family and 3 concerning friendships. The scale is scored out of 30, with a greater score representing a larger social network. It is been shown to have a high internal consistency (α= .78; Lubben & Gironda, 2003).

Adherence to a Mediterranean diet was assessed using the EPIC Food Frequency Questionnaire (FFQ; Bingham et al., 2007). A value of 0 or 1 was assigned for each of 9 indicated categories with the use of the sex-specific median as the cut-off; thus adherence to a Mediterranean diet score ranged from 0 to 9, with a greater score representing a greater adherence to a Mediterranean diet (Cade et al., 2011; Trichopoulou et al., 2003).

E.2.2.3. Physical Status

Several physiological measures were taken to index physical status.

Handgrip strength was measured using a dynamometer (T.K.K.5401 Grip D, Accuracy: ±2.0 kgf). Using their dominant hand participants were instructed to squeeze the dynamometer as hard as they could. Participants repeated this procedure three times with the best score being recorded. In older adults handgrip strength has been found to be positively associated with

other muscle groups (Rantanen et al., 1994) as well was measures of physical activity (Bruce et al., 2002; Rantanen et al., 1994).

Mid-upper arm circumference (MUAC) was measured by placing a plastic tape measure gently but firmly around the relaxed arm, midway between the tip of the acromion (shoulder) and the olecranon process (elbow). Waist circumference was measured at the point of the iliac crest, whilst the calf circumference was measured around the largest point of the calf.

In addition, measurements of height and weight were used to calculated BMI (weight [kg] over height squared [m^2]). MUAC, calf circumference (CC), waist circumference (WC) and BMI have all previously been associated with nutritional status in an older adult population (Nykänen et al., 2013; Ruiz-López et al., 2003)

E.2.3. Procedure

Both the AD and the healthy older adults were consented and then tested individually. The battery of neuropsychology tests, incorporating the tasks reported in this paper and other cognitive measures reported elsewhere, lasted approximately 2-3 hours. The healthy older adult population were offered a 20-minute break during the battery, whilst the AD population were encouraged to take a break when needed. The pen and paper cognitive tasks conducted in the first part of the battery, and the computerised tasks in the second half. Participants subsequently completed the same measures approximately 1 year later.

E.2.4. Data analysis

Comparisons made between groups, or between different time-points, were analysed using a Student's t-test and paired t-test respectively. As not all data were parametric, a common resampling technique (bootstrapping) was employed. Bootstrap analysis is frequently used to address the problem of possible skewness in the distribution of a variable. This is achieved by

resampling the study data to create a large number of bootstrap samples. The present study used 1000 bootstrap samples which were bias-corrected and accelerated.

The measures DSST, Trails B, Map search task, COWAT and ACE-R verbal fluency subscale were entered into a principal component analysis (PCA). All measures moderately loaded (>.40) onto a single component and accounted for 54.09% of the variance. On this basis, a composite "executive function" was created and a z score composite was calculated using the average of the standardised variables. In the creation of the composite, listwise deletion was employed. In order to ensure that sufficient power was maintained, executive tasks were only included if they were completed by more than 75% of the sample population. Trails B had a high rate of non-completion in T_2 (27%). As a consequence the final "executive function" composite was made up of the DSST, Map Search Task, COWAT and ACE-R verbal fluency subscale. A second PCA was conducting entering measures of physical status (PASE, handgrip strength, MUAC, BMI, CC and WC). Two components were identified which, based on the interpretation of the skree plot, accounted for 62.86% of the variance. MUAC, CC, WC and BMI all moderately loaded onto a single component (>.40). As all these measures have previously been associated with nutritional status in older adults (Nykänen, Lönnroos, Kautiainen, Sulkava, & Hartikainen, 2013; Ruiz-López et al., 2003) the composite "nutritional status" was created. The PASE score and handgrip strength moderately loaded (>.40) onto the second component of the PCA. Both handgrip strength and PASE are associated with habitual physical activity (e.g. Bruce et al., 2002; Washburn et al., 1993), and as such the composite "habitual physical activity status" was created.

A structural equation model was created between baseline habitual physical activity status and executive function change score (executive function T_2 – executive function T_1).

Analysis included the following covariates: age, premorbid IQ, NPI, FCAS, LSNS-6, nutritional status and MeDi. A path was created between all covariates and executive function change. In the model covariates were allowed to correlate with each other and habitual physical activity status based upon significant bivariate correlations. Paths were eliminated initially based upon the lowest weighted non-significant path (p>.05); the elimination of any path was only kept if at least a single model fix index (see below) showed an improvement. If any model fit indices decreased, the eliminated path was reintroduced.

A standard two-wave cross-lagged panel design was used to test the existence of a causal relationship between the composite factor of physical activity (PASE and Handgrip strength) and executive function across the baseline and 12 month follow-up time points. Subsequently, for comparative purpose, a second two-wave cross-lagged panel analysis was conducted, this time investigating the relationship between physical activity and global cognitive function (MMSE).

Model fit was assessed using the following statistics: the χ^2 statistic, the Comparative Fit Index (CFI), and the Root Mean Square Error of Approximation (RMSEA). A non-significant χ^2 indicates a good model fit. For the RMSEA, values less than 0.07 indicate a good fit (Steiger, 2007), whilst a CFI value ≥ 0.95 is indicative of good fit (Hu & Bentler, 1999).

E.3. Results

E.3.1 Attrition

Of the initial 100 participants recruited, 85 participants provided useable data, following drop-outs and exclusions. A subset of seventy-one participants were available to contact the

following year, twenty six were lost to follow-up. Participants that were lost to follow-up had

a significantly lower baseline MMSE (p= .02) compared to those that were followed-up. Age,

premorbid IQ, years since diagnosis, gender, NPI and PASE score did not significantly differ

in those that were lost to follow-up (p>.05; See Table E.1).

Table E.1. The means (and SD) of key baseline characteristics of those that were lost and not lost to follow-up. Significance level reported (Based on 1000 bootstrap sample, 95% BCa)

	Followed-up (n=45)	Lost to Follow-up (n=26)	P
Age	81.5 (*6.0*)	81.2 (*5.2*)	.84
Gender	22 Male/23 Female	9 Male/ 17 Female	.24
Premorbid IQ	115.4 (*8.1*)	110.7 (*10.2*)	.06
MMSE	24.5 (*2.8*)	22.2 (*4.4*)	.02
Years since Diagnosis	1.1 (*1.7*)	.9 (*.9*)	.51
PASE	91.63 (*55.01*)	63.26 (*63.50*)	.06
NPI	5.0 (*7.8*)	8.4 (*10.6*)	.12

E.3.2. Baseline data comparison: healthy older adults vs AD patients

In comparison with the healthy older adults (Mean age = 72.14) the age-matched subset of 25

AD (Mean aged = 73.66) participants were significantly different on baseline demographics,

cognitive activities and lifestyle factors. Healthy older adults took part in significantly more

habitual physical activity, more cognitive activities, had a larger social network size and

adhered to more of a MeDi. (see Table E.2).

Table E.2. The means (and SD) of demographic and baseline lifestyle factors of a subset of AD patients (n=25) and healthy controls (n=18) . Significance level reported (Based on 1000 bootstrapped sample, 95% BCa).

	Healthy Controls	AD patients	p
Demographics			
Age	72.1 (*2.6*)	73.7 (*3.0*)	.08
MMSE	29.3 (*.8*)	22.8 (3.7)	<.01
IQ	119.8 (*4.3*)	111.8 (9.9)	<.01
Lifestyle Factors			
PASE	187.02 (*60.25*)	112.28 (*65.08*)	<.01
LSNS-6	20.8 (*6.5*)	16.1 (*5.2*)	.01
FCAS	48.4 (*7.2*)	35.4 (*12.3*)	<.01
MeDi	4.94 (*1.47*)	4.00 (*1.35*)	.05

E.3.3. Descriptive data

At baseline participants had a mean age of 81.5 (SD= 5.9), mean premorbid IQ of 115.4 (SD= 8.1), mean MMSE of 24.5 (SD = 2.8), and on average had been diagnosed for 1.1 years (SD= 1.7); 49% were male (Table E.1.). The means and standard deviations of cognitive and lifestyle outcomes at each time point are presented in Table E.3. Total PASE score, handgrip strength, FCAS and LSNS-6 all significantly declined between T_1 and T_2. Further inspection of PASE scores revealed that only household related physical activity significantly declined (p<.01), leisure and work related activities were unchanged (p>.05). Measures of global cognitive function (MMSE and ACE-R) both significantly declined between T_1 and T_2 (p≤.01). Following the creation of an executive composite at both time points (DSST, Map search task, COWAT and ACE-R fluency subscale) a significant decline was reported between T_1 and T_2 (p=.01).

Table E.3. The means (and standard deviations) of lifestyle and cognitive measures. A paired t-test was conducted between time points (based on 1000 bootstrapped sample, 95% BCa).

	T_1	T_2	p
Measures of habitual physical activity			
PASE total	93.03 (55.40)	64.75 (47.41)	<.01
Leisure subscale	20.85 (28.76)	17.75 (25.67)	.17
Household subscale	71.77 (40.57)	46.72 (35.97)	<.01
Work Subscale	.42 (2.03)	.28 (1.83)	.12
Handgrip Strength (kg)	26.00 (9.32)	24.68 (9.59)	<.001
Other Lifestyle Measures			
Cognitive Activities	34.5 (11.3)	27.7 (10.1)	<.01
LSNS-6	16.8 (4.9)	15.4 (4.7)	.03
Global Cognition			
MMSE	24.5 (2.8)	23.0 (4.6)	<.01
ACE-R Total	70.7 (9.7)	67.3 (13.1)	.01
Executive measures			
Trail B –Trails A (seconds)	90.62 (50.43)	86.86 (44.15)	.63
Map Search (total correct)	32.0 (16.1)	36.5 (18.4)	.12
DSST controlled (time per item)(seconds)	3.57 (4.28)	3.82 (4.54)	.81
COWAT (total correct)	27.3 (11.1)	26.7 (11.7)	.65
ACE-R fluency (total correct)	7.4 (2.6)	6.1 (3.1)	<.01

E.3.4. Structural Equation Modelling

A structural equation model examined whether the moderate change in executive function observed over the 12 month follow-up could be linked to differences in habitual physical activity. An initial model was created: $\chi^2(23) = 9.50$, p = .994, CFI = 1.00, RMSEA = .00. Three non-significant paths were identified (NPI T1 → Executive function change; NPI T1 →age; nutritional status T1 → Executive function change), in which deletion improved the model fit index (χ^2). A final model was therefore created without these paths: $\chi^2 (26) = 9.84$, p = .998, CFI = 1.00, RMSEA = .00 (Figure E.1). A significance path was found between habitual physical activity status and executive function (HPA status T1 → Executive Function Change = .27, p = .04). Age (Age → Executive function change = .29, p = .01), premorbid IQ (premorbid IQ → Executive function change = .35, p < .01) and cognitive activities (FCAS → Executive function change = .34, p = .02) all significantly predicted executive function change. Adherence to a MeDi (MeDi → Executive function change = -.23, p = .06) also trended toward significantly predicting executive function change. The only covariate that did not significantly predict executive function change was social network size (LSNS-6 → Executive function change = .13, p = .29) although removing this path did not improve the model fit.

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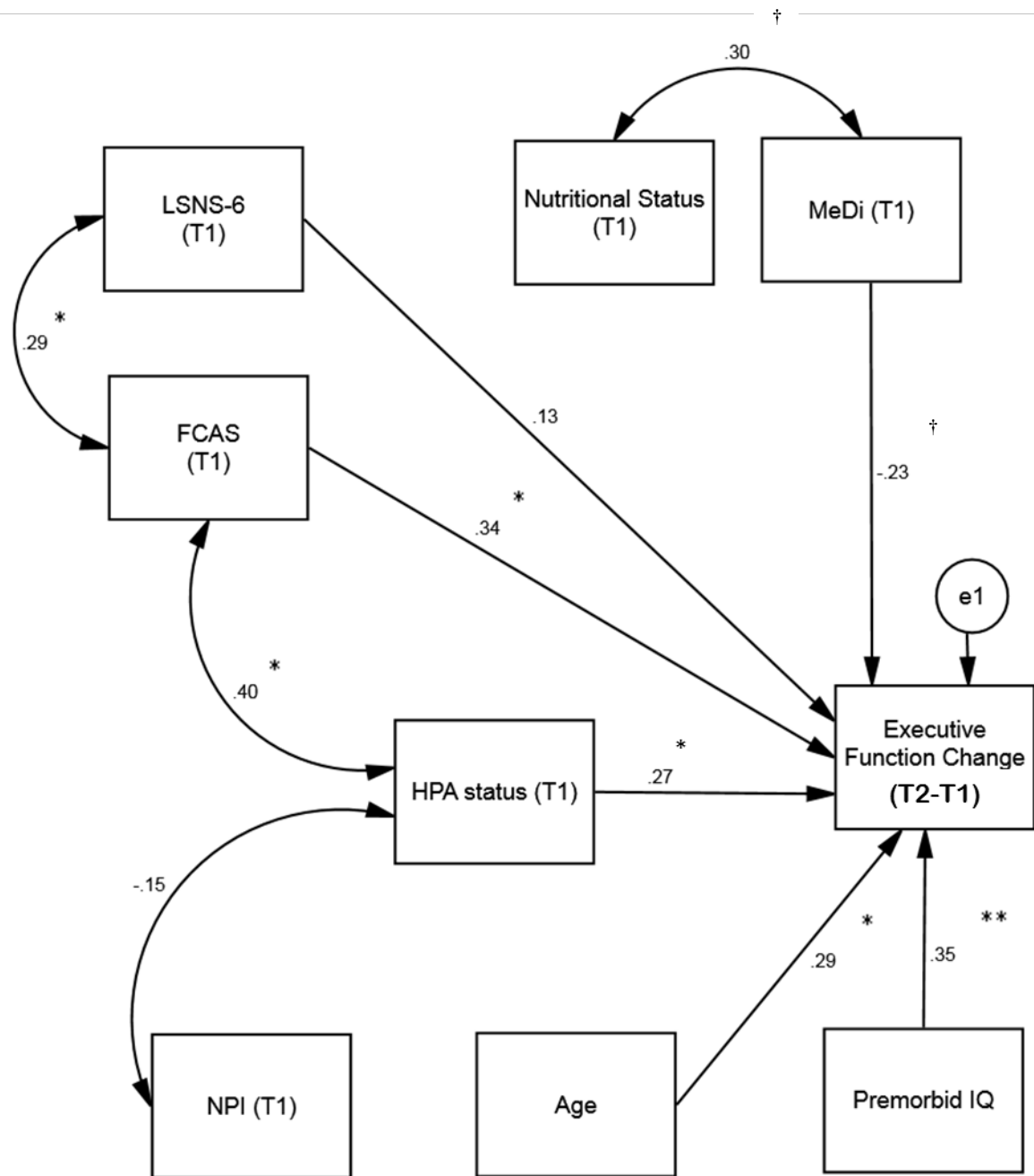
Figure E.1. The effects of Habitual Physical Activity (HPA) status on executive function change over 12 months in an AD population, the final model. Age, premorbid IQ, Florida Cognitive Activity Scale (FCAS), Lubben Social Network Scale-6 (LSNS-6), nutritional status, and Adherence to a Mediterranean Diet (MeDi) were all controlled for. Standardised regression weights showed. . [†] p ≤ .06, * p< .05, ** p < .01, *** p< .001.

E.3.5. Cross-lagged panel analysis – Executive Function

In the cross-lagged panel analysis, habitual physical activity composite was split into PASE and handgrip strength to explore which aspect of habitual physical activity effects cognitive change. Between the two time points, paths between habitual physical activity (PASE T1 → PASE T2 = .75, p < .001), handgrip strength (Handgrip T1 → Handgrip T2 = .92, p < .001) and executive function (Executive function T1→ Executive function T2 = .85, p < .001) were significant.
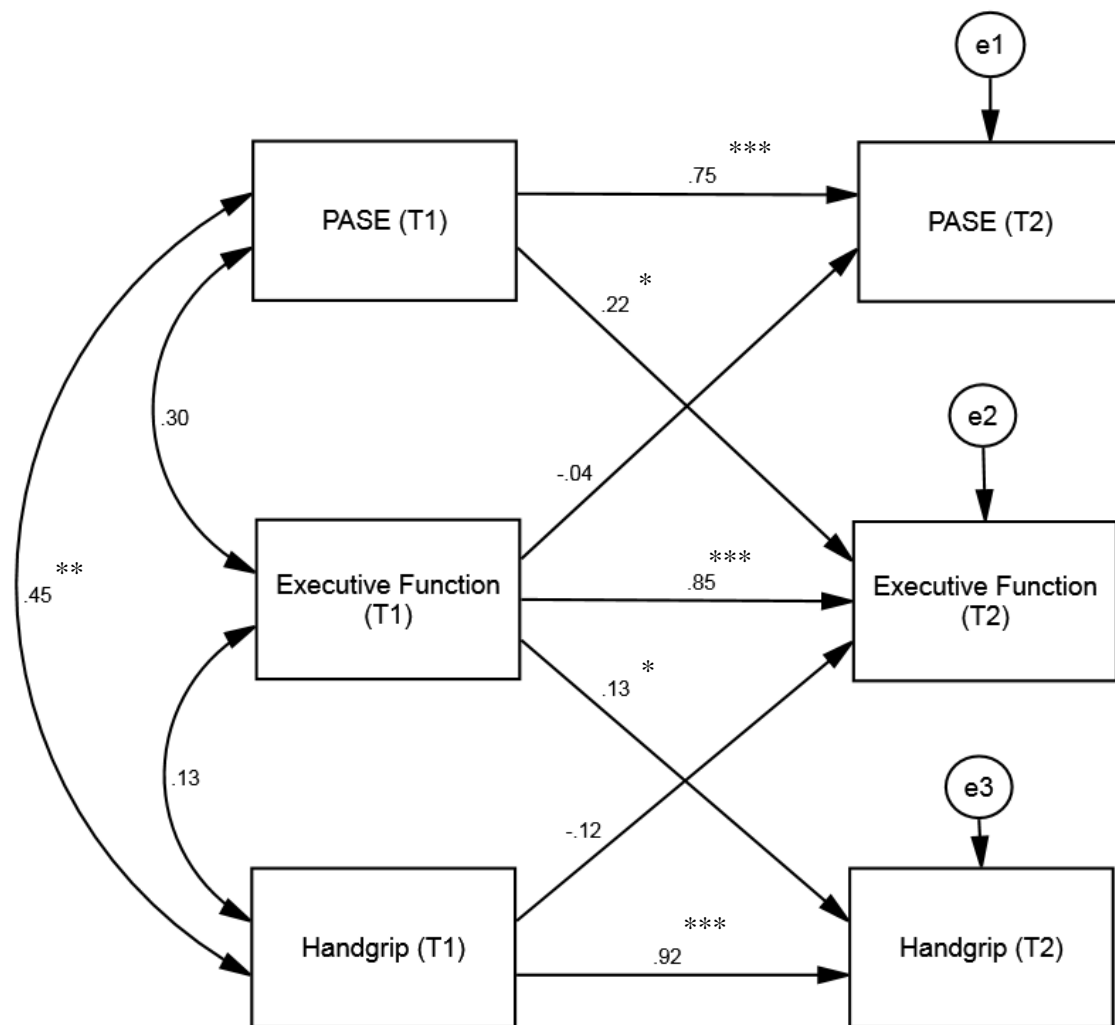
Figure E.2. A cross-lagged panel analysis between PASE, handgrip strength and executive function. * p< .05, ** p < .01, *** p< .001.

Cross-lagged paths from PASE (T_1) to executive function at follow-up were significant (PASE T1 → Executive function T2 = .22, p= .01) but baseline executive function did not significantly predict habitual physical activity at follow-up (Executive function T1 → PASE T2 = -.04, p =.70). Baseline handgrip strength did not predict executive function at follow-up (Handgrip T1 → Executive Function T2 = -.12, p = .14) but executive function at baseline did predict handgrip strength at follow-up (Executive Function T1 → Handgrip T2 = .13, p= .01). The data significantly fit the model (χ^2 (5) = 3.02, p = .70, CFI = 1.00, RMSEA = .00 (Figure E.2)).

E.3.6. Cross-lagged panel analysis – Global cognitive function

Between the two time points, paths between habitual physical activity (PASE T1 → PASE T2 = .72, p < .001), handgrip strength (Handgrip T1 → Handgrip T2 = .94, p < .001) and global cognition (MMSE T1→ MMSE T2 = .71, p< .001) were significant. However, cross-lagged paths between PASE and MMSE, and between handgrip strength and MMSE were non-significant (p>.05). For full model see Figure E.3. The data significantly fit the model (χ^2 (5) = 5.22, p = .39, CFI = 1.00, RMSEA = .03.
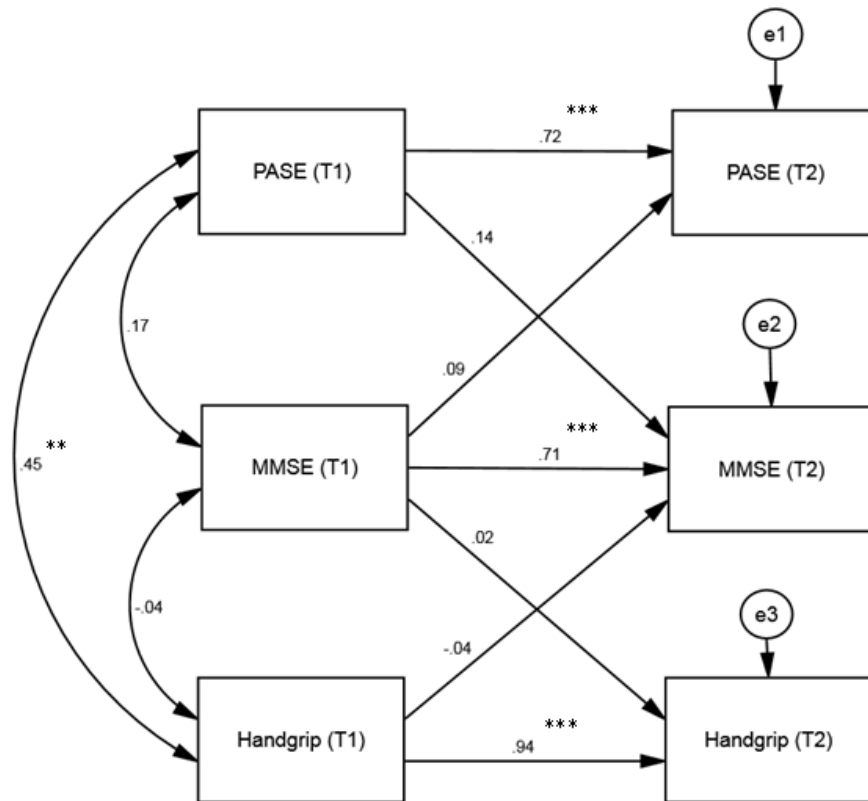
Figure E.3. A cross-lagged panel analysis between PASE, handgrip strength and MMSE. * p< .05, ** p < .01, *** p< .001.

E.4. Discussion

The objective of the current study was to determine whether habitual physical activity significantly predicts executive performance change over one year in an AD population. Following the creation of a SEM, and supported by a cross-lagged panel analysis, the data support the hypothesis that in the cohort of AD patients tested here, habitual physical activity significantly predicted executive function change over a period of 12 months.

The executive function composite significantly declined between T_1 and T_2. Somewhat surprisingly, the mean performance of many executive function tasks (DSST, TMT, Map Search and COWAT) did not significantly decline between T_1 and T_2 in our AD volunteers. The ACE-R verbal fluency subscale was the only individual executive task to significantly

decline between T_1 and T_2. The apparent stability in performance in any cognitive measure is surprising in an AD population. In the present study, the stability could be as a result of considerable individual differences and a lack of power to detect an effect. Another explanation is that practice effects masked executive performance decline. In healthy adults, practice effects have been reported in several executive tasks over a 12 month period (Basso, Bornstein, & Lang, 1999). However, the authors note that practice effects appear to be moderated by task complexity, and therefore tasks that require relatively simple strategies (i.e. TMT and verbal fluency tasks) for successful completion do not show such effects. In addition, preliminary data reported by Machulda and colleagues suggested that practice effects are less present in MCI and dementia patients compared to healthy older adults over 15 month intervals (Machulda et al., 2013). Machulda and colleagues found that in those with MCI or dementia, measures of attention, visuospatial function and language showed no practice effect. In the present study, the stability in executive function could also be due to an increased familiarity with the experimenter and with the session format of the research programme. However, if familiarity of the task was the primary factor, it would be expected that cognitive measures taken as part of regular clinical follow-ups (e.g. MMSE) would exhibit similar effects, which was not the case. To date, relatively few studies have investigated change of executive measures longitudinally in an established AD population, though it has been reported that global measures of cognition do sometimes exhibit a period of plateau during the course of the disease (Bozoki et al., 2009; Haxby et al., 1992). It may be possible that domain specific cognitive plateaus occur in an AD population, and like global cognitive function are dependent on a range of factors.

Using a SEM, the present study demonstrated that there was a significant path between habitual physical activity status and executive function change over one year in an AD

population, supporting our initial hypothesis that habitual physical activity affects the trajectory of executive decline. Importantly, this relationship remained after controlling for confounding variables such as age, premorbid IQ, cognitive activities, social network, nutritional status and adherence to a MeDi. As stated in a recent review by Smith and colleagues, it is important that other lifestyle factors such as diet and cognition are accounted for, since they tend to cluster together (Smith, Potter, McLaren, & Blumenthal, 2013). Health behaviours in particular are often clustered, and a change in one is often associated with a change in another (Pate et al., 1996). For example individuals that voluntarily increase their physical fitness were more likely to change their dietary habits than those that do not (Blair, Goodyear, Wynne, & Saunders, 1984; Wilcox, King, Castro, & Bortz, 2000). In addition, there is substantive evidence that they too may affect the onset of dementia (e.g. Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Sattler, Toro, Schönknecht, & Schröder, 2012; Wilson et al., 2002).

A cross-lagged panel analysis was conducted to further interrogate the data. The cross-lagged analysis revealed a stronger path between PASE (T1) and Executive function (T2) compared to the path between Executive function (T1) and PASE (T2). This provides some evidence for a directional relationship between habitual physical activity as measured by the PASE and executive function change. As the present sample had both participants that improved executive function as well as declined it is possible that there is threshold level of habitual physical activity that the individual has to achieve to impact executive function decline. Further work should explore this with a larger sample of volunteers and over a longer time frame. Interestingly the association between PASE (T1) and change was present after controlling for handgrip strength (T1). This finding allows for us to better determine what type of physical activity affects executive function change in AD. Controlling for handgrip

strength highlights that the activities measured in the PASE do not have to be of a type or intensity to elicit muscle development. This finding needs further research, but offers preliminary support for the notion that a variety of physical activities is more beneficial that a specific type or intensity (Bielak, 2010). Notably, the ability of PASE to predict cognitive decline only existed for the executive function measures. When a similar cross-lagged panel analysis was conducted with global cognitive function change as the dependant variable, neither PASE score nor handgrip strength predicted MMSE change. This potentially highlights that habitual physical activity may selectively affect cognition rather than global cognition. This supports previous evidence from healthy older adults (Colcombe & Kramer, 2003) and an MCI population (Gates et al., 2013) that physical activity selectively affects executive function, though the evidence is far from conclusive (e.g. Angevaren et al., 2008; Smith et al., 2010).

All lifestyle measures taken at baseline (habitual physical activity, social network, cognitive activities and adherence to a MeDi) were found to be significantly lower in the AD subgroup compared to age matched controls. In addition, habitual physical activity, cognitive activities and social network were also all found to significantly decline between T_1 and T_2 in AD. Little research has been conducted into longitudinal change in leisure activities in AD. In healthy older adults, there is evidence that individuals may reduce leisure time physical activity in older age (Dallosso et al., 1988; Yusuf et al., 1996). However, different constraints are likely to underlie participation by cognitively impaired populations. In the present study also, when analysing the subcomponents of the PASE score only the household related activities significantly declined between T_1 and T_2. It is important that future research explores the motivations of AD patients to participate in habitual physical activity, particularly if it can affect executive function change. Whilst there is evidence that leisure

physical activity levels decline with age (e.g. Dallosso et al., 1988), early evidence within an AD population confirm that certain physical activity types, such as walking and general aerobic activities, may remain relatively stable (Cedervall, Kilander, & Aberg, 2012; Vidoni, Honea, et al., 2012). This is in line with the present study which found that leisure activities, which include walking and other aerobic activities, did not decline between baseline and follow up.

In summary, the present study has extended previous literature by investigating the effects of habitual physical activity on longitudinal change in executive function in an AD population over a 12 month period. In support of the initial hypothesis, there was evidence that habitual physical activity status significantly predicted executive function change. In addition, a cross-lagged panel analysis inferred a stronger, causal relationship by establishing a significant path between baseline PASE score and executive function change, but not between baseline executive function and PASE change. Future research needs to determine the optimum physical activity to elicit an effect on executive function in AD. However, the promotion of non-specific habitual physical activity may prove to be beneficial for this clinical population.

F. Discussion and Conclusion

Each article in the thesis provided a unique contribution to the relationship between physical activity and cognition in AD. However, it is important to acknowledge that there are limitations and areas that could be further developed.

F.1. Limitations

Article IV was designed to address longitudinal change over a 1 year period, and as anticipated there was attrition between baseline and follow-up. Whilst this was inevitable in an AD population due to disease progression and death, this attrition does result in bias. Based on baseline comparison between key factors, only MMSE was found to significantly differ between those followed-up and those that were lost to follow-up. There are two major ways in which attrition can bias the sample (Miller & Hollist, 2007). First, attrition bias can affect the external validity of the study, as dropouts result in the follow-up sample not representing the original population recruited. For example, in *Article IV* as the MMSE of participants that dropped out was significantly lower than those that were followed-up the longitudinal sample is less likely to be representative of a more moderate severity AD population. Second, systematic attrition may also negatively affect the internal validity of the research. For example, in *Article IV* as those with a more severe diagnosis of AD are underrepresented at follow-up it may lead to correlations between variables that differ from correlations of the original sample. Therefore it is important that interpretations of *Article IV* are limited to the follow-up sample (and their demographics) alone, not the original baseline sample.

Another shortcoming associated with the high attrition rates in *Article IV* is that it resulted in a smaller sample size, which potentially limits the interpretation of statistical analyses used in the article. Specifically, structural equation modelling (SEM) was used in *Article IV* to determine whether habitual physical activity was associated with executive change after controlling for cofounding variables. Whilst SEM is usually considered a large sample

analysis technique, little consensus exists on the required sample size needed for SEM (Sivo, Fan, Witta, & Willse, 2006). Researchers have previously suggested having 10 participants per free parameter (Schreiber, Nora, Stage, Barlow, & King, 2006) whilst others have stated that a minimum of 200 participants is required (Hoelter, 1983). These rule-of-thumb estimates are considered by others to be conservative and "simplistic", with SEM successfully being performed well even with smaller samples (e.g. n=50; Iacobucci, 2010). The strength of the analysis was improved through using only key confounding variables so as not to inflate the number of free parameters. Also, model fit was assessed using several goodness-of-fit indices rather than chi squared alone, which is influenced by sample size. Notably, the significant association between habitual physical activity and executive change found in the SEM was substantiated in the cross-lagged panel analysis. The presence of a significant association enables for the conclusion that the effect size of habitual physical activity was large enough to be detected in that sample. However, the smaller sample size of the articles does prevent non-significant results (or 'negative associations') from being interpreted as having no association as it may be lacking enough power to detect an effect.

Notably, there are some limitations in the interpretation of elements of analysis conducted through the thesis due to the nature of AD. AD, by definition, means there is a presence of significant cognitive and functional impairment. In *Article IV* comparisons were made between an AD group and a cognitively healthy elderly population on cognitive and functional variables. The primary aim of the comparison was to determine the extent by which AD affects lifestyle habits, and therefore the potential for increasing levels of physical activity in the AD population. The findings confirm that habitual physical activity levels are lower in the AD, however as functional impairment is a key outcome of AD it was likely that this would be the case. Another limitation, closely tied to the nature of AD is the relationship between the disease and habitual physical activity. As functional impairment is a symptom of AD, habitual physical activity may therefore be a consequence of a longer or steeper decline prior to diagnosis. Determining the exact effect of the disease on habitual physical activity is particularly difficult as individuals can experiences impairment up to 12 years prior to

diagnosis of dementia (Amieva et al., 2008). However, as stated in *Article IV* (E.4.) the cross-lagged panel analysis conducted does provide evidence to support there is direction in effect between habitual physical activity and cognitive decline in AD.

The AD sample used throughout the thesis was recruited from memory clinics, with no criteria set for the amount of physical activity being presently conducted. Whilst the majority of participants were physically active, usually participating regularly in walking or in household activities, most participants tended not to participate in more intensive leisure activities. Whilst such a finding is likely to be an accurate representation of habitual physical activity levels in a community based AD population, it may preclude interpretation about individuals participating the highest amounts of physical activity. One potential method to resolve this is to implement inclusion criteria of physical activity levels. Another possible solution would be to recruit AD patients from sheltered housing that provides residents the opportunity to attend exercise classes, by doing so it would allow for a comparison to be made between those that participate in the exercise classes and those that do not. An advantage of this method would be that many potential confounding variables will be relatively controlled for (e.g. social and cognitive stimulation, diet, severity) in a closed environment.

In *Article III,* multiple correlations are made between executive function, habitual physical activity, demographic variables and other lifestyle factors. It is believed that if you test long enough (i.e. the more comparisons that you make), the more likely you are to find something significant (i.e. a false positive). As such some believe that if multiple measures are tested, the p-value should be adjusted to reduce the chance of incorrectly finding a statistical significance (e.g. Bender & Lange, 2001). Notably, in *Article III* the Spearman's Correlations were not controlled for multiple comparisons and therefore any significant results are more likely to be due to Type I errors. However, controlling multiple comparisons through p-value adjustments is far from a perfect system, with no gold-standard. In particular, p-value adjustments have been criticised because you increase the chance of making Type II errors,

which are no less important than Type I errors (Rothman, 1990). Ultimately there is still disagreement in the best method to deal with multiple comparisons. Feise (2002) has recommended that the quality of the study and effect size of the finding should be considered when interpreting statistical significance, with all findings being interpreted with caution until it has been replicated.

Another consideration for future research is the choice of measures of habitual physical activity. As noted in *Articles III and IV*, the use of a PASE alongside handgrip strength provides an insight about both the intensity and frequency of physical activities being conducted. The PASE score represents the proxy-reported frequency, duration and intensity of physical activities activity, whilst handgrip strength represents activities that result in muscle development. The composite measure, however, does not differentiate between the types of physical activities being conducted. One of the purposes of the composite measure was so to compensate for shortcomings of individual tasks. For example, although the handgrip task is associated with other physical activity measures (Bruce et al., 2002; Rantanen et al., 1994; Syddall, Cooper, Martin, Briggs, & Aihie Sayer, 2003), it is also likely to be affected by other factors because it is primarily a measure of muscle strength. Factors such as the age, gender and frailty have all been implicated in influencing handgrip strength (Bassey & Harries, 1993; Vianna, Oliveira, & Araujo, 2007). Similarly, achieving the level of detail accurately through questionnaires (e.g. PASE) alone has been previously criticised. It has been noted that questionnaires do not sufficiently differentiate between aerobic and resistance activities, and do not accurately measure intensity and calories burned (Shephard, 2003). Physiological measures are also difficult in an AD population due to frailty and cognitive impairment. Frailty may prevent participants from performing physical assessments (e.g. VO2 max), whilst memory impairment may prevent participants remembering to record on going physical activity habits (e.g. diary or accelerometer). During my thesis I experienced such difficulties. In early sessions, I did also attempt to measure habitual physical activity through spirometry to gauge lung function (e.g. forced vital capacity). Lung function has previously been found to be associated with physical activity levels (Cheng et

al., 2003), and as such the inclusion of lung function would have strengthened the composite measure of habitual physical activity. However, the data provided was of limited quality as participants consistently struggled to follow the standardised instructions required in achieving an accurate measure of lung function, and a decision was made that therefore the data could not be used. Measuring lung function in a cognitively impaired population has previously been shown to be problematic particularly those that have a moderate-severe cognitive impairment (MMSE < 24; Allen & Baxter, 2009; Allen, Charlton, Backen, Warwick-Sanders, & Yeung, 2010; Allen, Yeung, Janczewski, & Siddique, 2008). Allen and colleagues showed that inconsistent effort, incomplete lung emptying, failure to breathe in to total lung capacity prior to exhaling, and breathing in prior to completion were the most frequent errors made in a cognitively impaired population. Arguably there is currently no 'gold standard' measure of physical activity (see Hallal et al., 2013), and therefore it is difficult to recommend the best measure of physical activity particularly in an AD population. As utilised in the thesis, it is important that multiple indices of physical activity are taken to achieve the most accurate measure of habitual physical activity.

In *Article III* it was highlighted that previous systematic reviews have found that physical activity positively affects specific cognitive domains. It should be noted that each cognitive domain can be measured in a variety of ways. As such, the interpretation of an effect on a particular domain is dependent on the accuracy of the measure it represents. Even when measures theoretically have a similar underlying structure, as highlighted by a moderate to strong correlation between measures, differences in properties exist. Difficulties are more likely to arise in the instance of executive function, which has many (often broad) definitions (McCloskey & Perkins, 2012). For example, in the systematic review by Gates and colleagues, verbal fluency was the only measure of executive function to be affected by physical activity in an MCI population (Gates et al., 2013). In the *Article III* and *Article IV* a composite measure of executive function was created using several separate measures so to reduce the effect of differing properties of individual measures. However, it is important to

note that replication of the research using a different selection of measures may yield a different result.

The scope of the thesis did not seek to explore the relationship between habitual physical activity and cognitive domains other than executive function. Preliminary evidence from *Article IV* highlighted that measures of habitual physical activity did not predict MMSE change. Such a finding are perhaps surprising, with previous physical activity RCTs (see *Article I*) and other longitudinal studies (Vidoni, Van Sciver, et al., 2012; Winchester et al., 2013) reporting a positive effect of physical activity on global cognition and severity, typically utilising the MMSE. The MMSE is a blunt measure of global cognitive function, informing researchers little about domain-specific change, and therefore the findings should be interpreted with caution. Indeed, the MMSE does not specifically assess executive function and it is therefore plausible that physical activity could affect other cognitive domains. Meta-analyses of literature within healthy older adults and MCI support the notion that physical activity can positively affect other cognitive domains (e.g. Smith et al., 2010; Angevaren, Aufdemkampe, Hjj, Aleman, & Vanhees, 2008).

Whilst the present study did not implement a physical activity intervention, it could provide theoretical support for using physical activity to combat cognitive decline in an AD population. Primarily, it highlights that the type and intensity of physical activity required to produce a statistically significant effect on cognition is not outside the range of current physical activities being conducted by people with dementia. It therefore may be unnecessary for interventions to be overly intensive as observed in some previous trials (for example Kemoun et al (2010) required participants to take part in 1 hour classes involving articular mobilization, muscle stimulation, walking ergocyling, dance and stepping). Indeed, it could be that the promotion of an active lifestyle would be sufficient. Such health promotion methods may prove to be less resource intensive to healthcare providers compared a physical activity intervention, and, more importantly, much more acceptable to the population being

targeted and therefore much more likely to be sustainable over time and without formal (external) supervision.

F.2. Mechanisms

It is important to highlight that in this thesis that I did not explore the mechanism by which physical activity affects cognitive function in an AD population. This was in part due to the enormity of the task and the constrained time frame of the studentship. Whilst there is an ever expanding literature into the mechanisms by which physical activity potentially could affect cognitive function, the majority of literature exists in healthy populations and mice models of AD. In addition, it is likely that the mechanisms are multimodal in nature and therefore disentangling the respective effect of each mechanism is difficult. Bowes and colleagues, in a review of the literature broadly identified five potential mechanisms; 1) improving cerebral perfusion (vascular); 2) increasing endorphin and serotonin levels in the brain, which in turn increases the functioning of the central nervous system (neurochemical); 3) improving brain plasticity and synaptogenesis (cognitive reserve); 4) improving emotional feelings (stress); 5) facilitating spatial learning and memory (functional) (Bowes, Dawson, Jepson, & McCabe, 2013). It should be noted that incorporating data that control for confounding variables (as implemented in *Article III & Article IV*) does lend itself to determining potential mechanisms. For example, as an effect existed after controlling for neuropsychiatric measures, it is likely that improving emotional feelings is not the primary mechanism responsible for the differences measured in this study. In addition, finding an effect after controlling for cognitive activities would suggests that the functional and cognitive reserve mechanisms are not the primary responsible factor, as you would expect cognitive activities to have a greater effect if the route were through these pathways. However, whilst it is unlikely that any one mechanism is responsible for the effect of physical activity on cognition in AD, I would speculate that the vascular mechanism plays a major role. Poor vascular health is common pathology in AD (Kalaria & Ballard, 1999; Kalaria, 2002), which reduces cerebrovascular perfusion. Cerebrovascular perfusion is essential in ensuring that key nutrients and other

molecules reach their target cell, and to prevent neuronal degeneration. Physical activity has consistently been found to improve cerebrovascular perfusion (e.g. Ainslie et al., 2008; Rogers, Meyer, & Mortel, 1990), and cerebral blood flow declines with age in sedentary adults (Ainslie et al., 2008). Identifying the mechanism by which physical activity acts have implications on the role of other factors. For example, if vascular pathway is identified as the primary mechanism additional considerations should also be made about adhering to a healthy diet, as it plays a role in improving vascular and neuronal health. In *Article IV,* I reported that the AD participants in my cohort adhered significantly less well to a Mediterranean Diet compared to the healthy controls in my cohort. Further interrogation of the present sample (not reported in this thesis) found that the dementia participants were more likely to eat sugars and snacks, and less likely to eat seeds, nuts and fruit compared to the healthy controls (Hart et al., 2013). Ultimately, determining the mechanism by which physical activity affects cognitive performance in AD will make it easier for researchers to determine the optimum physical activity types as well as key points of interactions with other lifestyle factors. It also may allow for clinicians to develop treatments in patients that are physically unable to participate in physical activity.

F.3. Future Work

To resolve the small sample size in the Articles, future researchers need to confirm the findings in a larger sample. In particular, this will assist in determining whether previous non-significant results do in fact reflect a lack of an association or is a result of a Type II error. Future research should also look to develop this thesis by measuring cognitive function multiple times over several years. Multiple follow up sessions (2+) would allow researchers to better account for the non-linear nature of cognitive decline in AD (e.g. Suh, Ju, Yeon, & Shah, 2004). In addition, it would also allow researchers to determine the duration of effect that habitual physical activity has on cognition.

As in this thesis, future research should at minimum control for demographic and current lifestyle habits, but also should consider other potentially confounding variables. One factor in particular is the role of premorbid lifestyle habits. Evidence has found that current lifestyle activities in participants with mild AD at least partially reflect past lifestyle activities (or at least 10 years preceding; Scarmeas et al., 2003). It would be interesting to determine whether premorbid habitual physical activity levels or current habitual physical activity levels have the greatest effect on cognitive status in AD. In doing so, it would allow researchers to determine whether there is a 'window of opportunity' in which promoting physical activity can combat cognitive decline in AD. If the beneficial effects of habitual physical activity are as a result of premorbid behaviour, it has implications about the point in life in which clinicians could effectively target cognitive decline in AD.

Determining domain-specific effects are particularly important in an AD population as individual cognitive domains have different trajectories during of the disease (Carter et al., 2012), and hence physical activity may not have the same effect on all domains.

F.4. Summary and concluding remarks

The aims of this thesis was trifold; 1) to evaluate the literature on the effects of physical activity on cognitive function in AD; 2) to identify current methodological shortcomings of the research area; 3) to determine the impact of physical activity on the executive function status and subsequent executive change. I have provided an overview and theory surrounding the literature (Chapter *A* and *B*), original experimental articles (Chapters *C-E*) as well as broader limitations and implications (Chapter F). It is important for me to now summarise and conclude the thesis.

Article I identified that physical activity RCTs have a positive effect on global cognitive outcome in an AD population. However, it was apparent that there is heterogeneity between study designs (e.g. different intervention types, durations, and intensities) and that the

research in this field is still in its infancy (Lautenschlager, 2014). In particular, the replication and adaptation of previous RCT designs are required so that firmer statements can be made about the optimum intervention type and duration of physical activity on cognitive performance. It is also important to consider that physical activity interventions are relatively short-lived and may not reflect longer term physical activity habits, with the longest RCT in the article lasting 24 weeks (Venturelli et al., 2011).

Article II highlighted the importance of measuring a more sensitive and specific measurement of cognition in a cohort of people with AD. Whilst PM was found to be impaired in this cohort of people with mild AD, WM elements of the PM tasks appear to remain relatively intact compared to healthy controls matched in age and socioeconomic status. This coincides with evidence that WM remains intact in preclinical dementia (Spaan, Raaijmakers, & Jonker, 2005) and during the early stages of AD (for review see Huntley & Howard, 2010). Ellis (1996) stated that PM is composed of several stages; formation of intention, retention interval, retrieval context and execution and evaluation of intended action. The data presented here suggests that people with AD may still form the intention, but that the process is impaired either at the point of retrieval context, execution, or both. Future research should consider the implications of this finding. Specifically, measuring the cost of carrying a PM intention may allow for researchers to better target and develop techniques to prevent PM failures in an AD population.

In *Article III,* habitual physical activity was reported to be significantly associated with executive function in the AD cohort sampled here, even after controlling for key confounding variables. Such a result builds upon previous literature that has found that habitual physical activity impacts global cognitive function (e.g. Vidoni, Honea, Billinger, Swerdlow, & Burns, 2012; Winchester et al., 2013) but also supports the notion that physical activity impacts executive process, as revealed in healthy populations (see Colcombe & Kramer, 2003).

In *Article IV*, in support of the findings in *Article III*, habitual physical activity was associated with longitudinal executive function change in the AD cohort sampled. Primarily this supports a directional association between habitual physical activity and executive function. In the cross-lagged panel analysis it was also found that handgrip strength was not significantly associated with executive function change but that the PASE was. This may highlight that the physical activity level and intensity required does not need to be very high, which is supported by preliminary evidence that even walking (interventional and habitual) can combat cognitive decline (Venturelli et al., 2011; Winchester et al., 2013).

To date very little research exists investigating the role of habitual physical activity on cognitive decline in an AD population. This thesis supports the notion that physical activity conducted as part of the individuals daily routine is able to positively affect executive function and subsequent executive function change in people with AD. In addition, this thesis provides a range of methodological recommendations for researchers looking to explore the effects of physical activity on cognitive function in an AD population.

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