An Investigation and Feasibility Study in Using a Multi-Stage Screening Approach Including Postal Screening for the Early Detection of Mild Cognitive Impairment In a Community Sample

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I can do all things through Christ who gives me strength – Philippians 4:13

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Abstract

The early and accurate detection of age-related cognitive declines, such as mild cognitive impairment (MCI), represents an important but elusive research goal. Previous screening techniques have demonstrated only limited effectiveness for identifying older adults with MCI, and these diagnoses have tended to be unreliable over time. Such screening approaches have traditionally either been expensive and time consuming, or brief but inaccurate. The objective of this thesis was to explore the utility of a multi-stage screening approach, including a range of postal screening tools as a novel way of identifying cases of MCI within a community sample of older adults (N = 114). Multi-stage screening was validated through assessing all participants with a neuropsychological testing battery. Cognitive decline was identified by the screening tools at a statistically significant rate, demonstrating the value of self- and informant-reports in the early detection of MCI. The screening measures also demonstrated strong psychometric properties, and validity for use as postal screening measures. Subtypes of MCI were explored, but the reliability of these diagnoses was limited. Instead, generalised cognitive profiles demonstrated that individuals experiencing early cognitive impairment were able to be differentiated from those of cognitively intact older adults. The present results demonstrated the utility of multi-stage cognitive screening for detecting cognitive impairment, and for overcoming previous limitations in this area. Furthermore, conceptualising early cognitive declines generally, rather than focusing on subtypes, was shown to aid diagnostic reliability.

List of Abbreviations

AAMI – Age Associated Memory Impairment

ACE-III – Addenbrooke's Cognitive Examination – III

AD – Alzheimer's Disease

ADL – Activity of Daily Living

ANOVA – Analysis Of Variance

ANCOVA – Analysis Of Covariance

ApoE4 – Apolipoprotein E4

AUC – Area Under the Curve

BSF – Benign Scensescent Forgetfulness

BVMT-R – Brief Visuospatial Memory Test–Revised

CANS – Computer Administered Neuropsychological Screen

CDR – Clinical Dementia Rating Scale

CIND – Cognitive Impairment-No Dementia

CSC – Clinically Significant Change

CVLT – California Verbal Learning Test

DHB – District Health Board

D-KEFS – Delis-Kaplan Executive Function System

DLB – Dementia with Lewy-Bodies

FTD – Fronto-Temporal Dementia

GAQ – General Activities Questionnaire

IQCODE – Informant Questionnaire on Cognitive Decline in the Elderly

IQCODE (IR) – Informant Questionnaire on Cognitive Decline in the Elderly Informant-Report

IQCODE (SR) – Informant Questionnaire on Cognitive Decline in the Elderly Self-Report

LCA – Latent Class Analysis

MCI – Mild Cognitive Impairment

MMSE – Mini-Mental Status Exam

NIA – National Institute on Aging

NZ – New Zealand

RAVLT – Rey auditory Verbal Learning Test

RCT – Randomised Controlled Trial

ROC – Receiver Operating Characteristic

ROCF – Rey-Osterrieth Complex Figure Test

SAGE – Self-Administered Gerocognitive Exam

SMC – Subjective Memory Changes

TMT – Trail Making Test

VaD – Vascular Dementia

1. Introduction and Literature Review

1.1 Impact of Cognitive Decline

Life expectancy is increasing throughout the developed world, and as a result age-related cognitive declines are becoming an increasingly significant burden on society (Anderson & Hussey, 2000). In developing countries life expectancy is also increasing (Kalaria et al., 2008) and consequently there has been an increase in the prevalence of age-related health concerns worldwide, including dementia. By 2025 the World Health Organisation estimates that 75% of older adults will be living in developing countries (World Health Organization, 2002), and by 2040, 71% of individuals with dementia will live in these nations (Ferri et al., 2006). Current estimates further posit that by 2040 there will be 81 million people worldwide suffering from varied dementias (Ferri et al., 2006; Rizzi, Rosset, & Roriz-Cruz, 2014), rising to 115.4 million by 2050 (Prince et al., 2013). Whilst these will increasingly become a problem for developing nations there are already significant costs associated with age-related declines in developed nations. For example, older adults presently account for 29% of government health expenditure in New Zealand (NZ) (Bryant, Teasdale, Tobias, Cheung, & McHugh, 2004) despite comprising only 12.1% of the population (Statistics New Zealand, 2013). During 1995 a mid-range estimate in the United States of America (USA) indicated the cost of each case of dementia was US$38,000 annually (Sloane et al., 2002); in 2005 the median health cost for each case of dementia in Europe was €28,000 annually (range €6614 - €64426) (Jönsson & Wimo, 2009), and worldwide in 2009 the estimated total cost of dementia, including informal care, was US$422 billion (Wimo, Winblad, & Jönsson, 2010). Although these financial costs are significant, the social costs of age-related cognitive declines are potentially even more severe. In particular due to the progressive nature of dementia causing increasing impairment and eventually death, those around the affected individual tend to suffer along with them for extended periods of time,

and often become responsible for their care (Mohamed, Rosenheck, Lyketsos, & Schneider, 2010).

1.2 Overview of Thesis

The present thesis aimed to explore the early detection of Mild Cognitive Impairment (MCI) in a representative community sample of older adults living in Canterbury, NZ. This was explored using multi-stage screening including self-report and informant-report postal screening measures, followed by more comprehensive neuropsychological testing. The present research aimed to demonstrate the diagnostic utility of this varied screening approach as an efficient means of determining community-dwelling older adults most likely to be experiencing early cognitive decline. There are a number of benefits to early detection of cognitive decline, but current screening methodologies have significant limitations including being inefficient and expensive.

The organisation of the thesis is as follows. First a literature review is presented (Chapter 1) which describes the theoretical perspectives of cognitive decline leading to the present conceptualisation of MCI, along with the progression of cognitive decline and neurological underpinnings of this process. Common neurocognitive disorders are briefly discussed, particularly in relation of disparate presentations of MCI, and some of the consequent diagnostic issues currently seen, including those who appear to revert from impaired to normal cognition. Commonly used screening tools are discussed, including the rationale for including measurement of subjective declines and objective deficits for determining those most likely to be suffering from MCI. Current theories regarding the prevention of cognitive declines and maintaining intact functioning even in the presence of neuropathological changes are discussed in relation to pharmacological and non-pharmacological treatment approaches being trialled, all of which would benefit from

improved MCI screening procedures. Finally, the direction and aims of the present thesis are discussed in further detail.

Chapter 2 describes the general method for the research, including the conceptualisation and the methodology followed for recruitment and data collection. Following this are five chapters which present the empirical results. These chapters cover the utility and reliability of using postal screening tools within a multi-stage screening approach for detecting likely cases of MCI within a community-dwelling population of older adults. In particular, the utility of this approach at Time 1 is initially analysed, followed by the reliability of the measures used over time and the relationship between self-report and informant-report measures and MCI. The overall effectiveness of this multi-stage screening methodology over time is then assessed, along with the reliability of MCI diagnosis within the sample group. Cognitively, physically, and socially stimulating activities, and the potentially beneficial impact of these on reducing cognitive decline is explored. Finally, MCI subgroups are compared and contrasted using latent class analysis to cluster participants and compare these to diagnostic groups. Following these empirical chapters, a general discussion (Chapter 8) summates the current findings and the implications of the present research. Limitations to the present results are also discussed further, as are some possible directions for expanding on the current findings.

1.3 Background of Early Decline

Dementia as a concept has existed for a long time, yet the progression into dementia and early stages of the disease process have not had the same attention. Since the 1990s a number of attempts have been made to describe and operationally define the period of abnormal cognition preceding dementia that is discernible from normal aging (Bruscoli & Lovestone, 2004). One of the first attempts was by Kral in 1962 describing *Benign Senescent*

Forgetfulness (BSF) as a memory difficulty that progresses slowly and is characterised by forgetting unimportant information, but is distinct from both normal cognition in the elderly, and from the malignant forgetfulness of dementia (Kral, 1962; Larrabee, Levin, & High, 1986; Ritchie & Touchon, 2000). Following up individuals diagnosed with BSF revealed a higher than expected conversion rate to dementia, with a small but significant decline in cognition in the remaining sample (O'Brien et al., 1992); however, no psychiatric or organic cause was attributed to the disorder, and no suggestion of the neurodegenerative processes occurring was included in the conceptualisation of BSF (Bamford & Caine, 1988). Early declines have also been described as *Mild Dementia* in a number of early epidemiological studies (Henderson & Huppert, 1984; Jorm, Korten, & Henderson, 1987). However, *Mild Dementia* appeared to be used to describe the prodromal stage of several neuropathologically distinct disorders, and was only vaguely defined. *Age-Associated Memory Impairment* (AAMI) first described by Crook et al. addressed some of these problems by quantifying the difficulties required for diagnosis, and acknowledging the progression of cases into dementia (Crook et al., 1986; Reisberg, Ferris, Franssen, Kluger, & Borenstein, 1986). The difficulty with AAMI was in the reliance on memory as the only possible area of decline, and comparisons in performance made with younger individuals in the diagnosis (Petersen & Negash, 2008); this meant AAMI was unable to identify those most at risk of continuing on to pathological conditions as opposed to normal aging processes (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003; Hänninen & Soininen, 1997). Another term that generated support was *Cognitive Impairment-No Dementia* (CIND), which unlike those above had a stronger evidence base and describes an intermediary stage of cognitive decline, whereby individuals demonstrate marked difficulties, but less than would be required for a diagnosis of dementia (Fisk, Merry, & Rockwood, 2003). Subcategories of CIND include delirium, chronic drug use, and intellectual disability, potentially resulting in a larger proportion of

individuals meeting diagnostic cut-offs than those currently showing signs of prodromal dementia (Graham et al., 1997; Ritchie & Touchon, 2000). The wide range of presentations included from the varied subcategories, and the environmental basis for some of these raises potential problems using this diagnostic criterion in research on age-related cognitive decline (Petersen & Negash, 2008).

The diagnostic label that has generated the most research and academic support is *mild cognitive impairment* (MCI), a neurodegenerative disorder theorised to represent prodromal dementia, and characterised by cognitive deficits beyond those expected of normal aging (Petersen et al., 1997). Unlike BSF and AAMI, MCI is based on a pathological conceptualisation of cognitive change, indicating that individuals with MCI are undergoing neuroanatomical changes and declines, more akin to dementia than to normal aging (Ritchie & Touchon, 2000). Petersen's MCI criteria include: subjective memory complaints; objective memory deficits as measured on a standardised neuropsychological measure; relatively intact Activities of Daily Living (ADL); otherwise intact cognition; and not meeting diagnostic criteria for dementia. These criteria were reconceptualised in 2011 by the National Institute on Aging (NIA) to account for the difficulties in self-reports, to include informant-reports or clinician judgement to fulfil the criteria of subjective memory complaints (Albert et al., 2011). While the common usage of these criteria lends an advantage in shared terminology, there are still disagreements between studies about how to define and diagnose MCI (Busse et al., 2003; Matthews, Stephan, McKeith, Bond, & Brayne, 2008). The most controversial issue is what to include in the concept of cognitive decline, with MCI initially describing discrete memory complaints with otherwise unimpaired cognition (Petersen et al., 1997). One problem is that older adults experiencing cognitive decline and memory difficulties often report difficulties in a range of cognitive aspects, including orientation (H. Wolf et al., 1998) and language (Flicker, Ferris, & Reisberg, 1991; Kluger, Gianutsos, Golomb, Ferris, &

Reisberg, 1997). Executive functions (e.g., abstraction (Binetti et al., 1996), divided and sustained attention (Crowell, Luis, Vanderploeg, Schinka, & Mullan, 2002)) are also commonly affected in the dementia disease process, and these can often be identified by informants (Rabin et al., 2006). However, memory complaints remain the most common early cognitive deficit, and individuals with amnestic decline are more likely than those with any other early complaints to develop dementia (Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006). Functional changes represented by ADL are also difficult to assess, and have led to disagreements between researchers as to the extent that impairment is expected in MCI (Burton, Strauss, Bunce, Hunter, & Hultsch, 2009). Furthermore, this leads to differences in operationally defining impairment in ADLs in the attempt to represent a stage between no impairment, and causing some interference with independence, which represents the diagnostic threshold for dementia (American Psychiatric Association, 2013). Functional impairment is typically conceptualised as a continuum, as the perceived difficulty of tasks increases and the ease of completion decreases (Farias et al., 2005). The diagnostic difficulty is therefore how much impairment is necessary for the diagnosis of MCI, and what degree of progression needs to occur before this represents dementia. Moreover, the measurement of functional difficulty is further obscured by the significant impact of comorbidities, such as physical complaints, on older adults' ability to complete such ADLs (Di Carlo et al., 2016). Overall, the result of this diagnostic difficulty is variation in how individual studies operationalise this impairment, and variation in resultant attempts to quantify ADL impairment and track it over time. Another significant disagreement is whether to use 1.0 (Busse et al., 2006; Ritchie, Artero, & Touchon, 2001) or 1.5 (Geslani, Tierney, Herrmann, & Szalai, 2005; Petersen et al., 1997; Petersen et al., 1999) standard deviations below age-adjusted norms to define objective cognitive impairment, which results in different estimates of prevalence as well as rates of progression to Alzheimer's Disease (AD) and reversion to

normal cognition, as discussed below. There are also no uniform guidelines for neuropsychological tests or batteries to use, so despite the same umbrella diagnostic criteria, different operational definitions for MCI have effectively been used in each study considering cognitive decline.

1.4 Progression to Dementia

Despite the common nomenclature for describing the early stage of age-related cognitive decline, there remain problems with the conceptualisation and diagnosis of MCI. These problems largely arise from the difficulties inherent in imposing a diagnostic classification upon what is a gradual and continuous disorder (Stewart, 2012). Even with the relative consensus on broad diagnostic features, each diagnostic criterion can be measured in various ways, and this has led to some confusion in the field. The problem with the current theory of MCI is demonstrated in the vast range in estimated prevalence rates, and the reported rates of conversion to dementia (Bruscoli & Lovestone, 2004). The expected incidence of dementia in older adults (65 years and older) is 1-2% per year (Petersen et al., 1999), and so any reliable estimate higher than this lends support to the theory that those with MCI are at greater risk of developing dementia than cognitively healthy older adults. Estimates of the MCI to AD conversion rate vary between 5.6% (Ritchie et al., 2001) and 41% (Geslani et al., 2005) per annum depending on study methodology and the sample used. However, from comparing rates across studies through meta-analyses the rate appears to be approximately 9.6-10.2% (Bruscoli & Lovestone, 2004; Mitchell & Shiri-Feshki, 2009); such analyses also identified that the rate of decline in clinical samples was twice that of volunteer studies. It appears that more inclusive criteria have the benefit of identifying individuals most at risk of subsequent decline, even if this inflates the false positive rate (Busse et al., 2003). The prevalence rate also varies between epidemiological studies depending on the populations used and criteria applied, resulting in disagreement across extant research. In

particular, by varying test cut-offs and neuropsychological tests used for screening and diagnosis, the reported prevalence rates vary between 5.3% (Hänninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002) and 53.8% (Koivisto et al., 1995). However, it appears that the prevalence of MCI among community dwelling older adults aged 65 and over is closer to 19%, although this rate typically increases with age to approximately 29% of individuals 85 years and older (Lopez et al., 2003).

As mentioned above, disagreement exists as to what criteria should be used to diagnose MCI, and in particular whether discrete memory difficulties are required for diagnosis, or whether cognitive decline more generally is indicative of prodromal dementia. This has led to an extended conceptualisation of MCI, including three major MCI subtypes: amnestic-MCI, non-amnestic MCI, and multiple-domain MCI (Busse et al., 2006). These subtypes involve the same diagnostic outline, but differ on the specific neuropsychological deficit observed on standardised testing (Petersen et al., 2001). These groups are then theorised to be prodromal stages of Alzheimer's Disease (AD), Fronto-Temporal Dementia (FTD), and Vascular Dementia (VaD) respectively (Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005); each of these are briefly discussed below. However, it is currently unclear whether these subtypes are useful for making predictions about ongoing decline, particularly as subsequent dementia diagnoses are not limited to the purported prodromal MCI subtype (Busse et al., 2006; Fischer et al., 2007).

1.5 Dementias

1.5.1 Alzheimer's Disease

AD represents the most common dementing disorder, with prevalence estimates between 66% (Kukull et al., 2002) and 80% (Mesulam, 2000) of all dementia cases involving AD neuropathology. It is characterised by increasing impairment and neurological decline eventually progressing to death. The neurocognitive decline is theorised to be caused by the

development of amyloid plaques and neurofibrillary tangles in the brain, which cause neuronal loss (Hardy & Selkoe, 2002). These changes begin in the temporal lobe and spread to the parietal and prefrontal areas as the disease progresses, accounting for the increasing range of cognitive aspects impacted (Schoenberg & Scott, 2011). Diagnosis of AD occurs when objective cognitive decline is assessed in at least two areas, one of which must be memory, along with impairment in social or occupational functioning (American Psychiatric Association, 2013). As previously noted, memory decline is the primary complaint in early AD, and this occurs on both measures of free and cued recall, indicating deficits in both consolidation and recall of new information (Schoenberg & Scott, 2011).

1.5.2 Vascular Dementia

VaD represents the second most common dementing disorder, estimated to account for approximately 10% of cases, and a further 15% of mixed aetiology dementia showing signs of VaD (Schoenberg & Scott, 2011). VaD has also been termed *multi-infarct dementia* due to the pattern of cerebrovascular disease causing impairment. Neuronal loss occurs after infarction in small- and medium-sized arteries in the brain and the resulting penumbra, which results in an inconsistent pattern of decline across cases of VaD (Sadock & Sadock, 2011). The nature of such ischemic events results in a stepwise progression, unlike the continuous progression of decline in other forms of dementia, and can lead to plateaus during which cognitive declines are halted (Schoenberg & Scott, 2011). VaD can be divided into cortical and subcortical presentations based on where infarcts occur, with overlap in cases of multiple ongoing vascular events. The most common declines seen in cortical VaD include recall memory deficits, along with lapses in attention and concentration, and psychomotor slowing, while unlike AD, recognition memory tends to be preserved (Chui, 2007; Fein et al., 2000). Declines progress as more infarcts occur, resulting in an exacerbation of symptoms and a wider range of deficits after multiple vascular events (Schoenberg & Scott, 2011). Therefore,

cortical VaD can often present in a similar manner to AD, and neuropsychological tests that differentiate healthy older adults from those with AD are also likely to detect VaD (Sadock & Sadock, 2011). Subcortical VaD tends to display a pattern more similar to FTD, with changes observed in personality and executive functioning as well as psychomotor slowing (J. A. Levy & Chelune, 2007; Lezak, 2004).

1.5.3 Fronto-Temporal Dementia

FTD is used to describe a variety of clinical syndromes that all involve frontal lobe degeneration, and are neuropathologically distinct conditions (Schoenberg & Scott, 2011). While the particular pattern of decline differs between conditions such as behavioural variant FTD, Semantic Dementia, and Primary Progressive Aphasia, some cognitive deficits observed tend to overlap, and there is little evidence as to differentiation of these subtypes at a prodromal stage (Hallam, Silverberg, LaMarre, Mackenzie, & Feldman, 2008). Cognitive deficits begin with changes to personality and social interactions, along with deficits in executive functioning and flattened affect, followed by language and speech deficits (Sadock & Sadock, 2011; Schoenberg & Scott, 2011; Stopford, Thompson, Neary, Richardson, & Snowden, 2012). Executive dysfunction can be assessed through measures such as attentional switching, and fluency tests requiring a degree of abstraction, as increased concrete thinking is indicative of executive functioning deficits (Schoenberg & Scott, 2011). As FTD progresses it becomes harder to distinguish from advanced AD because the deficits overlap, and the neuropathology of each begins to look similar as a larger range of brain regions are impacted (Lezak, 2004; Raj, Kuceyeski, & Weiner, 2012).

1.5.4 Dementia with Lewy-Bodies

Lewy-bodies are abnormal protein deposits that form in neural cells, which cause cell death and therefore cognitive impairment. Lewy-bodies forming in Dementia with Lewy-

bodies (DLB) are the same as form in Parkinson's Disease, and it is theorised that both of these disorders are related, as they tend to co-occur as they progress (Lippa et al., 2007). This shared aetiology is seen in the similar damage to the substantia nigra, leading to a dopamine deficit and extrapyramidal symptoms similar to the physical symptoms of early Parkinson's (Sadock & Sadock, 2011). The cognitive profile of DLB is similar to AD, but there is more likely to be the presence of hallucinations, and deterioration tends to be much more rapid (Schoenberg & Scott, 2011). Prodromal cases are difficult to detect without the use of biomarkers or neuroimaging, and can present as any of the other subcategories of MCI (Donaghy, O'Brien, & Thomas, 2015). However, there is some evidence that memory remains intact early in the disease process, and attentional and executive function deficits are affected first (Schoenberg & Scott, 2011).

Differentiating between dementias is a difficult task, particularly early in the disease process when there is significant overlap in symptoms, and differential diagnosis usually requires neuroimaging or biopsy to confirm the presence of particular pathology (Koeppe et al., 2005). Moreover, an estimated 15% of dementia cases may be of mixed AD/VaD aetiology showing the individual neuropathological characteristics of both, further complicating the process of differentiating between the diagnoses (Schoenberg & Scott, 2011; Zekry, Hauw, & Gold, 2002).

1.6 MCI Diagnostic Issues and Reverters

As previously discussed, there remain complications in the diagnosis and conceptualisation of MCI, along with practical difficulties for research and primary health care. A major issue with the conceptualisation of MCI is in the apparent lack of reliability of diagnosis, with many individuals appearing to revert to normal cognition over time despite initially appearing impaired. If MCI does represent a neurodegenerative disorder then large scale neurological recovery should not be possible, and in theory older adults should not

significantly improve on neuropsychological tests over time. This group are often referred to as *reverters* and despite the theoretical problems with older adults demonstrating improvements to cognition over time these individuals tend to be ubiquitous in research on age-related cognitive decline (Larrieu et al., 2002). Rates of participants appearing to revert to normal cognition vary, with studies placing them between 4.5% (Nordlund et al., 2010) and 53% of individuals diagnosed with MCI (Ganguli et al., 2011) along with one study reporting that 92% of participants reverted or changed MCI subtype over time (Ritchie et al., 2001). Individuals who revert from impaired to intact cognition appear to be a heterogeneous group, and are similar to impaired groups in age, sex, and neuropsychological performance at diagnosis (Palmer, Wang, Bäckman, Winblad, & Fratiglioni, 2002).

A range of possibilities have been offered to explain reverters, including initial misdiagnosis, psychometric test limitations, and other cognitive confounding variables (Sachdev et al., 2013). Confounding factors can include depression appearing as pseudo-dementia (Kumar, Jorm, Parslow, & Sachdev, 2006; Zandi, 2004) or anxiety about the testing (Sachdev et al., 2013). Such psychiatric conditions can be transient, which accounts for changes between testing sessions, and are not necessarily related to age-related cognitive declines. Moreover, there is significant variation in the way MCI is diagnosed across studies, and the use of liberal criteria such as 1.0 instead of 1.5 standard deviations below age-adjusted norms may account for some cognitively intact individuals incorrectly being identified as MCI (Ganguli et al., 2011). The reliability of diagnosis is even smaller when subtypes of MCI are considered, with many individuals appearing to move between these groups at follow up, as well as some reverting to normal cognition (Kochan et al., 2010). Collectively these issues lend support to one suggestion that individuals are better classified as *normal* or *impaired* rather than attempting to identify subcategories of MCI (Ganguli et al., 2011). A second possible explanation for the phenomenon of reverters is in problems with the

tests used to quantify objective deficits and inform the MCI diagnosis. This particularly arises when scores on the Mini-Mental Status Exam (MMSE) are solely used as a criterion of decline, because it demonstrably does not differentiate with accuracy between healthy older adults and those suffering early cognitive declines (Ahmed, de Jager, & Wilcock, 2012). Specific issues with screening and testing for declines are discussed later.

Several factors appear to increase the reliability of diagnoses and make reversion less likely, and in particular adding an informant-report to the subjective memory complaints increases the reliability of the diagnosis (Sachdev et al., 2013). Informants are likely to notice more significant complaints, and while relatively minor cognitive issues may subjectively bother individuals it is less likely that these come to the attention of their friends and family until they reflect something more pathological (Mackinnon & Mulligan, 2014). Reverters also appear to have larger hippocampal volume than individuals who progress to AD over the same period, and so while not an efficient screening option it may be that neurological changes are able to differentiate progressive cognitive declines from transient declines, regardless of the aetiology of the temporary difficulty (Sachdev et al., 2013). Finally, those who revert are less likely to show functional declines, and so assessing any change in participants' ADLs such as driving and handling finances may differentiate those likely to progress from those who may revert to normal cognition over time (Li, Jia, & Jia, 2012).

1.7 Screening Tools

Due to the relatively recent theoretical development of MCI as a stage of decline between normal aging and dementia, there are a lack of screening tests currently available (Ahmed et al., 2012). One of the difficulties in developing sensitive tools has been the shifting state of diagnostic considerations that constitute MCI, along with disagreements about the type and degree of impairments needed to meet such criteria. The research used as the basis of MCI conceptualisation, and the commonly used Petersen diagnostic criteria, offer

no suggestion as to how these deficits should be measured (Petersen et al., 1997), nor did the international working group tasked with integrating perspectives on MCI (Winblad et al., 2004).

1.7.1 Limitations of Commonly Used Measures

A large number of tests have been trialled to screen for cognitive declines, but few have been validated in the populations for which they are intended, or they have demonstrated poor accuracy (Cullen, O'Neill, Evans, Coen, & Lawlor, 2007). A robust screening test should succinctly and accurately provide evidence on the important aspects of cognition likely to be affected by age-related cognitive declines, and to indicate those most likely to need more extensive neuropsychological testing to make an accurate diagnosis. A large amount of diagnostic disagreement arises based on the tests administered, and there is no agreed upon neuropsychological measure that represents the gold standard for making a diagnosis of MCI. Furthermore, screening tools such as the MMSE and measures of impairment like the Clinical Dementia Rating scale (CDR) are often used in place of more valid and reliable neuropsychological tests (Diniz, Yassuda, Nunes, Radanovic, & Forlenza, 2007), despite this not being the function they were developed for.

The most commonly administered screening measure is the MMSE, which has widely been used by primary care professionals given its brevity and ease of administration (Cullen et al., 2007; Roalf et al., 2013; Shulman et al., 2006). However, there are significant shortcomings with the MMSE and other similar screening tools developed to screen for advanced cognitive decline. In particular, they are not sensitive enough to detect early signs of impairment, or to differentiate those with MCI from cognitively intact older adults (Ahmed et al., 2012; Hoops et al., 2009). This inability to rely on traditionally useful screening tools has led to a rapid rise in the development of brief cognitive screening measures, and this remains a current focus of research. Major limitations to this test development have included

problems with validation trials, and methodological issues with participant selection limiting generalisation of results (Cullen et al., 2007). This has particularly occurred when sample groups have been collected from clinical populations, rest homes, or memory clinics but the screening tool is then generalised for community settings, where different outcomes are typically seen (Farias, Mungas, Reed, Harvey, & DeCarli, 2009). When sample recruitment is heavily restricted and extensive exclusion criteria applied, the applicability of the measure to the older adult target population needs to be questioned, particularly given the high rate of comorbidity amongst these individuals.

1.7.2 Informant Reports

Currently there are no universally accepted screening tests indicated for the screening of MCI, but some have been used more frequently than others. In particular, for large scale screening, the Informant Questionnaire On Cognitive Decline in the Elderly (IQCODE, (Jorm & Jacomb, 1989)) has been used extensively (Cullen et al., 2007). The short-form version of the IQCODE reportedly demonstrates the same degree of reliability and validity as the longer version, and so given the abbreviated administration time for the 16 item short-form versus the 26 item original, it tends to be used exclusively in cognitive screening (Jorm, 2004). The IQCODE assesses changes in memory and ADL over a 10-year period, and is completed by an informant close to the individual who knows them well enough to comment on change over time. As the most widely used informant questionnaire assessing decline, versions of the IQCODE have been produced in a range of languages, including: Dutch, Finnish, Chinese, Polish, Korean, German, Japanese, Italian, Canadian French, Thai, and Spanish (Jorm, 2004). It has also been used with shorter duration of change (Barba et al., 2000), and retrospectively at post-mortem (Rockwood et al., 1998). Meta-analytic comparisons between the IQCODE and MMSE indicate the IQCODE has a significantly greater predictive validity, although there has been heterogeneity in the performance of both measures (Jorm, 2004). A further

advantage of the IQCODE is its negligible association with intelligence and education (Isella et al., 2006), as both of these are important to consider when assessing cognition and decline. The range of such correlations has been reported from r = -0.20 to 0.07, demonstrating that increasing levels of education or intellectual ability are not reflected in higher or lower scores, and that the IQCODE can be administered as a first-line screening tool without pre-emptively collecting these other variables (Christensen & Jorm, 1992; Fuh et al., 1995). The focus on ADLs also increases the reliability of the measure for predicting MCI, as older adults having trouble with everyday functioning are more likely to experience further decline, and are much less likely to revert to normal cognitive functioning over time (Peres et al., 2006; Purser, Fillenbaum, Pieper, & Wallace, 2005). Therefore, measuring any early impact in functional capacity is likely to have strong prognostic value for subsequent declines and for differentiating individuals with MCI who are likely to revert or remain stable from those likely to experience progressive and rapid decline (Li et al., 2012). Functional impairment is present across the varied subtypes of MCI, and so while the IQCODE has a focus on memory impairment it still provides some screening utility for disparate presentations of prodromal dementia (Li et al., 2012).

The goal of screening tests is to indicate those likely to experience further declines, and there is encouraging evidence that IQCODE scores can differentiate cognitively intact older adults from those likely to progress to dementia within two years (Louis, Harwood, Hope, & Jacoby, 1999), showing its utility as a screening tool. While it was not explicitly tested, these individuals were highly likely to represent those suffering MCI. Further research using a cut-off score of 3.19 on the IQCODE has reported sensitivity of .82 and specificity of .71 for detecting cases of MCI, indicating that this allows insight into those potentially suffering early declines in an efficient format (Isella et al., 2006; Li et al., 2012). There is additional evidence that scores on the IQCODE are predictive of subsequent

institutionalisation, although mortality was not significantly predicted in the same study (Jorm & Jacomb, 1989).

1.7.3 Comprehensive Screening Tools

More comprehensive screening tools have also been explored for detecting MCI, and in particular the Montreal Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination-Revised (ACE-R) both have high reported sensitivity at between 84% and 90% (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006; Nasreddine et al., 2005). The advantage of these tests lies in assessing a range of cognitive aspects, including those most likely to show early signs of decline, and are therefore not limited to detecting amnestic decline (Lonie, Tierney, & Ebmeier, 2009). The ACE-R incorporates the MMSE, and so utilises useful elements of this measure, including assessing orientation. By extending the MMSE the deficiencies in the original measure are compensated for, and cases of MCI can be differentiated from healthy controls. More recently the ACE-R was updated to the ACE-III in order to remove copyrighted elements of the MMSE, while maintaining the components shown to be useful in screening for MCI (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013; Noone, 2015). The ACE-III offers a more comprehensive measure of memory than the MoCA, and requires approximately five minutes longer to administer. Both measures assess attention, executive functions, and complex language abilities (Ahmed et al., 2012). This range of cognition assessed is important in detecting early declines, because while memory is the most reliable predictor of subsequent AD (Welsh, Butters, Hughes, Mohs, & Heyman, 1992) and conversion from MCI to AD (Isella et al., 2006; Morris et al., 2001; Petersen et al., 1999), there is evidence that the predictive validity of screening is improved by including varied cognitive processes. In particular, it appears that the range of screening elements offered by the ACE-III can be used as prognostic indicators for continuing declines (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008). However, both the ACE-III and the MoCA have

limited evidence for differentiating between progressive declines and non-progressive psychiatric disorders that can present in a similar way (Lonie et al., 2009). They also have not been trialled outside of memory clinics and so it is unclear how relevant they are for screening community samples (Jubb & Evans, 2015; Lonie et al., 2009). The elements of screening tools are important to consider for maximising the detection of early cognitive declines, and combining ADLs and a variety of aspects of cognition appear to provide the best diagnostic screening validity.

1.8 Multi-Stage Screening

Given the aforementioned difficulties in identifying cases of MCI and cognitive decline, one possible option to improve screening is to adopt a multi-stage approach. Face-to-face screening and neuropsychological examination are both costly and time consuming, and put significant pressure on primary care physicians who typically see the first presentation of early decline (S. E. Cook, Marsiske, & McCoy, 2009; Crooks, Clark, Petitti, Chui, & Chiu, 2005). In contrast, telephone and postal screening approaches require less time investment and are cheaper to administer widely, which would present an ideal first-line screening approach for detecting cognitive decline, provided that these demonstrate adequate reliability and validity (Jansen et al., 2008; Welsh, Breitner, & Magruder-Habib, 1993). In particular, postal screening offers an opportunity to identify those most at risk and in need of further assessment, and to briefly enquire about a range of issues without requiring presentation to a health professional at the point of first contact (Alessi et al., 2003). By adopting the universal approach to screening that is achievable through postal questionnaires it is also more likely that individuals who would not present to primary care physicians may be identified (Hábert, Bravo, Korner-Bitensky, & Voyer, 1996). In particular, males are more likely to be identified through both telephone and postal screening for cognitive decline than through memory clinic and medical attendance (Andersen et al., 2010).

Few tests have been trialled or developed for alternate screening approaches in this way, although the Telephone Interview for Cognitive Status (TICS) has been trialled with mixed success (S. E. Cook et al., 2009; van Uffelen, Chin, Klein, van Mechelen, & Hopman-Rock, 2007). Research using multi-stage screening methodology has the added advantage of allowing efficient community screening; a significant limitation across many studies of MCI and AD has been recruitment approaches through memory clinics and institutions, which has limited the generalisability of results (Andersen et al., 2010). Often postal screening as a first-line approach has been unsophisticated, and contained little more than asking outright "Do you have memory complaints" (e.g., (Alessi et al., 2003; Hábert et al., 1996; van Uffelen et al., 2007; van Uffelen, Hopman-Rock, Chin, & van Mechelen, 2005)). There is also limited but encouraging evidence that informant-report questionnaires and brief self-report cognitive screening tools are able to discriminate between cognitively intact individuals and those with MCI, when utilised through postal screening (Cullen et al., 2007; Jansen et al., 2008). The obvious limitation with postal and telephone screening lies in the amount of information gathered, as individuals are unlikely to complete overly time-consuming questionnaires. However, by focusing on well known risk factors, this brief screening can inform more detailed testing, and risk factors such as psychiatric history, physical comorbidities, and current cognitive concerns, can all be addressed in a brief format. Overall, while current evidence is limited, there are a number of potential advantages to adopting multi-stage screening for early cognitive declines, and utilising efficient tools such as validated postal or telephone screening measures would allow more targeted neuropsychological assessment for those most likely to be suffering decline.

1.9 Psychometric Testing

Neuropsychological measures used in the diagnosis of dementia need to reliably detect deficits and to differentiate cognitively impaired individuals from cognitively intact

individuals. Unlike screening tools these do not tend to be brief, and have the advantage of using more time to test cognitive domains robustly. Such neuropsychological measures also often have age-adjusted norms, which allows comparison of scores between individuals of different ages, without normal age-related changes having a significant impact on such comparisons. However, a criticism of current screening and detection efforts is the overly extensive use of psychometrics, which creates a burden on study volunteers, and individuals presenting to memory clinics (Potter & Attix, 2006). In order to determine valid diagnostic groups with any reliability the aspects of cognition that tend to decline must be assessed, and differential diagnoses limited as much as possible; in particular verbal and visual memory, attention and orientation, along with processing speed and general executive functioning collectively represent the target areas for determining the presence of varied dementias (Bäckman, Jones, Berger, Laukka, & Small, 2004; Stopford et al., 2012). Therefore, a trade-off is necessary between brevity and range, along with the ideal of double dissociations to ensure deficits are in the area assumed, for example ensuring that observed memory deficits are not being caused by a deficit in another area such as processing speed.

1.9.1 Assessing Verbal Memory and Learning

Verbal learning measures are useful predictors of memory decline due to the medial temporal atrophy seen in MCI and AD causing difficulties in verbal memory performance, through progressive reduction in hippocampal volume (Du et al., 2001; Jack et al., 2000). One such test that utilises learning trials and delayed conditions to test declines in memory and learning is the Rey Auditory Verbal Learning Test (RAVLT: (Rey, 1964), also referred to as the Auditory Verbal Learning Test, AVLT). The RAVLT has been used extensively to assess verbal memory deficits in a range of neurological conditions, including varied dementias (Estévez-González, Kulisevsky, Boltes, Otermín, & García-Sánchez, 2003). The RAVLT consists of five learning trials with 15 nouns read aloud one second apart by the

examiner, followed by a distractor condition featuring 15 different words. Immediate recall is then measured without prompts, and delayed memory assessed 20 minutes later, followed by a recognition trial. Participants are encouraged to repeat as many words as they can remember, and are given as long as required to do so. One advantage offered by the RAVLT over other similar tests is the allowances included in the standardised instructions so that older adult participants can be encouraged, and the difficulty of the task explained (Lezak, 2004); such instructions help to offset test anxiety and promote representative performance on psychometric tests. Between-groups differences have been shown on the delayed trial for cognitively intact, MCI, and AD groups, indicating the ability of this measure to detect early declines (Estévez-González et al., 2003; Tierney et al., 1996). The RAVLT has demonstrated reasonable psychometric properties, and in particular test-retest reliability of .51 to .72 for delayed and recognition trials. Furthermore, the RAVLT has been normed on a number of populations, including older adults (Delaney, Prevey, Cramer, & Mattson, 1992; Strauss, Sherman, & Spreen, 2006).

There are a number of verbal memory measures similar to the RAVLT, such as the California Verbal Learning Test (CVLT: (Delis, Kramer, Kaplan, & Thompkins, 1987)), which is one of the most commonly administered memory tests (Lezak, 2004). The largest difference from the RAVLT is that the CVLT contains 16 words divided into 4 categories, so the words are able to be easily grouped (Stallings, Boake, & Sherer, 1995). This creates a possible confounding effect when considering the impact of learning on such memory tests, as remembering the categories removes one of the primary challenges in word list recall, which is developing a strategy to remember seemingly unrelated words (Lezak, 2004). A further option for assessing memory is the Consortium to Establish a Registry for Alzheimer Disease (CERAD) Word List Memory test (Rosen, Mohs, & Davis, 1984), which was developed specifically to measure memory difficulties in AD, and so is less sensitive to early

declines, but is shorter than similar measures and so is less aversive for individuals struggling to recall any words (Greene, Baddeley, & Hodges, 1996; Lezak, 2004). A range of other verbal memory tests exist, and many have been trialled to detect early cognitive declines without evidence of success, or currently lack robust psychometric properties and normative data (Lezak, 2004).

1.9.2 Assessing Visual Memory and Learning

Along with verbal learning and memory it is also important to assess visual memory, with some indication that deficits in visual memory performance can precede AD (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991); one study identified signs of such decline up to 15 years before subsequent AD diagnoses (Kawas et al., 2003). Like verbal recall, visual memory is theorised to decline in the presence of hippocampal atrophy, so this occurs early in the pathological process of AD, while tests with additional visuospatial components also show decline when there are attentional difficulties (Alescio-Lautier et al., 2007; Du et al., 2001; Goldstein et al., 2009). The Brief Visuospatial Memory Test – Revised (BVMT-R: (Benedict, 1997)) was developed in order to provide a measure of visual delayed memory with six equivalent forms to minimise the likelihood of practice effects (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996). Although practice effects tend to disappear in advanced cognitive decline, this is not the case for individuals diagnosed with MCI, and on delayed memory tests scores can improve by repeated administration to the degree that individuals no longer appear impaired (Duff et al., 2008). The BVMT-R contains three learning trials followed by delayed and recognition conditions after 30 minutes. For each trial participants have 10 seconds to view 6 geometric shapes and then to replicate these in form and position on a response sheet. One of the largest advantages of a measure such as the BVMT-R is scoring criteria taking into account the motor ability of each individual through a comparison copy trial administered at the end of the test. Using a test such as the BVMT-R

alongside a measure of delayed verbal memory offers a further advantage given that individual patterns of strengths and weaknesses are less likely to confound the detection of early declines when verbal and visual components of memory are both measured.

The Rey-Osterreith Complex Figure Test (ROCF: (Osterrieth, 1944; Rey, 1941)) is one the most widely used and researched visual reproduction and memory measures, and has led to several alternate forms being developed (e.g., Taylor Figure (Taylor, 1979), Medical College of Georgia Figures (Ingram, Soukup, & Ingram, 1997), Emory Figures (Freides, Engen, Miller, & Londa, 1996), which allows multiple administrations of the test over time (Lezak, 2004). However, normative studies have consistently shown that these alternate forms are not all equivalent, and that scores tend to be higher on particular versions of the complex figure (Tombaugh & Hubley, 1991). There are also a range of scoring systems and normative datasets available, but even administration instructions vary between studies on complex figures (Lezak, 2004). Differences in scoring systems limit the generalisability of the norms developed, given that with such disparate scoring and administration instructions there is no clear consensus about which version and norms to use (Shin, Park, Park, Seol, & Kwon, 2006). Despite these methodological inconsistencies, there is some evidence that the ROCF can be used to differentiate cases of MCI from healthy controls, although research on using complex figures for this purpose is ongoing (Kasai et al., 2006). A possible problem of using this test with older adults struggling with cognitive declines lies in the difficulty of the task, and the potentially aversive experience that can occur on a task deemed too difficult or that elicits negative self-stereotypes (Hess, Auman, Colcombe, & Rahhal, 2003). Other visual learning and memory measures such as the Visual Spatial Learning Test (VSLT: (Malec, Ivnik, & Hinkeldey, 1991)) and the Ruff-Light Trail Learning Test (RULIT: (Ruff, Light, & Parker, 1996)) offer variations on the previously mentioned measures, where the novel stimuli vary but the test structure involving learning trials and delayed conditions does not.

Overall, there is a current lack of well researched and validated measures of visual memory, and many have not specifically looked at assessing early signs of cognitive decline, despite the inherent value in using such measures for this purpose.

1.9.3 Assessing Verbal Fluency

Measuring verbal fluency and semantic ability is another important facet of identifying early cognitive declines. Many tests of verbal fluency also allow higher order executive functions to be assessed, so deficits in either basic semantic ability or attentional switching can be identified (Lezak, 2004). A large number of fluency tests have been developed based on Thurstone's Word Fluency Test (Thurstone & Thurstone, 1962), with increasing complexity as they have been developed and used for more sophisticated diagnoses. The Controlled Oral Word Association Test (COWAT: (Benton, Hamsher, & Sivan, 1994)) is one of the most commonly used verbal fluency measures and includes three letter fluency trials using F, A, and S (Lezak, 2004). Letter fluency requires individuals to generate lists of words beginning with the letter in question in one minute. As such it relies on strategies to generate lists and to access varied vocabulary which requires executive functioning. The need to develop a strategy makes this difficult for individuals struggling with cognitive slowing, as well as individuals with poor lexical knowledge. A large range of norms are available for commonly used tests of letter fluency, and such tests have been trialled across various age groups and ethnicities (Lezak, 2004). Letter fluency forms a core component of many cognitive screening tests and is a reliable and brief way of assessing semantic ability and strategy development (Tallberg, Ivachova, Jones Tinghag, & Östberg, 2008).

Category fluency trials are typically easier than letter fluency for older adults, given that strategies for developing lists are easier to identify than they are for letters, and so performance remains higher across age-adjusted normative groups (Mitrushina, Boone,

Razani, & DElia, 2005). However, category fluency tends to be impacted in disorders affecting the temporal lobe, and so significant deficits can be observed on measures of category fluency in older adults with AD (Clark et al., 2009). Category Fluency (e.g., from the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency subtest) assesses participants' ability to list words from a particular category, with the most common being animals. While strategies are still necessary to do well on this task, participants tend to find it easier to develop these for categories than for letter fluency (Monsch et al., 1994). A further step has been included in the D-KEFS test protocol, with a switching condition adding further complexity by assessing individuals' ability to switch between categories and keep complex rules in mind while completing the task. Using two completely distinct categories (e.g., fruit and furniture, or vegetables and musical instruments (Delis, Kaplan, & Kramer, 2001)) participants are forced to continuously switch the cognitive set they need, and to efficiently do so while giving unique examples. Cognitive inflexibility is an early sign of frontal lobe damage, and so difficulty on switching or deviations from instructions may indicate such declines (Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998). These switching conditions have demonstrated some effectiveness at differentiating individuals with MCI from cognitively intact older adults (Nutter-Upham et al., 2008). One variation on verbal fluency that has previously been trialled involved writing words down, which encourages a more broad range of strategies for developing word lists (Lezak, 2004); however, such measures have not demonstrated the ability to differentiate accurately between impaired and non-impaired individuals (Cohen & Stanczak, 2000).

1.9.4 Assessing Non-Verbal Fluency and Construction

Non-verbal fluency offers a useful comparison to verbal fluency measures, and allows double dissociation of pathology by limiting the overall impact of individuals' innate verbal abilities and vocabulary across the fluency measures (Tucha, Smely, & Lange, 1999). The

Five Point Test (Regard, 1982) which involves creating unique designs by drawing lines between any number of the five dots presented in a page of 40 identical squares was the first widely used non-verbal fluency measure. This concept was expanded upon for the D-KEFS Design Fluency (Delis et al., 2001) which includes an inhibition condition and a switching task, as well as the original design task.

Furthermore, several measures involving visuospatial construction are commonly used to detect cognitive declines. In particular, clock-drawing is able to predict declines amongst dementing individuals despite its simplicity (Shulman, Pushkar Gold, Cohen, & Zucchero, 1993). Moreover, there is some indication that simple constructional tasks like clock-drawing can be used to screen for likely cases of MCI (Yamamoto et al., 2004), although mixed results using clock-drawing as a basis for diagnosis means caution is required in basing estimations of decline purely on this measure (Ehreke, Luppa, König, & Riedel-Heller, 2010).

1.9.5 Assessing Executive Functioning

Executive functions incorporating planning and decision making are an integral part of higher order cognitive functioning, and are necessary to adapt to novel situations and contribute to social, emotional, and cognitively demanding situations (Lezak, 2004). The frontal lobes are primarily involved in executive functioning, and so atrophy of cortical tissue across this area has a profound effect on individuals' higher order functions, integration of information, and planning (Schoenberg & Scott, 2011). Damage to the frontal lobes can also lead to significant personality changes and social inhibition; for example loss of social proprieties and tactlessness (Sadock & Sadock, 2011; Snowden et al., 2003). However, because executive functions rely on inputs from a range of brain regions, cortical and subcortical damage in other areas can affect this functioning; although not severely impacted early in the AD disease process, this is one reason why executive functions decline as the

disease progresses. Therefore, it is possible that small deficits in executive functioning, and in particular decreased inhibition and cognitive flexibility, may be observed in cases of amnestic-MCI. Executive function deficits appear much earlier in the pathological process of FTD and sometimes VaD, and so it is likely that that prodromal non-amnestic MCI may be detected by such deficits.

Along with Switching Fluency, a commonly used measure of executive functioning is the Trail Making Test (TMT: (Reitan, 1958)) as this allows a brief assessment of executive functions, processing speed, and visual scanning. First used for Army recruitment from 1944 this test is now commonly administered as part of neuropsychological batteries, and has alternate forms for retesting (Franzen, Paul, & Iverson, 1996). Trails B is a switching condition, meaning participants need to switch between letters and numbers, and keep track of both lists. This switching requires cognitive flexibility, and so scores 1.5 standard deviations below age-adjusted norms are indicative of impaired cognitive flexibility (Kortte, Horner, & Windham, 2002).

1.10 Subjective Memory Complaints

One of the Petersen criteria for MCI is Subjective Memory Complaints (SMC), indicating that it is necessary that individuals be able to self-identify some degree of deficit for a diagnosis of MCI. The 2011 update to MCI criteria expanded this criterion to include reports from informants who know the individual well, or from the observations of a skilled clinician (Albert et al., 2011). This change represents the realisation that a large number of individuals experiencing cognitive decline do not endorse SMC, or do not perceive such changes as problematic and are therefore unable to self-report subjective changes (Iliffe & Pealing, 2010). Also referred to as subjective memory impairment, SMCs often lead to individuals presenting to primary health professionals, and this is the most common manner in which early declines are identified in the community (Geerlings, Jonker, Bouter, Adèr, &

Schmand, 1999). SMCs tend to be highly prevalent among older adults, with estimates around 50% of older adults reporting some self-identified memory difficulties (Jonker, Geerlings, & Schmand, 2000). This value varies somewhat based on the operational definition and the methodology of assessing these subjective complaints, with studies ranging from a single question through to structured questionnaires with graded responses. Controversy regarding the utility and assessment of SMC as a predictor of cognitive declines is similar to issues with subjective assessment in general, whereby many researchers dismiss such reports as unreliable and too susceptible to confounds to use this as a measure or predictor of decline (Abdulrab & Heun, 2008; Lenehan, Klekociuk, & Summers, 2012). Interestingly there is some evidence that simplistic measures of SMC (e.g., simply asking older adults if they struggle with their memory) are able to divulge clinically significant information about memory functioning and decline (Mattos et al., 2003).

1.10.1 Limitations of Using Subjective Memory Complaints

A glaring issue with using SMC as an indicator of decline is the lack of strong associations between these and objective measures of memory across a number of cross-sectional studies (Hänninen et al., 1994; Jonker, Launer, Hooijer, & Lindeboom, 1996). Disparate conclusions about the utility of SMC have been reached on the basis of such outcomes, with some finding no relationship between SMC and quantifiable memory deficits (Jungwirth et al., 2004). If such research is accurate and representative it calls into question the appropriateness of subjective memory complaints as a diagnostic criterion for MCI. The functional use of a diagnostic category like MCI is for intervening and slowing or halting subsequent cognitive and functional declines, and so if the commonly used criteria are unable to identify those most at risk then this needs refinement. It is possible that the lack of significant findings reflects an issue with testing, whereby individuals suffering from early declines are sensitive to these before the declines cause impairment of 1.5 standard deviations

below age-adjusted norms (Abdulrab & Heun, 2008); this would strengthen the argument for taking SMC into account in diagnosing early decline. There are also studies that have shown a significant link between SMC and cognitive declines, including an awareness of a deficit preceding and existing through until mild dementia (Schmand, Jonker, Hooijer, & Lindeboom, 1996; Schofield et al., 1997). A meta-analysis of studies with longitudinal designs provided further evidence that subjective complaints may be a significant and reliable indicator of cognitive decline over time (Jonker et al., 2000). Furthermore, a review of this literature concluded that methodological limitations call into question the validity of many studies that found no association, and in particular raised questions about the appropriateness of drawing conclusions from cross-sectional studies instead of longitudinal research (Jonker et al., 1996). In contrast, a number of studies dispute the usefulness of SMC as a diagnostic criterion for MCI, citing the difficulties in measurement and inconsistencies in the observed relationship between SMC and progressive cognitive impairment (Yates, Clare, & Woods, 2015). In particular, one possible confounding factor of SMC are psychopathological mood and anxiety manifesting with difficulties in memory (McDougall, Becker, & Arheart, 2006), with an established relationship seen between depression and anxiety with SMC among older adults (e.g., (Minett, Da Silva, Ortiz, & Bertolucci, 2008; Zandi, 2004)).

Older adults experiencing SMC have been shown to have smaller hippocampal volume (van der Flier et al., 2004), were more likely to show white matter lesions on MRI (Purser, Fillenbaum, & Wallace, 2006), and are significantly more likely to display the Apolipoprotein E4 allele (ApoE4, (Small et al., 1999)). Reduced hippocampal volume, ApoE4, and white matter lesions have all been linked to increased likelihood of AD, meaning that if these are related to the expression of SMC, then it may be a good predictor of subsequent decline. Whereas both allele expression and neuroimaging have shown utility in diagnosing and predicting cognitive declines, neither are efficient screening tools, or able to

be administered widely to at risk older adults. If these risk factors were related to a behavioural presentation that could be identified efficiently this would be a useful tool in assessing cognitive declines (Lonie et al., 2009). Although such evidence is currently lacking, there is ongoing research in order to elucidate this relationship further and demonstrate the strength of links between SMC and neuropathological changes (Petersen et al., 2010). Overall, given the inconsistency of research findings to date, and vast range of sampling on SMC, more research is required to identify the best way of measuring SMC in order to inform MCI diagnosis and make predictions about disease progression.

1.10.2 Subjective Non-Memory Complaints

The concept of self-reporting cognitive difficulties in the context of non-amnestic declines is more problematic than for amnestic declines. Cognitive changes likely to present with non-amnestic and multiple-domain MCI, theorised to represent prodromal FTD and VaD, include changes in personality and deficits in executive functioning (Isella et al., 2006; Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999). Although individuals tend to understand the concept of memory and what a memory deficit may entail, it is unlikely that they are able to notice or verbalise changes to executive functions, which creates problems for criteria of decline based on self-report. Furthermore, individuals with poor insight into their functioning are also likely to be unable to self-report memory or other cognitive deficits. This has led to many researchers and the NIA working group expanding the operational definition of "subjective" complaints to include either self-reports, informant-reports, or clinician judgement of cognitive decline (Albert et al., 2011; Lenehan et al., 2012).

A final issue with the convoluted phenomenon of SMC arose through research linking SMC more strongly to personality characteristics than to memory deficits, arguing that such individuals' anxiety about memory difficulties was more likely to cause presentation of impairment than an objective memory deficit (Hänninen et al., 1994). According to this view,

worry about possible memory declines and its ramifications become self-fulfilling, which has been termed *stereotype threat*.

1.11 Stereotype Threat

Negative stereotypical beliefs about a group can have a significant effect on the performance of that group, with stronger belief in the stereotype increasing the impact (Spencer, Logel, & Davies, 2016). In particular there is some evidence that older adults who believe themselves to be declining, and believe that older adults in general perform poorly, will conform to this stereotype on neuropsychological testing (Hess et al., 2003). When individuals have such concerns these can increase cognitive load, and reduce the processing capacity for test taking (Cavanaugh, 1996; Chasteen, Bhattacharyya, Horhota, Tam, & Hasher, 2005). Even subtle or unconscious priming appears to decrease older adults' performance on memory measures, indicating the strength and cognitive accessibility of stereotypes of decreased memory and competence in old age (Barber & Mather, 2013; B. Levy, 1996; Stein, Blanchard-Fields, & Hertzog, 2002). In particular, working memory appears to be negatively affected by stereotype threat (Schmader & Johns, 2003); because working memory is often a construct used in diagnosing age-related cognitive decline, this may result in false positives through lowered neuropsychological scores. The existence of stereotype threat has important implications for research on age-related cognitive declines, so it is important to reduce the cognitive load associated with these worries as much as possible, as well as removing stereotype primes from the research procedure.

Stereotype activation can initiate a physiological stress cascade and increase cardiovascular effort, which can have a further negative impact on test performance (B. Levy, Hausdorff, Hencke, & Wei, 2000). The opposite does not appear to be true, as priming positive older adult stereotypes does not confer a protective effect, or reduce cardiovascular stress response (Chasteen et al., 2005; B. Levy et al., 2000). There is an established

relationship between elevated anxiety and decreased performance on neuropsychological tests (e.g., (Hickey, 1980; L. F. Wolf & Smith, 1995)), and one possibility is that stereotype threat may have a flow-on effect of causing anxiety, further affecting cognitive functioning of older adults. As mentioned previously, anxiety also has a potential impact on the SMC individuals report, and so it is possible that stereotype threat increases the presentation of MCI through elevating SMC in otherwise cognitively intact individuals.

The concept of stereotype threat is not without issues however, and in particular the impact of stereotypes appears to be moderated by the perceived importance of memory, where individuals attributing great importance to memory were significantly more affected by stereotype activation (J. Aronson et al., 1999; Hess et al., 2003). There are also potentially significant limitations in many of the studies in the area, including no direct measurement of stereotype activation, or generalisation being limited by the use of overly strong manipulations (e.g., explicitly stating that aging damages memory) (Chasteen et al., 2005; Hess et al., 2003). The outcome memory measures have also been questioned, again relating to the difficulties arising from a lack of standard neuropsychological batteries or approaches for measuring memory decline in older adults, as discussed above. Overall, the current evidence indicates that there is an impact of negative age-related self-stereotypes on neuropsychological performance, but that this is moderated by other factors. From a practical research view this means that stereotype activation needs to be limited, with efforts made through neuropsychological test administration to utilise non-specific encouragement and allow older adults to perform to their potential. This can be achieved subtly by deemphasising the memory component of tests, or more overtly by giving older adults positive information about aging (Hess et al., 2003).

1.12 Treatment and Prevention of MCI

Given the costs associated with dementia and age-related cognitive decline in general,

many attempts have been made to treat or prevent such declines, however with mixed success. There is also an increasing body of research work being undertaken to try and slow or prevent future decline, along with understanding the processes and risk factors involved in dementing disorders. Pharmacological and behavioural interventions are both being trialled, and novel treatment approaches are regularly being developed.

1.12.1 Neural Reserve Hypothesis

Theories of preventing cognitive decline are largely based around concepts such as the neural reserve hypothesis, which refers to the capacity for the brain to cope with age-related changes and disease pathology (Fratiglioni & Wang, 2007). This hypothesis is based on findings at autopsy, where many older adults did not demonstrate the level of impairment that the pathological changes in their brains would have predicted (Boyle et al., 2013; Riley, Snowdon, & Markesbery, 2002; Satz, 1993). It has then been theorised that maintenance of a healthy brain may offer protection from cognitive declines, or mean that a greater degree of pathological change is required before it has an observable impact (Kempermann, 2008). It is likely that susceptibility to dementia is comprised of a range of genetic, environmental, and biological factors, along with the impact and interaction of these across the life-span (Fratiglioni & Wang, 2007). If so, then through positive lifestyle factors and engaging in activities that positively impact neural health it is possible that the onset of dementia could be delayed or prevented (Scarmeas & Stern, 2003; Wang, Karp, Winblad, & Fratiglioni, 2002).

1.12.2 Life-Span Activities

The idea of cognitive activity and engagement over the lifespan having an impact on late-life cognitive health has been a growing area of research, based on the neural reserve concept. This has led to evidence that higher frequency of cognitive activity during formative periods are related to better cognitive function in old age (Wilson et al., 2005). Engagement

in cognitively stimulating work and leisure activities appear to contribute to neural reserve, with ongoing activity leading to increasing reserve in late life (Fritsch et al., 2007; Karp et al., 2006; Wilson et al., 2013). Conversely, the colloquial phrase, *use it or lose it*, appears to refer to the opposite side of developing neural reserve across the lifespan, whereby a deficit of neurologically stimulating activity can decrease individuals' capacity to cope with pathological neural changes in old age (Salthouse, 1991).

Research has demonstrated that being involved in leisure activities with cognitive, physical, and social components during mid-life and adulthood can improve memory functioning (Christensen & Mackinnon, 1993). An example of this is seen in research linking increased cardiovascular risk factors at mid-life (age approximately 40) to a 24% to 46% increased risk of dementia in old age (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). This has been specifically looked at in terms of ongoing physical activity promoting physical health and decreased cognitive impairment from mid-life through to old age (Singh-Manoux, Hillsdon, Brunner, & Marmot, 2005). Although there are few Randomised Controlled Trials (RCT) to test the impact of more frequent participation in these areas and the corresponding effect on neural reserve, longitudinal and correlational studies provide reasonable evidence in support, given that the trends are consistently observed (Karp et al., 2006). Overall, this indicates that neural reserve is a dynamic process and that lifestyle changes can have an impact at any stage of life, and even during old age there are protective benefits from maintaining a varied and active lifestyle (Wilson et al., 2013; Wilson et al., 2002b). Even small contributions of physical, cognitive, and social enrichment appear to have a significant impact on reducing the incidence of cognitive declines and dementia, with more engagement resulting in a lower likelihood of cognitive decline (Karp et al., 2006).

1.12.3 Participation in Cognitive Activity

Cognitive activity has been proposed as directly leading to neural reserve, and links

between cognitively demanding occupations and decreased likelihood of developing dementia are prevalent in literature on age-related declines (Karp et al., 2006; Sachdev et al., 2013). On a related note, education appears to have a similar protective effect, whereby those with a higher level of education have a lower likelihood of dementia in old age (Callahan et al., 1996; Wilson et al., 2013). This trend remains even when confounding effects such as cardiovascular health and age are controlled for (Ott et al., 1995). The interrelationship between education and occupation is important however, as neural reserve appears to be encouraged throughout the lifespan by cognitive load (Stern et al., 1994), and less time spent in schooling does not prevent individuals from working in cognitively stimulating occupations. These trends are further demonstrated by research from developing nations indicating the increased impact of a lack of education and demanding work for women resulting in higher prevalence rates of MCI for women (Ho, Woo, Sham, Chan, & Ashley, 2001; Zhang et al., 1990). These results contrast with those from prevalence studies conducted in Western countries with a longer history of opportunities for women, as the gender distribution of cognitive decline tends to be similar, particularly after controlling for age (M. K. Aronson et al., 1991).

Cognitive activity in old age remains important, with strong relationships observed between the frequency of cognitive engagement and cognitive health. This pattern appears to remain valid even when controlling for important factors such as age, education, and sex (Wilson et al., 2002a). One longitudinal study provided strong evidence for this trend and established that maintaining cognitive activity is a protective factor, where those reporting more frequent baseline cognitive activity were 47% less likely to be diagnosed with AD by the end of the 4.5 year trial (Wilson et al., 2002b). Observational studies have resulted in similar outcomes, with cognitive activity in old age consistently demonstrating benefits in terms of decreased likelihood of developing dementia (Verghese et al., 2006; Wilson et al.,

2002a). It is theorised that frequent cognitive activity promotes working memory and processing speed, which helps to overcome early deficits via providing a compensatory mechanism (Reuter-Lorenz et al., 2000; Stern, 2003). Overall, a pattern is seen in older adults engaged in frequent cognitively stimulating leisure activities, where age-related cognitive declines are slowed and normal cognition is maintained for longer (Ball et al., 2002; Sattler, Toro, Schönknecht, & Schröder, 2012; Spector et al., 2003; Verghese et al., 2006).

1.12.4 Participation in Physical Activity

Maintaining physical activity in old age has long been encouraged for physical health, but longitudinal studies provide evidence that cognitive declines can also be prevented or delayed by adequate physical exercise (Heyn, Abreu, & Ottenbacher, 2004; Lautenschlager et al., 2008). One such study following 5,925 women over an 8 year period demonstrated that those in the highest quartile for physical activity were 37% less likely to experience cognitive declines than those in the lowest quartile (Barnes, Whitmer, & Yaffe, 2007). This is not an isolated finding, as other longitudinal research has demonstrated protective benefits of between 30% and 50% reductions in cognitive decline and dementia (Abbott et al., 2004; Karp et al., 2006; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Wilson et al., 2002b). While the majority of these studies looked at dementia, it is expected that the protective effect of physical activity on cognitive decline would also occur early on in the process of decline, given the range of evidence as to the benefits of ongoing physical activity. For example, continued exercise in late-life also reduces the likelihood of obesity and vascular events, including cerebrovascular damage (Heyn et al., 2004; United States Department of Health & Services, 1996). Moreover, based on animal models it is currently thought that physical activity directly contributes to neurogenesis and synaptogenesis, as well as elevated levels of neurotrophic factors, all of which contribute to neural health and the ability to compensate for pathological damage (Adlard, Perreau, Pop, & Cotman, 2005;

Cotman & Berchtold, 2002; Kronenberg et al., 2006). There is also emerging evidence for these processes outside of animal models, and a number of advantages to continuing to be physically active after retirement have been demonstrated, including: prevention of significant declines in cerebral perfusion (Lucas et al., 2012; R. Rogers, Meyer, & Mortel, 1990); increased production of neurotrophic factors (Dishman et al., 2006), and maintenance of higher neural tissue density even after adjusting for age (Colcombe et al., 2003).

Short-term physical interventions with older adults have demonstrated a statistically significant improvement in cognitive performance, and in particular executive functioning and processing speed appear to improve with cardiorespiratory fitness (Barnes et al., 2007; Colcombe & Kramer, 2003). This trend also appears with older adults already experiencing cognitive decline, further demonstrating the dynamic protection and restorative effect that lifestyle choices can have on cognitive health (Colcombe & Kramer, 2003; Diesfeldt & Diesfeldt-Groenendjik, 1977; Heyn et al., 2004). However, many of the studies on the positive benefit from exercise have suffered from methodological shortcomings, in particular small sample sizes or exclusion criteria removing older adults with cognitive disorders (Heyn et al., 2004; Keysor & Jette, 2001). Therefore, there is a possibility that protective effects may not be as large as reported for older adults in general, and correlational studies of this type need to be interpreted with caution.

The impact of physical activity on preventing early cognitive declines is less clear, with some research indicating that between-group physical activity levels were not related to MCI (Broe et al., 1998; Middleton, Kirkland, & Rockwood, 2008; Sumic, Michael, Carlson, Howieson, & Kaye, 2007; Wang et al., 2002), whereas other studies have demonstrated a significant risk reduction of developing MCI with higher frequencies of physical activity (Etgen et al., 2010; Geda et al., 2010; Lytle, Vander Bilt, Pandav, Dodge, & Ganguli, 2004). Furthermore, a RCT specifically looking at introducing exercise as a non-pharmaceutical

intervention in MCI found significant cognitive improvements in the treatment group, but this trend was much stronger for women than men (Baker et al., 2010). Although the majority of studies support the view that lower frequency of physical activity has a significant effect on the likelihood of developing dementia, one possibility for contrary findings for MCI may arise from the heterogeneity of older adults, and the vast range of presentations amongst those at risk of early decline. The effect of exercise on the biological mechanisms hypothesised to offer protection from cognitive declines may become more apparent as the disease progresses, and therefore some cases of MCI may represent *prevented AD,* whereby individuals demonstrate the neuropathology of AD but not the behavioural presentation of the disease (Middleton et al., 2008). A meta-analysis looking at physical activity across 15 studies and 33,816 participants indicated a 38% decreased likelihood of cognitive decline amongst highly physically active older adults, and a 35% difference for those engaging in low to moderate physical activity (Sofi et al., 2011).

1.12.5 Participation in Social Activity

As with physical and cognitive considerations there is now extensive evidence that social integration and an active social support network have beneficial effects on health outcomes (Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; House, Landis, & Umberson, 1988; Kawachi et al., 1996; Saczynski et al., 2006). There are strong links between social support and quality of life (Becker et al., 1998), mortality (Welin, Larsson, Svärdsudd, Tibblin, & Tibblin, 1992), and psychiatric disorders (Litwin, 1998). Health outcomes and the progression of age-related cognitive declines also tend to be worse for single older adults, and those without close family support (Cervilla & Prince, 1997; Fratiglioni et al., 2000; Nicholson, 2012). Given the impact of a socially-integrated lifestyle on a range of physical and psychological outcomes, it has been theorised that social activity could delay the onset of cognitive decline because of its impact on mental and emotional

stimulation, and other physical health benefits (Ho et al., 2001; Saczynski et al., 2006; Steptoe, Shankar, Demakakos, & Wardle, 2013; Wang et al., 2002); it is possible with adequate social support that individuals would be better placed to cope with MCI or other minor age-related difficulties (Fratiglioni et al., 2000). Through such meaningful social interactions the environment of older adults is enriched, and this in turn promotes cognitive health and neuroplasticity (Nithianantharajah & Hannan, 2006; Rosenzweig & Bennett, 1996; Wang et al., 2002). Another possible mechanism for this protective effect comes from findings that social activity in old age can affect the immune system, specifically by reducing inflammatory markers in the brain, which are hypothesised to decrease the neuropathological processes of dementia (Fratiglioni et al., 2000; Karp et al., 2006; Seeman, 1996). Engaging in pleasurable social activities regularly appears to offer protection from subsequent cognitive declines, and research shows a consistent pattern of lower incidence rates of dementia and age-related cognitive decline amongst individuals that remain socially engaged in older adulthood (Karp et al., 2006; Saczynski et al., 2006; Wang et al., 2002). The degree of social integration necessary for an effect to be seen appears to be minor, suggesting that there is a dose response effect with decreasing incidence rates correlated with higher social integration (Verghese et al., 2006; Wang et al., 2002). For individuals with little or no social support the risk of dementia is up to 60% greater than those with close family or friends (Fratiglioni et al., 2000; Verghese et al., 2006); it also appears that for individuals who experience social disengagement as they age there is a far greater likelihood of developing dementia (Saczynski et al., 2006; Wang et al., 2002).

1.12.6 Pharmacological Treatment

Pharmacological therapies for dementia have attracted a large amount of research attention, and multiple attempts have been made to reduce the neuropathology associated with dementing disorders, as well as their behavioural sequelae. Cholinesterase inhibitors

such as donepezil are readily prescribed for individuals with AD to increase the acetylcholine available for neurotransmission, which reduces the impact of AD pathology (Doody et al., 2001; Fillit et al., 2002; S. Rogers, Doody, Mohs, & Friedhoff, 1998). While the impact of such medications is small, any reduction in impairment is worthwhile, and so the use of cholinesterase inhibitors is common. Another potential treatment is Vitamin E, with some evidence that this can have a small impact on slowing the rate of subsequent decline (Giraldo, Lloret, Fuchsberger, & Vina, 2014; Sano et al., 1997), although there have been few controlled studies supporting this (Farina, Isaac, Clark, Rusted, & Tabet, 2012). The ubiquitous nature of pharmacological treatment approaches have led to trials being conducted looking at adapting medications used to treat AD for treating MCI, attempting to halt the declines before they reach the level of AD (Petersen et al., 2005). There have been mixed results from such trials, with no impact from Vitamin E, but a possible slowing from cholinesterase inhibitors seen in one study (Feldman & Jacova, 2005). Other pharmaceutical options have been considered based on animal models, such as muscarinic agonists (Avery, Baker, & Asthana, 1997) and glutamate modulators (Winblad & Poritis, 1999) but so far no pharmacological treatment has been shown to be an effective and efficacious treatment for MCI (Farina et al., 2012; Fillit et al., 2002; Gauthier, 2004; Ströhle et al., 2015). Overall, findings to-date have been statistically significant but lacking practical clinical benefits. However, research into novel pharmacotherapeutic treatment of MCI is likely to continue, with ongoing studies experimenting with medications targeting neuropathological substrates of cognitive decline (Karakaya, Fußer, Schroder, & Pantel, 2013; Raina et al., 2008). In particular the focus appears to be on developing symptomatic pharmacotherapy to slow or halt decline, and to demonstrate clinically significant effects, beyond what has been shown to date (Jelic & Winblad, 2003).

1.12.7 Non-pharmacological Treatment

Due to the evidence that maintaining cognitively enriching and stimulating leisure activities can prevent or delay the onset of MCI, a number of interventions have been trialled for increasing this protective effect (Acevedo & Loewenstein, 2007). Non-pharmacological therapies have been advanced, in part due to the lack of success with trials of pharmacological treatments. Cognitive and physical interventions have been trialled, with the intention of demonstrating an improvement in episodic memory and executive functioning, given that these cognitive aspects are often the first impaired in the process of cognitive decline (Teixeira et al., 2012). Experimental cognitive interventions have typically either been one of two therapy modalities, cognitive training or cognitive rehabilitation. Cognitive training has a focus on training a specific memory deficit, such as episodic memory, through the use of mnemonics and semantic elaboration techniques (Belleville, 2008; Clare & Woods, 2004; Rapp, Brenes, & Marsh, 2002). Cognitive rehabilitation focuses on supporting cognitive functions that are still preserved by utilising occupational and behavioural therapy (Cipriani, Bianchetti, & Trabucchi, 2006; Kurz, Pohl, Ramsenthaler, & Sorg, 2009; Talassi et al., 2007). Despite the strong theoretical basis for such interventions the results have been mixed, with some studies indicating only small or non-significant effects (Rapp et al., 2002; Talassi et al., 2007), while others suggest significant cognitive improvements even for individuals already suffering MCI (Ball et al., 2002; Belleville, 2008). The trend of results is encouraging but far from unanimous, and better quality trials for determining what types of cognitive enrichment and rehabilitation are successful are required (Acevedo & Loewenstein, 2007; Clare & Woods, 2004).

Physical interventions have the benefit of increasing cardiovascular fitness, with the associated positive outcomes mentioned previously, such as improved cerebral perfusion and preventing obesity and diabetes (Singh-Manoux et al., 2005; Teixeira et al., 2012). The area

that physical interventions appears to have the greatest impact on is executive functions (Colcombe & Kramer, 2003); this is theorised to be directly due to the improvement in cerebral perfusion allowing increased frontal lobe metabolism (Scherder et al., 2005; Teixeira et al., 2012). Individuals in treatment groups for physical activity interventions have demonstrated cognitive stability at 12 months follow-up, significantly higher than treatment-as-usual groups (Olazaran et al., 2004). A modest improvement in cognition was demonstrated after an 18 month follow-up in a RCT of a 24-week in-home exercise program for participants with self-reported memory difficulties (Lautenschlager et al., 2008). The exercise in question was relatively small, with only 150 minutes per week recommended, involving participants being encouraged to walk for 50 minutes at a time, on three occasions per week; importantly this only equated to an average of 20 minutes per day more than the treatment as normal condition. This demonstrates that even modest changes to physical activity are likely to have an impact, which is a conclusion often not shown in observational research comparing very physically active individuals against sedentary individuals (Barnes et al., 2007; Weuve et al., 2004). As an RCT this provides stronger evidence as to the causal relationship between physical activity and cognition; previous observational and correlational studies are unable to conclusively determine whether decreases in physical activity precipitate, or are a result of cognitive decline (James, Wilson, Barnes, & Bennett, 2011; Wilson et al., 2002b). Although there are few RCTs establishing the causality of cardiovascular fitness and decreased likelihood of developing age-related cognitive declines, the weight of evidence, and the presence of plausible biological mechanisms, suggests that maintaining physical fitness has a protective effect in old age. However, there remains a need for more physical intervention trials for preventing cognitive decline, as few RCTs have been conducted, and the evidence on prevention of dementia as opposed to short-term improvement in cognitive function is lacking (Valenzuela & Sachdev, 2009).

Social interventions have not been researched extensively, but the inclusion of a social component in physical interventions for AD appears to encourage treatment compliance (Tappen, Roach, Applegate, & Stowell, 2000). Other behavioural and social interventions have been poorly controlled and evaluated, which severely limits the conclusions that can be drawn from these (Zarit & Leitsch, 2001). Based on the impact of social supports and networks for maintaining cognitive and physical health in the presence of age-related cognitive decline, it is likely that interventions aimed at boosting social contact would be beneficial. However, it remains to be seen whether this is a viable treatment approach and whether the necessary controls can be implemented for valid conclusions to arise from such trials (Voigt-Radloff et al., 2011; Zarit & Leitsch, 2001).

1.13 Direction of the current study

1.13.1 Interim Summary

From the review above it can be seen that research on MCI is complex and with little agreement between studies as to the prevalence, diagnostic criteria, and screening methods to be used. It is also clear that persevering with attempts to detect older adults most at risk of developing dementia is financially and socially important, and will become an increasingly important health focus over the next 40 years. It is currently estimated that with increasing lifespans and the resulting increased prevalence of age-related cognitive decline that 115.4 million individuals worldwide will have dementia by 2050 (Prince et al., 2013). Current treatment approaches to dementia have demonstrated only limited success, and only temporarily slow the progression of decline. Novel treatment approaches including pharmaceutical and cognitive therapies are currently being trialled, but due to diagnostic difficulties individuals are not identified early enough in the disease process for such treatment to be effective. The most promising intervention target to halt cognitive declines appears to be *mild cognitive impairment*, a neuropathological condition involving deficits

beyond those expected as part of normal aging, but falling short of the diagnostic severity required for a dementia diagnosis. Individuals with MCI progress to dementia at a significantly higher rate than older adults in general, leading to hypotheses that MCI represents a prodromal stage of dementia.

There is no single agreed upon approach to detecting MCI, although the most common criteria were proposed by Petersen, and include subjective and objective memory deficits along with relatively intact activities of daily living and general cognition. More recently it has been theorised that non-AD dementias are associated with diverse presentations of MCI, and so it has been suggested that these criteria be expanded to include non-amnestic deficits. The particular tests used to measure early cognitive deficits are also debated, but the common approach is to measure a range of cognitive facets including memory, orientation, attention, and executive functioning. The major limitation in such detection has been in finding individuals early in the disease process, and this has led to a proliferation of short screening measures being developed. At present, many of these lack adequate evidence as to their reliability, validity, and screening utility. Moreover, traditional pen-and-paper tests are not necessarily efficient enough to utilise clinicians' time whilst identifying all those at risk. One possible solution to this is through a more global screening approach, and utilising more efficient techniques such as postal or telephone measures as a first-line screening methodology. At present the evidence in support of these alternative screening approaches is limited, due to methodological problems and issues with sampling; in particular, a reliance on inpatient groups hampers the generalisability of findings.

1.13.2 Objectives and Hypotheses of the Current Research

The principal aim of the present research was to explore the utility of a postal screening approach as a first-line screening methodology to detect cases of MCI amongst a community sample of older adults. This was undertaken using a combination of self-report,

informant-report, and cognitive screening measures in order to gather a diverse range of information pertinent to predicting cognitive decline. Frequency of participation in cognitively, physically, and socially stimulating activities was also collected as part of the screening approach, to research what impact such engagement has on MCI.

A neuropsychological battery was administered to all participants to validate the screening measures, and to indicate how accurate the screening tools were for predicting likely cases of MCI. Given the measures chosen to be used in the postal screening it was hypothesised that the postal measures would detect cases of MCI significantly better than chance, and that this approach could be shown to be a valid multi-stage screening methodology. In particular, SMCs as measured through self- or informant-reports have been linked with subsequent cognitive declines, and generally older adults are able to accurately identify the early signs of amnestic impairment. Furthermore, due to the importance of SMCs in the diagnosis of cognitive declines it was hypothesised that a self-report measure would increase the diagnostic utility of a postal screening tool.

One issue across the field of research on MCI and the prediction of further cognitive declines has been reliability of diagnoses, with individuals appearing to revert to normal cognition from an impaired state. It has previously been theorised that informant-reports may be unaffected by the transient declines seen in this group, and thus it was hypothesised that the combination of a self-report and informant-report would help to differentiate cases of transient cognitive decline from progressive neuropathological conditions.

The second stage of the present research aimed to test the reliability of the screening tools used by reassessing the participant group after 12 months. Whilst one year is a relatively short retesting period, between 5.3% and 41% of individuals with MCI are predicted to decline into diagnosable dementia over this period; meaning that even a 12-month follow-up

should be long enough to detect further declines amongst some participants, while seeing a reliable pattern of scores amongst cognitively intact older adults. Thus, it was hypothesised that the screening tools trialled in the current study would demonstrate high reliability at a 12-month follow-up. Moreover, a further possibility was that the self-reports and informant-reports of decline could be predictive of further declines, so that Time 1 postal measures may have predictive validity for subsequent cognitive deterioration.

Reliability of diagnoses have been inconsistent across previous research into MCI, particularly when subtypes of MCI are considered. Therefore, the present research aimed to assess the reliability and consistency of MCI diagnoses amongst a community sample. It was of interest whether MCI diagnoses based on the Petersen criteria demonstrated reliability over time, given that this is the most common diagnostic schedule in use. A further aim was to explore the reliability of an expanded Petersen criteria to include MCI subtypes including amnestic, non-amnestic, and multiple-domain MCI. Finally, the disparate nature of these theoretical subgroups can be explored through using multivariate statistical methods such as cluster analysis, by determining whether the resulting groups correspond to the predicted subtypes and whether they are able to be independently detected from neuropsychological data. The current sample size was limited, so these analyses are considered exploratory, but if MCI subtypes represent orthogonal groups then such statistical clustering may demonstrate this.

A final aim was to collect information about current and historical engagement in stimulating activities to test the relationship between such involvement and cognitive declines over time. Based on the neural reserve hypothesis it was predicted that older adults with more frequent involvement in cognitively, physically, and socially stimulating activities would show less incident decline, represented by less change between Time 1 and Time 2. Similar engagement throughout the lifespan has also been theorised to offer protective benefits in old

age, and such information was also collected to test this alongside the impact of current activities on cognitive health.

1.13.3 Summary

The current research aimed to explore cognitive screening with a more generalisable community sample than previous work, along with demonstrating the utility of first-line postal screening through a meaningful comparison with standardised neuropsychological measures. The practical benefit of such community screening is in reducing the burden on health practitioners, and allowing in-depth psychometric administration to be used only where necessary. A further aim was to assess the presence of varied MCI subtype presentations amongst a representative community group, and to investigate the reliability of such diagnoses over time.

2. General Methods

2.1 Participants and Procedure

Participants were recruited from Canterbury, NZ, from a range of sources. Community groups (e.g., Rotary, Probus) were initially contacted, and they passed project information on to interested members. An advertisement was also placed in *Age Concern*, a free local newsletter with an older adult target population. The remainder of the sample were recruited from the New Zealand Brain Research Institute (NZBRI) volunteer database, containing names and contact information from 1,300 older adults who were healthy at the last point of contact. Before beginning to recruit from this database the order of individuals was randomised so that participants were not more likely to be contacted based on particular demographic variables. Contact was made with a total of 145 individuals who expressed interest in the present research. Contact was attempted with approximately even proportions of male and female volunteers from the NZBRI database, but more female individuals were able to be contacted, and therefore offered participation. The sample size was maximised given the resource and time constraints of the project, where N=110 participants were needed for an estimated power of 90% to detect a significant correlation of $r = .3$ with $\alpha = .05$ (two tailed). It was also thought that participant drop-out of 20-30% was possible, so recruitment continued beyond the N=110 calculated.

Postal screening measures were sent to all interested individuals, and after a two-week period all were contacted again, and a neuropsychological testing session was organised. At the same time participants were reminded to bring corrective lenses and hearing aids as required for the neuropsychological testing. In total 114 participants (70 Female, 44 Male) completed the postal screening and neuropsychological testing at Time 1. Participants provided verbal consent upon initial contact, and written consent at the testing session. All participants were provided with full information about the nature and purpose of the study.

Ethical approval for the project was obtained from the University of Canterbury Human Ethics Committee (Appendix A).

After 12 months all individuals who completed participation at Time 1 were contacted again and were invited to take part in the second stage of the research, looking at any changes over time. In total 78 participants took part in both stages of the research (68.4%), including 49 females and 29 males.

2.2 Instruments

The postal screening questionnaires used included self-report and informant-report versions of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Appendix B and Appendix C), the Self-Administered Gerocognitive Examination (SAGE; Appendix D), and the General Activities Questionnaire (GAQ; Appendix E).

The IQCODE is a measure of change over time, and is comprised of 16 questions regarding memory and instrumental activities of daily living, such as handling finances (Jorm, 1994). Each item is scored on a five-point Likert scale, from *Much Improved* to *Much Worse* based on informants' ratings of change over the preceding 10 years, with the average of these used as a measure of memory and functioning change over time. The IQCODE has been used as a screening tool for a number of disorders and sources of cognitive decline including AD and VaD (Cherbuin & Jorm, 2011, 2013). It has also been used to assess post-stroke damage (Cullen et al., 2007; Jorm & Jacomb, 1989), and there is limited but encouraging evidence for using the IQCODE to detect MCI (Isella et al., 2006; Li et al., 2012). For the present research two versions of the IQCODE were completed by each participant, an informant-report, and a self-report. Each participant gave the informant copy to somebody who had known them for at least 10 years, and collected this back before returning the questionnaire. No contact was made with these informants, and therefore no

data were collected regarding them. Each participant was able to identify an appropriate informant.

The SAGE was developed to screen for MCI amongst older adults and involves assessing a range of aspects of cognition including orientation, memory, visuospatial abilities, and executive functioning (Scharre et al., 2010). The SAGE has 11 items which are scored out of 22 and summed to give a total score which has encouraging evidence for differentiating MCI and healthy older adults. The current study used an updated version of the SAGE with New Zealand demographic options, and modified currency terminology.

The GAQ was adapted from a semi-structured interview used by Robert Wilson in research on the effect of life-course and late-life involvement in stimulating activities on cognitive decline in older age (e.g., (Wilson et al., 2005; Wilson et al., 2013; Wilson et al., 2002b)). Questions assess involvement in cognitively stimulating activity during childhood, teenage, young adulthood, and middle age, as well as cognitively, physically, and socially stimulating activity at present. Each item was scored on a four-point frequency scale, from *Every day or almost every day* to *Several times a year/Rarely* with the scores averaged for each time point as an estimate of cognitive activity participation. As this questionnaire was adapted for the present research the psychometric properties are not known, but as a semi-structured interview the questions have demonstrated reasonable reliability and validity (Wilson et al., 2013).

Neuropsychological measures used in the objective cognitive testing were the Rey Auditory Verbal Learning Test (RAVLT), Brief Visuospatial Memory Test - Revised (BVMT-R), Trail Making Test (TMT), Verbal Fluency (including Letter Fluency, Category Fluency, Switching Fluency, and Switching Accuracy), and the Addenbrooke's Cognitive Examination – 3rd edition (ACE-III). Each of these were administered at Time 1, and

alternate forms used in retesting at Time 2 where these were available, to reduce any practice effects. Further information along with reliability and validity for these measures are provided below.

2.3 MCI Screening

Following completion of both postal and neuropsychological stages of the research, individuals were classified based on MCI criteria suggested by Petersen and the NIA (Albert et al., 2011; Petersen et al., 1997), including: a score of at least 1.5 standard deviations below age-adjusted scores on a standardised neuropsychological memory measure; generally intact cognitive functioning; SMC by self-report or informant-report; relatively intact ADLs; and not meeting diagnostic criteria for dementia. Current ADL difficulty was assessed through postal measures and by interview when participants came in for the neuropsychological testing session.

2.4 Empirical Results

The results from the present research are presented in five empirical chapters exploring different facets of the collected information. The number of participants varies between each of these chapters based on the analyses being conducted, and the number of available responses for these. Each chapter was prepared as a manuscript to be submitted for publication, and therefore some necessary repetition of introductory and methods material is included, although attempts have been made to minimize the redundancy.

Initially postal screening is looked at in the sample collected, with a focus on the utility of using postal screening tools as a first-line screening approach among a community sample of older adults (Chapter 3). The reliability over time of self-report and informant-reports is then explored, with a particular focus on how each of these relate to cognitive decline, and their ongoing applicability for multi-stage screening of MCI (Chapter 4). The

effectiveness of screening approaches over time is then analysed, with a focus on including cognitive screening, self-report, and informant-report in such screening approaches (Chapter 5). Following this, the relationship between life-course and late-life engagement in stimulating activities is explored in the context of subsequent cognitive declines, and the theoretical potential of such activity participation offering a protective effect for older adults (Chapter 6). Finally, subtypes of MCI are examined using cluster analysis, with a particular focus on the reliability of these distinct groups, and the practical usefulness of separating MCI diagnoses into subtypes early in the process of decline. All statistics were calculated using SPSS version 23 (IBM Corp, 2013), except for cluster analyses which were calculated using the Mclust package (Fraley & Raftery, 1999) in R (R Core Team, 2013).

2.5 Outcomes and Results

Participants were all offered a summary of results to be sent to them at the conclusion of the research. Given the potential impact of a diagnosis of MCI each participant was also offered a brief summary of their results if they so choose, including the recommendation that they speak to their GP if they had one or more low scores and were concerned about this. Given the potential impact of a false positive, care was taken during testing and in providing feedback so as to not cause alarm, as well as not overstating the accuracy of the results for any particular individual. However, it is also important that participants were given the opportunity to seek intervention if they were experiencing cognitive difficulties.

3. Postal Screening Effectiveness

3.1 Introduction

Age is the strongest risk factor for dementing disorders, such as Alzheimer's Disease (AD), which represent a growing concern in the developed world as medical interventions have prolonged the average lifespan (Anderson & Hussey, 2000). Although preventing dementia is increasingly a research focus, practical difficulties inhibit progress in developing interventions. One of these challenges is the early identification of those most at risk of dementia, and in particular older adults meeting criteria for mild cognitive impairment (MCI). MCI is theorised to represent prodromal dementia in an intermediate stage of cognitive decline, beyond that expected with normal ageing but without meeting full dementia criteria (Fischer et al., 2007). There is an increasing awareness that current screening methods are not sensitive enough to detect the majority of individuals with MCI, and typically deficits are only noticed once they progress in severity and meet the full criteria for AD (Ahmed et al., 2012). An efficient and reliable screening process for MCI is crucial for progress in developing interventions to reduce the impact of AD (Petersen & Negash, 2008). If MCI can be detected, then early treatments developed to slow or halt declines are more likely to have a clinically significant effect on cognitive and adaptive functioning of older adults.

Currently the identification of MCI is limited by the tools available to primary care physicians when screening for cognitive difficulties (Cullen et al., 2007; Kazui et al., 2005; Lindeboom & Weinstein, 2004). MCI assessments by physicians tend to be brief and easy to administer, but are relatively insensitive in the detection of the subtle decline associated with MCI (Scharre et al., 2010). This means at present the accurate diagnosis of MCI is reliant on lengthy and costly neuropsychological assessment (Petersen et al., 1999), and there remains a need for cost-effective, brief, reliable, and accurate first-line screening.

A large number of brief screening tools for AD have been developed and have extensive research support, and several of these have been trialled for detecting MCI, with varying degrees of success (Ahmed et al., 2012). Screening tools such as the Mini-Mental Status Examination (MMSE) and the Clinical Dementia Rating scale (CDR) have demonstrated only limited success for use in detecting MCI, despite being extensively used and relied on for the detection of dementia (Ahmed et al., 2012; Petersen, 2003). In contrast, there is growing evidence that the Informant Questionnaire Of Cognitive Decline in the Elderly-Short Form (IQCODE) (Jorm & Jacomb, 1989) may be an effective screen for MCI (Ehrensperger, Berres, Taylor, & Monsch, 2010; Isella et al., 2006; Li et al., 2012). Additionally, an increasing number of novel tests such as the Self-Administered Gerocognitive Examination (SAGE) and the Computer Administered Neuropsychological Screen (CANS) have been developed specifically for use in detecting cases of MCI, all with the goal of increasing diagnostic utility without being costly and difficult to administer (Cullen et al., 2007; Scharre et al., 2010; Tornatore, Hill, Laboff, & McGann, 2005). However, a significant limitation of all these screening tools is the necessity of face-to-face administration, meaning that even the few screening tests with adequate psychometric properties are still time consuming and are not cost effective.

A number of studies exploring multi-stage screening for MCI have been conducted, with the majority of these using telephone interviews to increase participant convenience and decrease clinician administration time (Jansen et al., 2008; Welsh et al., 1993). The drawback with telephone interview screening is that it still requires appropriately trained individuals to administer the test, and therefore does not completely remove the problems with traditional face-to-face screening approaches. Using postal questionnaires as a first-line screening approach would circumvent this time investment further and allow a more global approach to cognitive screening, potentially assessing a wider range of individuals than would likely

present to primary care physicians, and to detect declines before they advance to the point that individuals seek medical help (Andersen et al., 2010; Hábert et al., 1996). Once such first-line screening has been administered the individuals most likely to be experiencing early cognitive impairment can then be assessed further, thereby reducing the extent of testing to only those most likely to meet MCI criteria.

However, limitations of scope and design have largely restricted how useful such postal and telephone screening attempts have been in the past (Cullen et al., 2007; Jansen et al., 2008). Some problems have included testing of self-report measures without having a criterion for comparison (Jansen et al., 2008); only examining memory deficits and neglecting other possible cognitive declines early in the AD process (Beversdorf et al., 2007; Cullen et al., 2007); and screening tools only being compared to the MMSE, which has consistently been shown to be a poor predictor of MCI (Ahmed et al., 2012; Lonie et al., 2009; Petersen, 2003). A further limitation with some trials of postal or telephone screens is that neuropsychological tests have only been administered on those identified as MCI by the screening measure, therefore providing no way to assess the specificity of the measures (van Uffelen et al., 2007).

The present study attempted to address these limitations by testing the utility of postal screening measures and following all participants up with neuropsychological testing, which allowed MCI to be diagnosed. Specifically, our goals were 1) To validate a postal screening approach to identifying individuals in the community with MCI; and 2) To compare the effectiveness of the IQCODE and SAGE as postal screening tools. This was explored by administering cognitive screening via postal questionnaires and following this up with a brief neuropsychological battery in order to look for patterns indicative of early decline in a community sample.

3.2 Method

3.2.1 Participants

Community groups in Christchurch, NZ, (e.g., Rotary and the Alzheimer's society) were contacted, and an advertisement was also placed in *Age Concern*, a free newsletter with an older adult target population. Further participants were recruited from the NZBRI volunteer database, containing names and contact information from 1,300 older adults who were healthy at the last point of contact. In total 145 individuals were contacted for the present study, of whom 114 completed both the postal and neuropsychological stages of the study. The only inclusion criteria were that participants were at least 65 years old. The only exclusion criterion was that participants had not received a diagnosis of dementia.

All interested participants were mailed the screening questionnaires, and after a two-week period were again contacted to organise face-to-face neuropsychological testing. At this time they were reminded to bring corrective lenses and hearing aids as needed to the testing session. 114 participants took part through to the completion of the neuropsychological examination.

All participants gave informed consent at the testing session, and were fully informed about the nature and purpose of the study. Ethical approval for the project was obtained from the University of Canterbury Human Ethics Committee (Appendix A).

3.2.2 Instruments

To maximise the effectiveness of the brief screening it is important to get a range of information, namely a change from previous levels of functioning along with early signs of cognitive deficits in areas including memory and executive functions (Beversdorf et al., 2007;

Fischer et al., 2007). Several postal screening measures were used to efficiently gather information in these areas.

3.2.2.1 Postal screening measures

The Self-Administered Gerocognitive Examination (SAGE; Appendix D) is a recently developed screening measure for detecting early AD and MCI, and examines a range of facets of cognition including, memory, executive functions, orientation, and visuospatial manipulation (Scharre et al., 2010). It is comprised of 11 questions scored out of 22, and together these items are summed to give a total score, which has previously demonstrated effectiveness for differentiating individuals with MCI from both healthy individuals and those with dementia (Scharre, Chang, Nagaraja, Yager-Schweller, & Murden, 2014). We used an adapted version of the SAGE, with demographic questions that were appropriate for NZ, and modifications between USA and NZ terminology for money calculation questions.

The IQCODE includes 16 items asking about changes in memory over time, as well as difficulties in instrumental ADLs (Jorm, 1994). It has been used as a screening tool for a number of disorders including AD, VaD, MCI, and to assess post-stroke damage (Cullen et al., 2007; Jorm, 1994; Jorm & Jacomb, 1989). Each item is scored on a five-point scale from *Much Improved* to *Much Worse*, and the average score is taken from the 16 items (Jorm, 2004). The IQCODE items assess memory functioning, as well as instrumental ADLs such as handling finances or using familiar household products (e.g., Microwave oven). Participants were asked to complete two versions of this measure, an informant-report (IQCODE (IR); Appendix B), to be completed by someone who had known them for at least 10 years, and a self-report (IQCODE (SR); Appendix C). Reviews of the use of the IQCODE in assessing cognitive decline indicate limited evidence for a cut-off on this measure indicative of MCI (Cherbuin & Jorm, 2011, 2013), but two studies have demonstrated that

3.19 represented the optimal sensitivity and specificity for differentiating MCI and healthy older adults (Isella et al., 2006; Li et al., 2012).

3.2.2.2 Neuropsychological measures

The Brief Visuospatial Memory Test Revised (BVMT-R; (Benedict et al., 1996)) is a measure of visual learning and memory including delayed recall and recognition. It involves participants remembering the shape and location of six geometric objects, and reproducing these immediately for three learning trials, and then reproducing these objects after a 30 minute delay. The BVMT-R was developed to address a lack of memory assessment instruments appropriate for repeated administrations, including multiple forms to reduce practice effects. Test-retest reliability is reported at .63 to .92 for delayed recall and total recall conditions, with an inter-rater reliability of .97 (Benedict, 1997). Moreover the BVMT-R appears to have good construct validity, with correlations of .62 to .77 with other memory and visuospatial construction measures (e.g., the Hopkins Verbal Learning Test and the ROCF), and .25 to .30 with tests of language ability (e.g., Boston Naming Test and Verbal Fluency) (Benedict et al., 1996).

The Rey Auditory Verbal Learning Test (RAVLT; (Rey, 1964)) assesses short- and long-term verbal memory, as well as recognition memory. Participants are presented with a list of 15 words read out 1-per-second and at the conclusion of the list have to repeat as many as they can remember for five learning trials, then after a 20 minute delay they are asked again to verbally list as many words as they can remember. The RAVLT has high test-retest reliability of .61 to .86 for the trials, and .51 to .72 for delayed and recognition conditions (Delaney et al., 1992). It also appears to have good content validity, correlating highly (.33 to .47) with other verbal learning and memory tasks, such as the CVLT (Macartney-Filgate & Vriezen, 1988).

Trails A and B from the Trail Making Test (TMT; (Reitan, 1958)) give information about executive functions, processing speed, visual scanning, and have also shown some utility in previous research for detecting MCI (Ashendorf et al., 2008). Participants are required to draw connections between items in ascending order as quickly and accurately as they are able. The TMT correlates fairly highly with other visual searching tasks (e.g., Digit Symbol Coding from the WAIS-III at .63), and in general tends to have high reliability coefficients reported at .65 and above (Lezak, 2004). Trails B is also correlated with measures of mental flexibility such as the Wisconsin Card Sorting Test (.59) (Kortte et al., 2002).

Verbal Fluency from the D-KEFS (Delis et al., 2001), including Letter Fluency, Category Fluency, Switching Fluency, and Switching Accuracy, gives a further measurement of executive functioning including inhibition control and cognitive flexibility, as well as divided attention (Gomez & White, 2006). Participants are required to generate a list of as many words as possible that fit the Letter Fluency condition within one minute. In older adults test-retest reliability is .70 or greater for Letter Fluency, which is considered more difficult than Category Fluency (Snow, Tierney, Zorzitto, Fisher, & Reid, 1988). Verbal Fluency is also only modestly correlated with memory measures (e.g., Wechsler Memory Scale short stories =.22, Selective Reminding Test =.17), meaning measurement on this task should not be particularly impacted by memory deficits (Ruff, Light, Parker, & Levin, 1997).

Finally, the ACE-III is a brief tool used to detect likely cases of MCI through an assessment of orientation, memory, visuospatial ability, and verbal fluency (Mioshi et al., 2006). The ACE-III subscales are correlated well with convergent neuropsychological measures, and it appears the ACE-III is a valid measure of these. Additionally the ACE-III correlated very highly with the ACE-R (.99) giving evidence that the many uses and validation studies completed on the previous version are likely to remain valid (Hsieh et al.,

2013). Collectively these neuropsychological tests briefly measure the most common early deficits seen in cognitive decline, and have been shown to be sensitive at detecting MCI and early deficits in AD (Aggarwal, Wilson, Beck, Bienias, & Bennett, 2005; Busse et al., 2006).

3.2.3 Procedure

Screening measures were mailed to all consenting participants. Three screening tools, the IQCODE (both versions) and the SAGE were mailed out together to screen cognitive functioning. Implied consent was obtained by telephone, and this was followed with written consent when participants attended the testing session. Participants all underwent the same battery of tests administered in the same order by a clinical psychology PhD student who had been specifically trained, and the testing took between 50-80 minutes.

3.2.4 MCI Screening

All psychometric tests were administered by a single clinician trained in their use, and this individual subsequently scored and interpreted the results which led to MCI classification. Individuals were classified as MCI based on the commonly used Petersen criteria (Petersen et al., 1997), including: a score at least 1.5 standard deviations below age adjusted norms on at least one memory test, along with subjective memory complaints; relatively intact ADLs; generally intact cognitive functioning; and not meeting diagnostic criteria for dementia. As per Petersen's criteria and NIA recommendations objective cognitive deficits were judged to be present if any one score was below the 1.5 standard deviation cut-off.

3.2.5 Data Analysis

Descriptive statistics were used to characterise overall responding. Following these analyses, *t*-tests were used to assess differences between MCI and non-MCI participants on

the postal measures used, and Receiver Operating Characteristic (ROC) curves calculated for each of the postal questionnaires assessing how well each predicted MCI. Odds Ratios (OR) were then calculated using logistic regression for each significant ROC analysis. Internal consistency of the Postal measures was calculated using Cronbach's alpha followed by an item analysis, and subsequent attempts at improving the predictive accuracy of the postal measures as assessed by ROC area.

3.3 Results

3.3.1 Participants

Participants were aged between 65 and 93 years at the time of testing (M = 75.04, SD = 5.88). In total 70 females and 44 males took part in the present study. Their ethnicity was similar to the expected distribution in Canterbury based on District Health Board (DHB) data from the 2013 census (Statistics New Zealand, 2013), with 95.7% of the sample NZ European/Pakeha, 1.8% British, 1.8% Asian, 0.9% Maori, and 0.9% other. Demographic information for participants are provided in Table 1.

Table 1
Participant Demographic Data

	Male N	Female N	Overall
Sex Total	44 (38.6%)	70 (61.4%)	114
Age			
- 65-69	8 (29.6%)	19 (70.4%)	27
- 70-74	10 (33.3%)	20 (66.7%)	30
- 75-79	14 (46.7%)	16 (53.3%)	30
- 80-84	10 (47.6%)	11 (52.4%)	21
- 85+	2 (33.3%)	4 (66.7%)	6
Ethnicity			
- NZ European/Pakeha	42 (38.9%)	66 (61.1%)	108
- Maori	1 (100%)	0 (0%)	1
- British	0 (0%)	2 (100%)	2
- Asian	1 (50%)	1 (50%)	2
- Other	0 (0%)	1 (100%)	1
Highest Level of Education			
- High School	27 (46.6%)	31 (53.4%)	58
- Post-school Training	3 (60%)	2 (4%)	5
- Undergraduate Qualification	8 (19.0%)	34 (80.9%)	42
- Postgraduate Qualification	6 (66.7%)	3 (33.3%)	9

Participants were categorised as either MCI or non-MCI based on the commonly used Petersen criteria (Petersen et al., 1997). Of the 114 participants, 34 were classified as MCI based on their reports of subjective complaints, normal ADLs, and neuropsychological test results. There was no significant difference in gender between participants in the two groups, with 20 females (28.6%) and 14 males (31.8%) meeting MCI criteria, χ^2 (2, 114)=.136, *p*=.712. The MCI group were significantly older than those without MCI (*M*=77.62, *SD*=5.26

vs. *M*=73.95, *SD*=5.82 years, *d*=.662). The age range was similar for both groups (69-85 for MCI and 65-93 for non-MCI).

3.3.2 Postal Measures Descriptive Statistics and Comparisons

Descriptive statistics for postal and neuropsychological tests are presented in Table 2 and the numbers of participants below cut-off values are also shown. For postal measures these are given at previously established cut-offs (Cherbuin & Jorm, 2011; Isella et al., 2006; Li et al., 2012; Scharre et al., 2010), and for the neuropsychological measures this is given by 1.5 standard deviations below age-adjusted norms.

Table 2
Descriptive Statistics for Postal and Neuropsychological Measures

	Mean	Standard Deviation	MCI Mean	MCI SD	Non-MCI Mean	Non-MCI SD	No. Below Cut-off
IQCODE (IR)	3.14	.37	3.27	.39	3.09	.35	62
IQCODE (SR)	3.16	.35	3.20	.45	3.14	.29	68
SAGE	19.28	2.73	18.24	3.96	19.73	1.86	10
BVMT-R							
- Delayed Recall	6.89	3.2	3.35	2.59	8.39	2.13	26
- Total Recall	17.26	7.07	9.91	5.97	20.39	4.85	25
RAVLT							
- Delayed Recall	9.11	3.4	6.38	3.60	10.28	2.61	8
- Total Recall	47.21	9.75	40.32	9.90	50.14	8.11	2
Verbal Fluency							
- Letter	40.64	12.21	37.41	12.57	42.01	11.88	12
- Category	37.82	8.64	35.00	7.82	39.01	8.74	11
- Switching Total	12.59	2.61	11.59	2.64	13.01	2.50	13
- Switching Accuracy	11.28	3.08	10.50	3.18	11.61	2.99	13
Trail Making Test							
- Trails A	36.58	13.15	41.62	16.30	34.44	10.99	3
- Trails B	97.54	59.82	133.09	85.16	82.44	36.25	12
ACE-III	88.42	6.98	83.76	8.26	90.40	5.28	41

Scores on the neuropsychological measures were converted to age-adjusted standardised scores based on established norms. Overall the present sample were significantly different from established age-adjusted norms and this was tested using single sample *t*-tests with 100 for standard scores, and 10 for scaled scores as the comparison. The only test that was not significantly different from previous norms was Trails B ($t(113)=1.75$, p=.083, M=103.84, $SD=23.42$). However, differences existed in both directions, for example on RAVLT Delayed Recall and Total Recall the sample scored significantly higher than expected $t(113)=5.38$, $p<.001$, $d=.50$ and $t(113)=9.86$, $p<.001$, $d=.92$ respectively. In contrast, both BVMT-R measures were lower than expected based on norms, Delayed Recall $t(113)=-2.64$, $p<.001$, $d=.23$ and Total Recall $t(113)=-5.03$, $p<.001$, $d=.47$.

There was significant variation in participants' scores across the three postal measures, as well as a ceiling effect observed on the SAGE where 14 participants reported the maximum score. Boxplots of these tests are shown on Figure 1, where z-scores were used for comparison between the different measures. A number of outliers were observed in the present result, indicating that while most participants were grouped closely together a number reported more extreme positive and negative cognitive changes, these outliers are shown by circles and stars on the figure and are more than 1.5 standard deviations from the median.

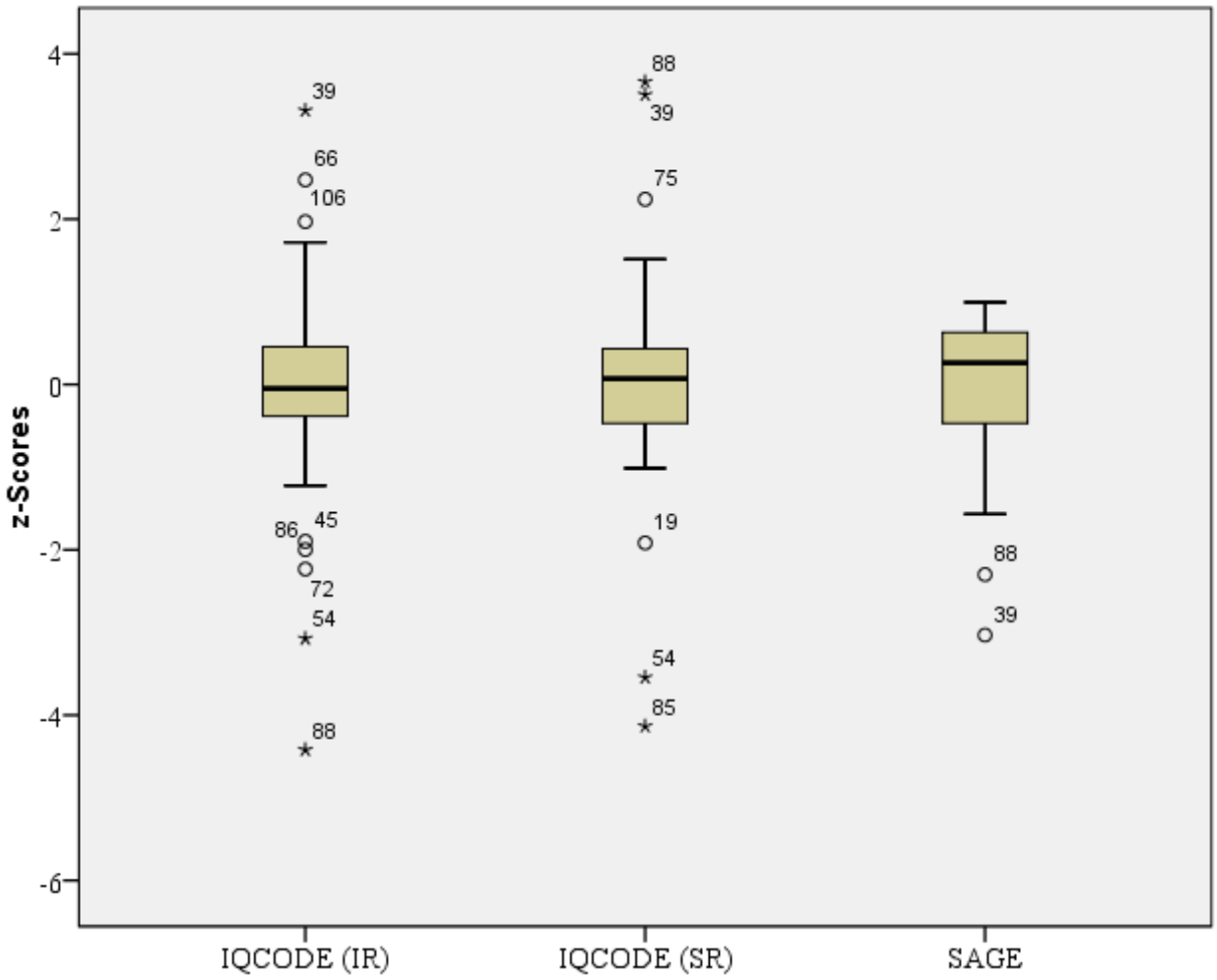

Figure 1. Boxplots of Postal Measures z-scores.

On two of the postal measures scores differed significantly between groups. Participants with MCI scored significantly below non-MCI individuals on the SAGE, $t(39.3)=2.74$, $p=.043$, $d=.48$ ($M=18.24$, $SD=3.96$ vs. $M=19.725$, $SD=1.856$). Moreover, on the IQCODE (IR) scores were significantly higher for those with MCI, indicating a higher level of memory difficulty $t(99)=-2.35$, $p=.021$, $d=.51$ ($M=3.27$, $SD=0.39$ vs. $M=3.08$, $SD=0.36$). However, for the IQCODE (SR) there was no significant difference between mean scores for the MCI and non-MCI groups, $t(104)=-.841$, $p=.125$, $d=.16$ ($M=3.20$, $SD=0.45$ vs. $M=3.14$, $SD=0.29$). Despite not being part of the postal screening, a planned comparison showed that the two groups differed on the ACE-III, with the MCI group scoring significantly lower $t(44.89)=4.321$, $p<.001$, $d=.96$ ($M=83.77$, $SD=8.26$ vs. $M=90.4$, $SD=5.28$.

3.3.3 Predicting MCI

ROC curves were calculated for each of the three postal measures (SAGE and both versions of the IQCODE). Each cut-off was also compared to cut-offs previously reported in the literature. The IQCODE (IR) had an optimal cut-off at 3.22, which gave a sensitivity of 57% and specificity of 70%. The Area Under the Curve (AUC) of the ROC curve for this analysis was 0.685 (p=0.004), and represented the highest predictive value of the three postal measures used. A follow up logistic regression gave an OR = 4.62, 95% CI (1.152, 18.56). The IQCODE (SR) had an AUC of 0.578 (p>.05), and the optimal cut-off was 3.20 with 46% sensitivity and 69% specificity. Two previous studies identified an estimated optimal cut-off at 3.19 using the IQCODE (Isella et al., 2006; Li et al., 2012) and using this value made no appreciable improvement to sensitivity or specificity of the current sample for either self-report or informant-report conditions. For the SAGE, the AUC was 0.624 (p=0.036), and the best cut-off was at 20.5, much higher than the previously reported 16 (Scharre et al., 2010). At a cut-off of 20.5 the SAGE had sensitivity of 77% and specificity of 46%. Using the established cut-off of 16 gave 14.7% sensitivity and 95.6% specificity in the present sample. The Odds Ratio for the SAGE was OR = 1.24, 95% CI (1.04, 1.49). Table 3 shows the correlations between the three postal measures and the neuropsychological measures collected. The SAGE was moderately significantly correlated with all neuropsychological measures used, while the IQCODE (SR) was only significantly correlated with both switching measures from Verbal Fluency, and the IQCODE (IR) was significantly correlated with the BVMT-R and the ACE-III.

Table 3
Correlations between Postal Measures and Neuropsychological Tests

	SAGE	IQCODE (IR)	IQCODE (SR)
Verbal Fluency			
- Letter Total	.342***	-.059	-.080
- Category Total	.252**	-.021	-.077
- Switching Total	.390***	-.094	-.202*
- Switching Accuracy	.393***	-.111	-.195*
Trail Making Test			
- Trails A	-.259**	.024	-.012
- Trails B	-.420***	.059	.083
BVMT-R			
- Delayed Recall	.311***	-.180*	-.095
- Total Recall	.323***	-.221*	-.089
RAVLT			
- Delayed Recall	.246**	-.047	-.114
- Total Recall	.329***	-.055	-.129
ACE-III Total Recall	.591***	-.236**	-.142
SAGE		-.096	-.175
IQCODE (IR)			.323**

* $p<.05$, ** $p<.01$, *** $p<.001$

3.3.4 Internal Consistency

Cronbach's alpha was calculated to measure the internal consistency of the items used in postal screening, and the IQCODE had high internal consistency (α=.915 informant-report, and α=.872 self-report). Internal consistency of the SAGE was lower than the IQCODE (α=.591), although assessing this item by item showed only a marginal improvement by removing one question (α=.605).

Despite strong internal consistency of items, an item analysis looking at the correlation of each postal question with MCI indicated that some questions were not contributing to the predictive power of the measure. Items from the three measures with correlations less than ±0.07 ($p>.50$) were removed and ROC analyses recalculated. Three items were removed from the IQOCDE (IR), five from the IQCODE (SR), and three items

from the SAGE. Two of these recalculations resulted in modest improvements to the AUC, with IQCODE (IR) remaining the same, although the significance increased slightly (p=0.003). The improved AUCs were IQCODE (SR) AUC=.620 (p=.049), and SAGE AUC=.645 (p=.014). The degree of AUC change was measured using Hanley and McNeil's methodology (Hanley & McNeil, 1983), which showed that both z-scores were below the 1.96 cut-off, meaning the increase in AUC was not large enough to be statistically significant (.61 and 1.39 for IQCODE (SR) and SAGE respectively).

The items removed did not vary much between versions of the IQCODE, except that overall the item analysis indicated less relationship between individual items and MCI grouping with the IQCODE (SR). Items removed from the IQCODE (IR) included: Making decisions on everyday matters; Handling money for shopping; and Handling other everyday arithmetic problems (e.g., knowing how much food to buy, knowing how long between visits from family or friends). IQCODE (SR) items removed included: Learning new things in general; Following a story in a book or on T.V; Making decisions on everyday matters; Handling money for shopping; and remembering his/her address and phone number. SAGE items removed included: Today's date; Item similarity; and 3-D figure construction.

3.4 Discussion

Difficulties in screening for early cognitive decline have stimulated the development of a large variety of brief cognitive screening measures. Despite this development, significant limitations with existing tests mean that there are a lack of sensitive and simple to administer, yet efficient, cognitive screening measures available for clinicians working with older adults. There are numerous advantages for patients if accurate early screening were possible, including decision making about the future, as well as the increasing possibility of interventions aimed at slowing such declines (Jansen et al., 2008; Lonie et al., 2009).

The present study aimed to 1) Validate the use of a postal screening approach as a first line screening method for detecting cognitive decline and 2) Assess the effectiveness of three measures used as postal tools. The IQCODE was used in both self-report and informant-report forms, and the SAGE was a pen and paper task that could be filled in without clinician input.

Participants were categorised as having MCI based on the commonly used Petersen criteria (Petersen et al., 1997), with a particular focus on subjective memory complaints and relatively unimpaired everyday functioning, backed by deficits on neuropsychological testing carried out during the current study. As a result of this 29.8% of the current sample were classified as having MCI; while this number appears high it is not outside of inclusive estimates from previous studies (Petersen et al., 2001). For the current study an inclusive definition of individuals scoring 1.5 standard deviations below age-matched norms on a delayed or total memory measure was used as the neuropsychological criterion for MCI. An inclusive measure of MCI should allow for the best assessment of whether postal screening appears an effective first choice screening procedure, and indicate those most at need of further testing to assess declines.

The SAGE was designed to be a sensitive measure of cognitive decline, meaning that cognitively intact older adults are not expected to be particularly challenged by the items, resulting in a ceiling effect where a large number of participants got all items correct. Despite the resulting differences in the variance between groups there was still a significant difference in the observed mean score for individuals classified as MCI. Although group differences were observed on mean scores, there was less evidence of a clear cut-off on the SAGE that could be used to identify individuals with MCI given how high the calculated cut-off score was.

Sensitivity and specificity were also substantially lower than has been previously reported (Scharre et al., 2010), although this could be for a number of reasons. Firstly, the SAGE assesses a range of cognitive functions and this could account for why it did not appear to be particularly sensitive to MCI as measured by ROC curve analyses. In particular if older adults are experiencing difficulties in areas consistent with fronto-temporal decline this may not be detected in early stages using a criterion of decline based primarily on memory. Another potential complication resulted from problems scoring whether participants had been able to recall the date. This makes up 4 of the 22 points on the SAGE, and by the admission of several participants they had checked the date before writing it down (despite instructions to the contrary). Recalling the date is a good measure of orientation and memory that by itself can give some indication into memory decline (O'Keeffe, Mukhtar, & T O'Keeffe, 2011), and so without this being reliably completed the measure loses some utility. Therefore, it was not surprising that remembering the date had such a weak correlation with MCI from the item analysis, and that the removal of this improved the predictive accuracy of the SAGE.

IQCODE (IR) responses represented an area of significant difference between MCI and cognitively intact groups, indicating that informants close to older adults are sensitive to detecting early declines, and are able to report this effectively on a questionnaire. This finding is consistent with previous studies looking at informant-reports and early stage cognitive decline (Cullen et al., 2007; Jorm, 1994; Jorm & Jacomb, 1989), and represents some evidence that this trend is maintained through a postal screening format. The IQCODE (IR) showed the best predictive validity in the current study, with an AUC of .685 and an optimal cut-off at an average score of 3.22. This cut-off is very close to previously reported cut-offs for the detection of MCI, and appears to show that this tool has measured individuals in a comparable way to previous reports (Li et al., 2012).

In contrast, there was no significant difference in mean scores on the IQCODE (SR) for MCI and non-MCI groups in the present study. Self-report and subjective declines are an important part of identifying MCI, but tailoring self-report questions to areas of memory and daily functioning that increase diagnostic accuracy could cut down on false positives from screening measures such as those in the present study. This was demonstrated by the improvement in the AUC for IQCODE (SR) of .578 to .620 when items that appeared unrelated to cognitive status were removed. These items included those assessing ADLs (such as everyday decision making and handling finances), which may be expected to remain intact until cognitive decline had progressed beyond mild impairment (Petersen & Negash, 2008).

Prior to removing the poorly correlated items, the predictions of the IQCODE (SR) were no better than chance. Individuals' ability to estimate their current cognitive functioning may be increasingly impaired as they develop MCI or other age-related cognitive declines, meaning they are less likely to rate themselves highly on measures such as the IQCODE. In contrast, cognitively intact older adults may be very sensitive to information consistent with potential declines, given how worrisome this possibility is for many people, and the impact that such declines would have for them (Chasteen et al., 2005; Hess et al., 2003). Future work looking at this anxiety, or difficulty in self-assessment of memory and ADLs would be useful to explore further.

Collectively, these findings do indicate that using postal measures as a first-line screening modality has merit. In particular each of the three measures, with minor modifications, were better than chance at identifying individuals with MCI. Although further work is needed to modify and improve such measures, the current results are encouraging. The observed results are also in line with previous work looking at postal screening, despite methodological differences (Jansen et al., 2008).

Of the three postal measures trialled the SAGE was the most highly correlated with the neuropsychological test battery, with the magnitude of correlations ranging from .246 to .591, and all correlations being significant at the $p<.01$ level. Of particular interest was the relationship between the SAGE and measures of memory and executive functioning from the neuropsychological tests. The two switching conditions on Verbal Fluency are used as measures of executive functioning and divided attention, and correlations of .390 and .392 represent a moderately strong relationship between these tests, and may indicate that the SAGE is measuring executive functioning. This conclusion is further supported from the correlation (-.42) with Trails B from the Trail Making Test, which also assesses executive functioning and cognitive switching. The correlations with measures of memory were expected, given the nature of the SAGE and what it was attempting to assess. The strongest observed relationship was between the SAGE and the ACE-III, a longer measure of cognitive decline with some evidence for detecting MCI (Ahmed et al., 2012). This lends further support for the validity of the SAGE in terms of detecting difficulties in memory, executive functions, visuospatial abilities, and verbal fluency.

The IQCODE (IR) was significantly correlated with the BVMT-R, thus providing some evidence that it is measuring a similar construct to this memory test, as well as with the ACE-III. This may indicate that there is utility for using the IQCODE (IR) for detecting cognitive decline more generally. The IQCODE (SR) was only significantly correlated with the two Verbal Fluency switching measures, and it is unclear from the present research why self-reporting on cognitive decline would be related to executive functioning or fluency ability, but not to memory; this relationship would be worthwhile exploring further in future research.

Several limitations may have had some impact on the observed results. Firstly, problems with following instructions to report the date on the SAGE (i.e., participants

consulting a calendar to check that the date was correct) likely led to an underestimation of memory difficulties. There were also several participants who mentioned having multiple attempts answering items on this test, and any deviation from instructions could have had an impact on the representativeness of subsequent responses. There were also a number of missing responses on the IQCODE, due to participants sometimes failing to return both self- and informant-responses at the initial screening. In particular, five individuals with MCI were missing one of their IQCODE responses, and it is possible that this added data could have had an impact on the observed trends.

Overall, the present results are an encouraging step towards developing cost effective and easy to administer screening for age-related cognitive declines. Although the ROC analyses did not demonstrate ideally high levels of sensitivity and specificity, the postal screening measures had significant predictive validity for MCI. Future work should focus on tailoring tests and test instructions so there is more clarity about how to respond, and changing items as needed so that they can be appropriately scored. In particular, removing the date question on the SAGE in favour of a more appropriate measure of memory would improve the likelihood of accurately identifying MCI cases. Examples of such questions used in other measures include who is the current prime minister, or who is the current president of the USA. MCI remains a difficult condition to identify even with extensive psychometric testing, and any screening procedure that would reduce the demand on clinician time and resources for those most at risk is worthy of research and consideration.

4. Self-Report versus Informant-Report

4.1 Introduction

Industrialised nations are increasingly struggling with aging populations. There are particular challenges for healthcare and medical practitioners, including extensive comorbidity and age-related declines associated with an increase in older patients. Of these cognitive declines, dementia and Alzheimer's Disease (AD) have enormous financial and social costs for the individuals affected and for their families (Anderson & Hussey, 2000; M. K. Aronson et al., 1991). The insidious and progressive course of dementing conditions means that the pain and cost suffered by older adults with these diseases can last for extended periods of time. Due to the severity and impact of age-related cognitive pathologies the development of interventions for improving or consolidating aspects of cognition associated with declines have generated significant research interest. While theoretically sound and building on the concept of neural reserve and enrichment interventions, this research has encountered significant difficulties (Acevedo & Loewenstein, 2007; Grundman, Dibernardo, Raghavan, Krams, & Yuen, 2013).

One major challenge with developing effective interventions is the difficulty with early identification, which results from the progressive nature of dementing conditions. The diagnosis of individuals most at risk, or during prodromal stages, remains problematic due to the lack of clarity of stages of degeneration, and large heterogeneity within and between these disorders (Fischer et al., 2007). MCI refers to a stage between normal ageing and dementing conditions, where deficits are greater than would be expected based on age, yet are not substantial enough to impair the ADLs or to meet criteria for dementias such as AD (Petersen & Negash, 2008). The criteria of MCI have varied since it was initially proposed, but the most commonly used criteria are those of Petersen and adapted by the NIA (Albert et al.,

2011; Petersen et al., 1997), including subjective memory complaints, relatively intact ADLs, with quantified deficits on standardised neuropsychological measures.

Although there is increasing support for the hypothesis that MCI represents a prodromal phase of decline (Aggarwal et al., 2005; Bruscoli & Lovestone, 2004; Fischer et al., 2007), there are still problems with this view. In particular, a number of studies have identified individuals appearing to revert from MCI back to normal cognitive function (Ganguli et al., 2011; Gauthier et al., 2006; Kumar et al., 2006; Sachdev et al., 2013), whereas others have reported vastly different rates of further decline among individuals categorised as MCI (Busse et al., 2006; Fischer et al., 2007). Overall, the emerging evidence indicates that older adults experiencing early cognitive decline are a heterogeneous group, and that identifying early deficits should take this into consideration.

Early detection of cognitive decline would potentially lead to a number of benefits, including making decisions about end-life care, as well as the possibility of interventions to decrease, halt, or partially compensate for cognitive declines (Li et al., 2012). A number of tests have been used to screen and diagnose AD, the most common of which is the MMSE; (Ahmed et al., 2012). Such tests work because of the large differences in cognition between healthy and dementing older adults, but such discrepancy does not necessarily present during early stages of decline. Consequently, tests such as the MMSE or the CDR have not consistently shown utility for detecting more subtle prodromal changes (Ahmed et al., 2012; Petersen, 2003). By necessity, MCI diagnosis is based on neuropsychological testing, which can be very resource intensive in terms of time and financial costs (Petersen et al., 1999). This has led to an increasing body of work looking for cost-effective screening measures in order to reduce the burden on medical practitioners of identifying age-related cognitive declines (Ahmed et al., 2012). A number of such tests have had promising research support

for their effectiveness, but at present MCI screening remains a time consuming and expensive endeavour.

The IQCODE (Jorm & Jacomb, 1989) has been used to assess changes in cognition associated with AD, VaD, and post-stroke damage (Cullen et al., 2007; Jorm, 1994; Jorm & Jacomb, 1989). This is an informant-report questionnaire that measures changes in memory and functional ADLs over a 10-year period, and as such appears to assess areas of interest in MCI. Although there are few examples of the IQCODE being used to screen for MCI (Li et al., 2012), if a measure like this were shown to have predictive validity for MCI it would resolve some of the difficulties in terms of time and cost for front-line screening.

One of the Petersen criteria are subjective memory complaints, meaning that for an MCI diagnosis individuals, or informants who know them well, need to be able to detect and comment on changes in memory. Therefore, self-reports are an important consideration in identifying cases of MCI, despite potential problems with the accuracy of self-reports in the midst of cognitive declines; for example, lack of awareness of difficulties, or being unable to access their own cognitive processes (Hess et al., 2003; Nisbett & Wilson, 1977; Rabbitt & Abson, 1990). The IQCODE has previously been trialled as a self-report measure in order to test a predictive relationship with cognitive decline (Jansen et al., 2008), but this was only a feasibility study and the comparison measures used were limited. It is possible that individuals are able to notice early difficulties that they are struggling with before this cognitive decline becomes apparent to those close to them. However, if early difficulties can be readily compensated for then these may not be noticed by anybody else until they progress further (Buckner, 2004). Consequently, it is important to look at both self and informant-reports to compare and contrast the information that each provide about cognitive decline. Informants have long been considered a more reliable resource in assessing declines, but given the importance of some degree of self-awareness for diagnosis it is possible that a

combination of self- and informant-reports may improve the screening accuracy beyond the use of either alone in identifying likely cases of MCI.

The IQCODE has high reported test-retest reliability at .75 (Jorm, 2004), an impressive reliability coefficient given the older adult target population. With good test-retest reliability, and assuming reasonable content validity, it is expected that scores on this measure should remain stable over time; the exception being if individuals are showing declines subsequent to initial testing. Thus, we predicted that any substantial declines over time in IQCODE scores would indicate increasing cognitive impairment and likely MCI.

The goals of the present study were: 1) To explore the relationship between self-report and informant-report versions of the IQCODE, with a particular focus on how each of them relate to MCI; and 2) To evaluate any change in scores of self- and informant-reports over a 12-month period, along with the reliability of each measure. If changes in scores on these measures align with objective neuropsychological evidence of deficits then this lends support for the use of the IQCODE as an MCI screening tool. It is also important to establish whether the self-report and informant-report versions of the IQCODE have similar psychometric properties.

4.2 Method

4.2.1 Participants

Participants were initially recruited through contacting local community groups with older adult members, such as Rotary and Probus clubs. An advertisement was also placed in *Age Concern*, a free newsletter with an older adult target population. The remainder of participants were recruited through the NZBRI volunteer database, which contained the details of 1,300 older adults who were healthy at the last point of contact. In total 114

individuals completed the first stage of the research, with 92 (80.7%) individuals providing both IQCODE responses at Time 1.

After 12 months all 114 participants were contacted again through phone calls or by sending a written invitation to participate in the second stage of the study. Of this group 78 participants took part in both stages of testing. For the remainder of analyses only those with full responses are included. In the present analyses 77 participants returned at least one pair of IQCODE responses, although only 68 individuals returned all four IQCODEs. All 77 participants who participated in both stages and sent back at least one pair of IQCODES were included in the current analyses as appropriate.

The only exclusionary criterion applied during recruitment was that participants not be suffering dementia at the initial presentation, so that the sample would be as representative of the population as possible. The only inclusion criteria was that participants be 65 years or older before the first testing session. All participants provided both verbal and written consent, and ethical approval for the project was given by the University of Canterbury Human Ethics Committee.

4.2.2 Instruments

4.2.2.1 Postal Screening Measures

In order to obtain both self- and informant-reported changes to memory and daily functioning, two versions of the IQCODE; (Jorm, 1994; Jorm & Jacomb, 1989) were sent to participants; the self-report measure included the same questions as the original measure, but with modified instructions. The IQCODE is comprised of 16 items assessing changes in memory and associated ADLs such as handling finances or learning to use a new gadget around the house. Each of these items were scored on a five-point Likert scale, from *Much Improved* to *Much Worse*, with the average from the 16 items giving the individual's score,

and higher scores indicating increasingly significant impairment. The IQCODE has been used to screen for a number of disorders (e.g., AD, delirium, and post-stroke damage (Jorm, 2004)), in a number of settings (e.g., inpatient, outpatient, and community samples (Cullen et al., 2007; Jansen et al., 2008)), and with disparate geographical populations (e.g., Chinese, Dutch, French, and Norwegian population groups (Jorm, 2004; Li et al., 2012)).

4.2.2.2 Neuropsychological Measures

Neuropsychological measures were used to give a criterion measure of decline in order to validate how well the self- and informant-reports assessed cognitive difficulties. The neuropsychological tests used for this included: 1) the Brief Visuospatial Memory Test – Revised (BVMT-R; (Benedict et al., 1996)), which measures visual working and delayed memory as well as spatial orientation. 2) The Rey Auditory Verbal Learning Test (RAVLT; (Rey, 1964)) measures verbal working and delayed memory, as well as assessing recall and recognition abilities. Together these two memory measures have been shown to differentiate individuals with amnestic MCI from non-impaired older adults (Luis et al., 2011; Small, La Rue, Komo, Kaplan, & Mandelkern, 1995), and collectively assess verbal and visual delayed memory, which together are the most common areas of early deficits in amnestic cognitive decline (Small et al., 1995). 3) The Trail Making Test (TMT; (Reitan, 1958)) offers an evaluation of executive functioning, along with processing speed and visual scanning. It is less reliant than other measures on working memory, and so offers a measure that is somewhat resistant to memory deficits (Kortte et al., 2002). 4) Verbal Fluency from the D-KEFS (including Letter Fluency, Category Fluency, Switching Fluency, and Switching Accuracy conditions) (Delis et al., 2001) offers a further measure of executive functions, along with divided attention and semantic ability (Gomez & White, 2006). This has been shown to be a reliable measure over time (Snow et al., 1988), and is only modestly correlated with memory measures, giving another test with results that are expected to be resistant to

amnestic declines (Ruff et al., 1997). 5) Finally, the Addenbrooke's Cognitive Assessment – III (ACE-III; (Hsieh et al., 2013; Mioshi et al., 2006)) was administered as a comparison test. This was developed as a standalone screening tool of cognitive functioning, and provides a brief measure of memory, orientation, visuospatial ability, and verbal fluency (Hsieh et al., 2013). Collectively these areas are those most likely to be affected throughout early stages of cognitive decline, and so this test offers some utility to screen for MCI (Aggarwal et al., 2005; Busse et al., 2006).

4.2.3 Procedure

The two versions of the IQCODE were mailed out along with information and consent forms to all participants who had indicated they wanted to take part in the present research. Following this postal questionnaire all participants underwent a brief neuropsychological examination to identify likely cases of MCI, taking approximately one hour. Implied consent was initially given over the phone, with written consent then collected at the beginning of the neuropsychological testing. Administration of these tests was in the same order for all participants and tests were conducted by a clinical psychology student trained in their administration.

After 12 months participants were contacted again, and were invited to participate in the second stage of the research, looking for any changes over time, and the test-retest reliability of the postal measures used. The testing procedure was then repeated, with different forms administered where possible. Test administration was by the same researcher, and again all individuals consented to participating in the research.

4.2.4 MCI Screening

Individuals were classified as MCI based on the commonly used Petersen criteria (Albert et al., 2011; Petersen et al., 1997), including: a score at least 1.5 standard deviations

below age adjusted norms on at least one memory test, along with self-reported or informant-reported subjective memory complaints; relatively intact activities of daily living; generally intact cognitive functioning; and not meeting diagnostic criteria for dementia.

4.2.5 Data Analysis

Differences between scores on the two versions of the IQCODE were initially explored using *t*-tests. Regression analyses were used to explore the relationship between each version of the IQCODE at each point in time. Test consistency over time and internal consistency coefficients were calculated, including an item analysis, followed by intraclass correlations for both versions of the IQCODE. Finally, convergent validity was explored through correlations with neuropsychological measures.

4.3 Results

4.3.1 Demographic Data and Descriptive Statistics

Participants were aged between 65 and 86 (*M*=74.90, *SD*=5.42), and included 48 females and 29 males. Participants' ethnicity was similar to expected proportions of older adults based on Canterbury District Health Board data from the 2013 census (Statistics New Zealand, 2013), with 94.9% NZ European/pakeha, 1.3% Māori, and 3.8% other. Participant demographics for Time 1 and Time 2 are presented in Table 4.

Table 4
Participant Demographic Data at Time 1 and Time 2

	Time 1		Time 2	
	Male N (%)	Female N (%)	Male N (%)	Female N (%)
Sex Total	44 (38.6)	70 (61.4)	29	48
Age				
- 65-69	8 (29.6)	19 (70.4)	5 (29.4)	12 (70.6)
- 70-74	10 (33.3)	20 (66.7)	7 (31.8)	15 (68.2)
- 75-79	14 (46.7)	16 (53.3)	10 (45.5)	12 (54.5)
- 80-84	10 (47.6)	11 (52.4)	7 (50)	7 (50)
- 85+	2 (33.3)	4 (66.7)	0 (0)	2 (100)
Ethnicity				
- NZ European/Pakeha	42 (38.9)	66 (61.1)	28 (38.4)	45 (61.6)
- Maori	1 (100)	0 (0)	1 (100)	0 (0)
- British	0 (0)	2 (100)	0 (0)	2 (100)
- Asian	1 (50)	1 (50)	0	0
- Other	0 (0)	1 (100)	0 (0)	1 (100)
Highest Level of Education				
- High School	27 (46.6)	31 (53.4)	19 (46.3)	22 (53.7)
- Post-school Training	3 (60)	2 (4)	2 (11.8)	15 (88.2)
- Undergraduate Qualification	8 (19.0)	34 (80.9)	2 (18.2)	9 (81.8)
- Postgraduate Qualification	6 (66.7)	3 (33.3)	6 (75)	2 (25)

In total 10 participants were classified as MCI at both Time 1 and Time 2, with a further 24 meeting this criteria at one time or the other. Overall, this means 43.6% of the present sample met the criteria for MCI. However, nine participants that met criteria for MCI at Time 1, did not continue to meet these criteria at Time 2; this group appeared to revert from MCI to normal cognitive functioning. For each of these individuals, neuropsychological

memory measures indicated that they were at least 1.5 standard deviations below age-adjusted norms at Time 1, but they were not below this cut-off at Time 2.

Means and standard deviations for each of the four IQCODE collections were initially calculated and are presented in Table 5. These show that similar means and standard deviations were observed on both tests at Time 1 and Time 2.

Table 5
Descriptive Statistics for Time 1 and Time 2 Postal Measures

	Time 1		Time 2	
	M	*SD*	*M*	*SD*
IQCODE (SR)	3.150	.344	3.206	.282
IQCODE (IR)	3.142	.329	3.129	.373

Self- and informant-reports were compared using *t*-tests of dependent means for Time 1 and then for Time 2. At Time 1 this difference between the two forms was not significant $t(62)=-.89$, $p=.377$, $d=.39$. However, there was a significant difference between self- and informant-reports seen at Time 2, with self-report ratings indicating a higher degree of impairment $t(76)=-2.31$, $p=.024$, $d=.90$ ($M=3.206$, $SD=.282$, and $M=3.129$, $SD=.373$ for self- and informant-report respectively).

At Time 1 there was a positive linear relationship between self- and informant-report scores on the IQCODE ($r(63)=.644$, $p<.001$), which is shown on Figure 2.

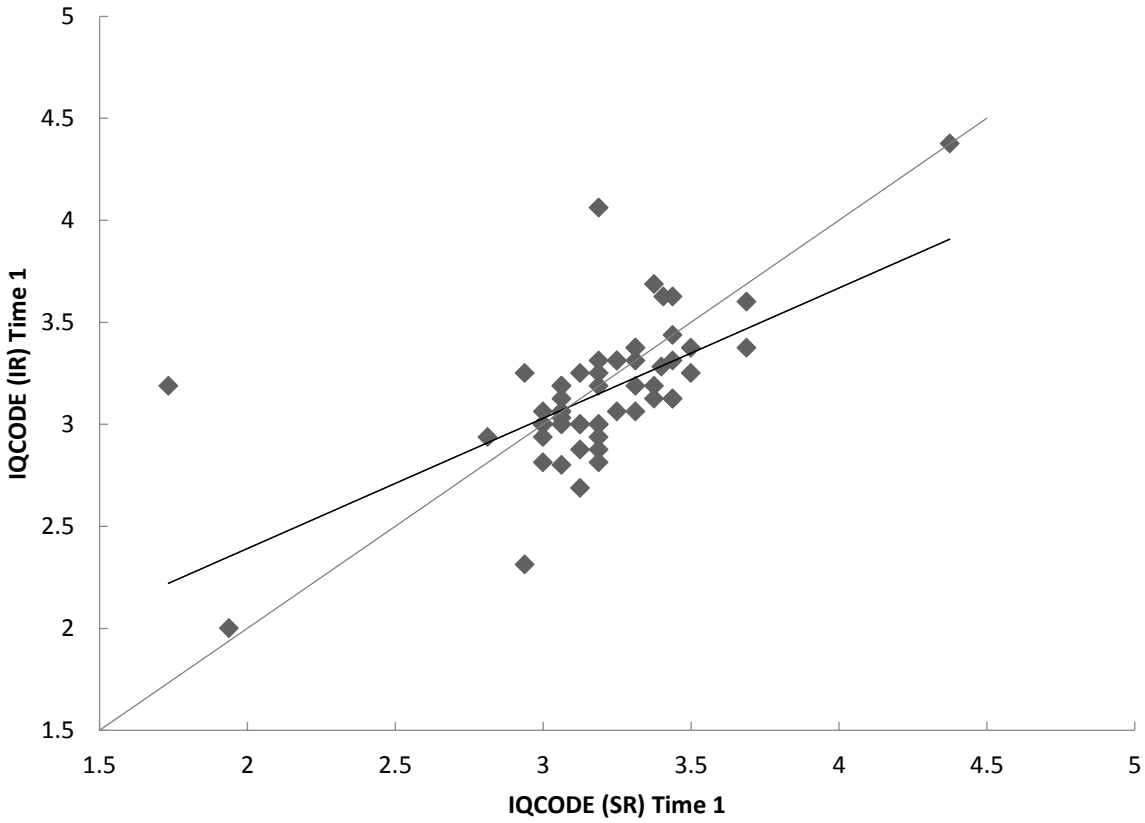

Figure 2. Scatterplot of self-report and informant-report IQCODE scores at Time 1. The grey line represents equality (x=y) and trend line of y=.6385x+1.1139, R^2=.415.

Figure 3 shows a similar scatterplot for Time 2 scores. As with the scores at Time 1, Figure 3 shows the strong linear relationship between both versions of the questionnaire at Time 2 ($r(77)=.633$, $p<.001$), with few points deviating from the tight grouping of data, indicating that scores on both forms tended to be similar.

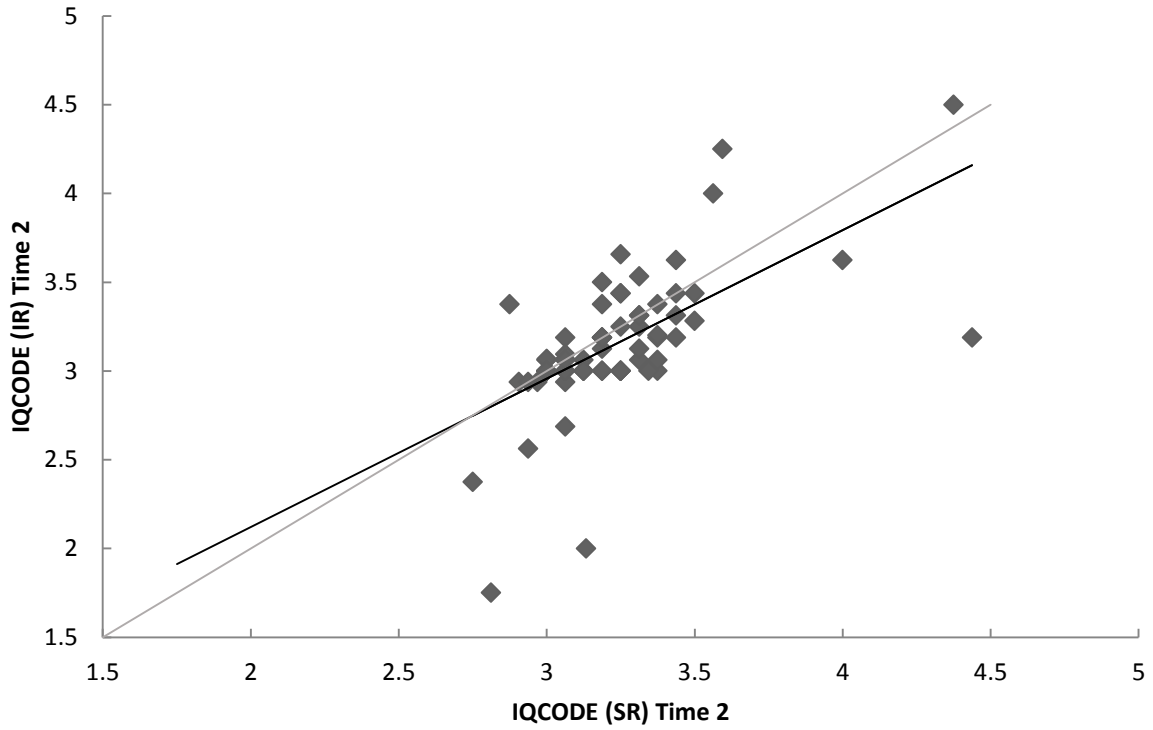

Figure 3. Scatterplot of self-report and informant-report IQCODE scores at Time 2. The grey line represents equality (x=y) and trend line of y=.836x+.4489, R^2=.400.

Regression analyses were then conducted to test for differences in the two IQCODEs, in particular to see if there was evidence that deficits were under-reported on the self-report IQCODE. To this end a regression analysis for Time 1 with the IQCODE (SR) as the dependent variable was calculated which gave a significant result, $\hat{Y}$=.650X+1.13, $t(61)=6.58$, $p<.001$. At Time 2 a similar pattern was observed $\hat{Y}$=.479X+1.71, $t(75)=7.08$, $p<.001$, this indicates that while linearly related, scores on these two measures did not increase at the same rate, with a slope less than 1. Due to the intercepts at 1.13 and 1.71 for Time 1 and Time 2 respectively it may also indicate that under-reporting was occurring at the lower end of responses on the self-report IQCODE.

4.3.2 Test-Retest Reliability

The coefficient of reliability was calculated for both versions of the IQCODE and gave values of: IQCODE (SR) $r(70)=.595$, $p<.001$ and IQCODE (IR) $r(77)=.627$, $p<.001$.

The scatterplots of these relationships are shown on Figure 4 and Figure 5 for Time 1 and Time 2 respectively. Both figures show that the majority of responses are closely clustered, although more deviation from the group can be seen in the IQCODE (IR) over time, indicating that informant responses may vary more over time.

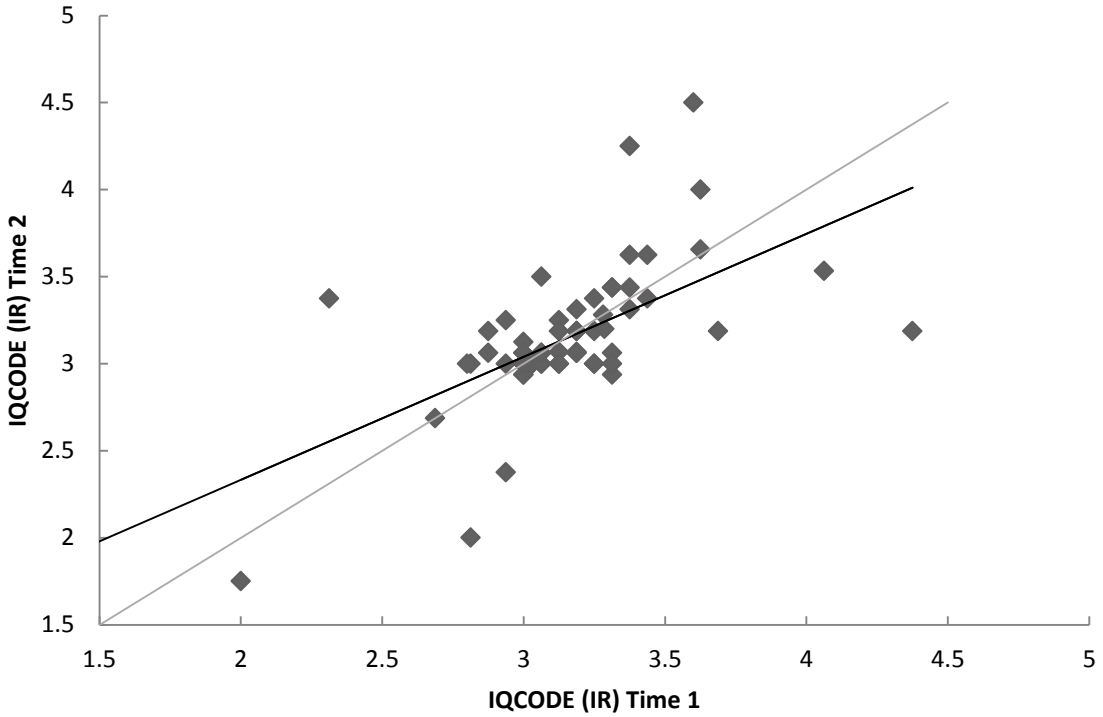

Figure 4. Scatterplot of Time 1 and Time 2 IQCODE informant-report scores. The grey line represents equality (x=y) and trend line of y=.7069x+.9193, R^2=.356.

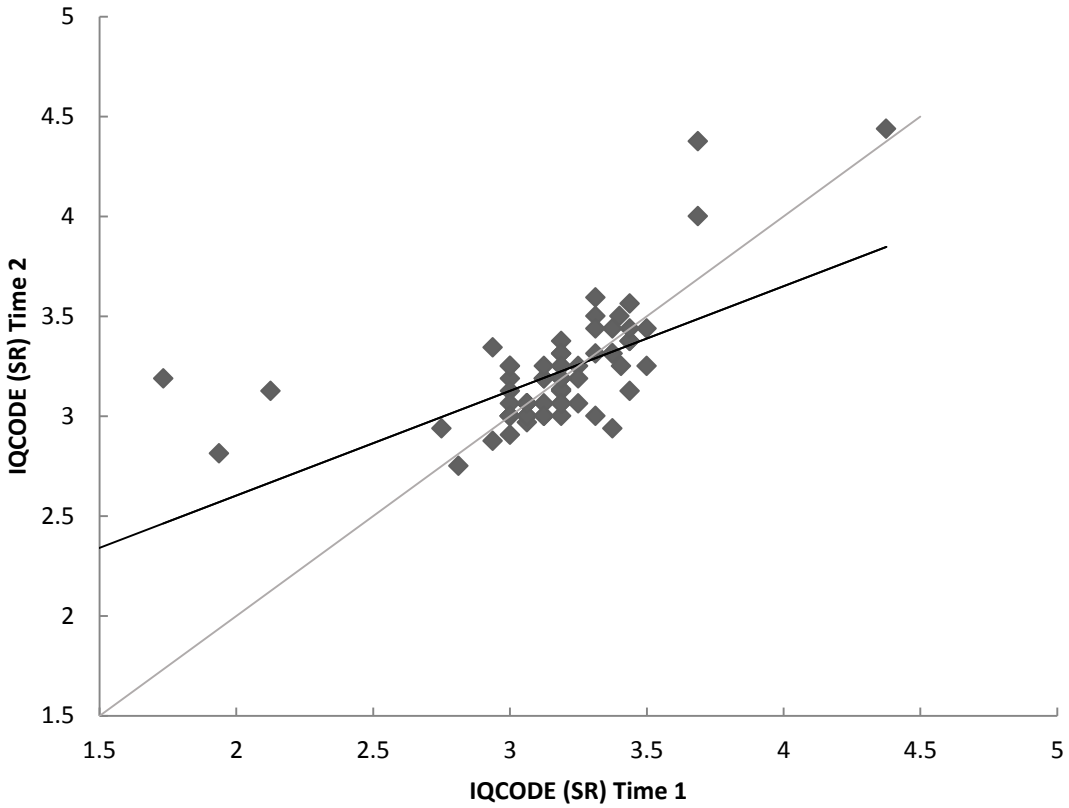

Figure 5. Scatterplot of Time 1 and Time 2 IQCODE self-report scores. The grey line represents equality (x=y) and trend line of y=.5239x+1.555, R^2=.393.

Repeated measures *t*-tests were calculated for both versions of the IQCODE to look for differences in mean scores across the 12 months, and these demonstrated no significant differences for either version: IQCODE (SR) *t*=(78)=-1.686, *p*=.096, (M_{Dif}=.051, SD_{Dif}=.269); and IQCODE (IR) *t*(71)=.176, *p*=.861 (M_{Dif}=.0067, SD_{Dif}=.319). This indicates that the questionnaires demonstrated high stability over time, and that across the sample these scores stayed constant.

Correlations between scores over time were then calculated again for the four groups of participants; those that did not meet criteria for MCI (non-MCI); participants that met criteria at Time 2 (MCI-single); participants that met MCI criteria at Time 1 but not at Time 2 (Reverters); and participants that met criteria at both Time 1 and Time 2 (MCI-both). Correlations for these groups on both versions of the IQCODE are presented in Table 6. The

IQCODE (SR) had significant consistency over time for all groups except Reverters, whereas the IQCODE (IR) only had significant test-retest reliability for Reverter and non-MCI groups.

Table 6
Test-Retest Correlations for each MCI Category

	IQCODE (SR)		IQCODE (IR)	
	r	N	*r*	N
MCI-both	.719*	10	.038	9
MCI-single	.709**	13	.339	13
Reverters	.088	9	.744*	8
Non-MCI	.673***	42	.746***	37

* $p<.05$, ** $p<.01$, *** $p<.001$

Paired samples *t*-tests were then run on these four groups to look for differences in mean scores across a 12-month period. Results of these analyses are shown in Table 7. The only statistically significant observed difference across the 12-month period was for the MCI-single group on the IQCODE (SR).

Table 7
Repeated Measures t-tests for each MCI Category

	IQCODE (SR)				IQCODE (IR)			
	M_{Diff}	*t*	df	*d*	M_{Diff}	*t*	df	*d*
MCI-both	-.305	-2.07	9	.54	-.079	-.364	8	0.12
MCI-single	.096	2.26*	12	.53	-.103	-1.21	12	.33
Reverters	-.102	-.732	7	.25	-.047	-.778	7	.26
Non-MCI	-.034	-1.23	41	.18	.069	1.83	36	.29

* $p<.05$

4.3.3 Internal Consistency

Cronbach's alpha was calculated for both versions of the IQCODE at each time point to measure internal consistency of the items when used in postal screening. All four of these alpha calculations showed high internal consistency (IQCODE SR: Time 1 α=.879, Time 2 α=.879; IQCODE IR: Time 1 α=.915, Time 2 α=.931). Moreover, item-total statistics

indicated that these values of Cronbach's alpha would not be improved by removing any of the items.

The consistency of items across time was also measured to assess whether any of these were changing over a 12-month period. This was done by calculating repeated measures *t*-tests for each IQCODE item at both time points. For the IQCODE (IR) the means of one item were significantly different between Time 1 and Time 2: "Remembering where to find things which have been put in a different place from usual", $t(71)=2.04$, $p=.045$, $d=.24$. Three items on the IQCODE (SR) showed significant differences over time: "Following a story in a book or on T.V", $t(78)=-2.35$, $p=.021$, $d=.26$; "Handling money for shopping", $t(78)=-2.00$, $p=.049$, $d=.23$; and "Handling other everyday arithmetic problems, e.g., knowing how much food to buy", $t(78)=-2.109$, $p=.038$, $d=.24$. All other pairwise comparisons showed non-significant changes over time, but not all were significantly correlated with each other. On the IQCODE (IR) "Remembering what day and month it is", and "Using his/her intelligence to understand what's going on and to reason things through" had correlations of $r=.191$ ($p=.108$) and $r=.185$ ($p=.128$) respectively. Similarly, four items on the IQCODE (SR) were not significantly correlated over time: "Remembering things that happened recently" $r=.200$ ($p=.079$); "Making decisions on everyday matters" $r=.098$ ($p=.394$); "Handling money for shopping" $r=-.100$ ($p=.380$); and "Handling other everyday arithmetic problems" $r=.215$ ($p=.057$).

Intraclass correlations were calculated for the means of both versions of the IQCODE, with Time 1 and Time 2 as two items being assessed. A high degree of reliability was found between the two measurements of the IQCODE (SR), ICC=.759 $F(72,72)=4.22$, $p<.001$, $\eta^2=.80$. The IQCODE (IR) also had a high degree of reliability across the two measurement points, ICC=.744 $F(66,66)=3.86$, $p<.001$, $\eta^2=.79$. This process was again repeated after splitting the participants based on MCI category, and the results of the intraclass correlations

are presented in Table 8. These demonstrated that statistically significant ICCs were observed for each group except Reverters on the IQCODE (SR), but only for Reverter and non-MCI groups on the IQCODE (IR).

Table 8
Intraclass Correlations for each MCI Category

	IQCODE (SR)		IQCODE (IR)	
	ICC	*F*-value	ICC	*F*-value
MCI-both	.768	5.384*	.072	1.070
MCI-Single	.787	5.873**	.468	1.909
Reverters	.088	1.091	.851	6.43*
Non-MCI	.780	4.585***	.843	6.713***

* $p<.05$, ** $p<.01$, *** $p<.001$

4.3.4 Convergent and Divergent Validity

Validity of the IQCODE as used in postal screening was further tested through comparisons with neuropsychological measures of memory, and the ACE-III which measures a range of cognitive areas, in order to explore convergent and discriminant validity. These correlations are presented in Table 9 and Table 10 for Time 1 and Time 2 respectively.

Table 9

Correlations Between Postal Questionnaires and Neuropsychological Tests at Time 1

	IQCODE (SR)	IQCODE (IR)
	r=	*r*=
BVMT		
- Total Recall	-.094	-.283*
- Delayed Recall	-.056	-.326**
RAVLT		
- Total Recall	-.191	-1.75
- Delayed Recall	-.223	-.174
ACE-III		
- Attention	-.023	-.103
- Memory	.137	-.044
- Fluency	.288*	.293*
- Language	.177	.038
- Visuospatial	.221	-.079
- Total	.236*	.027
Trail Making Test		
- Trails A	.006	-.113
- Trails B	.000	-.075
Verbal Fluency		
- Letter	.054	-.130
- Category	.011	-.005
- Switching	-.139	-.199
- Switching Accuracy	-.130	-.208
IQCODE (IR)	.644***	

* $p<.05$, ** $p<.01$, *** $p<.001$

Table 10

Correlations Between Postal Questionnaires and Neuropsychological Tests at Time 2

	IQCODE (SR)	IQCODE (IR)
	r=	*r*=
BVMT		
- Total Recall	-.300**	-.328**
- Delayed Recall	-.407***	-.455***
RAVLT		
- Total Recall	-.445***	-.346**
- Delayed Recall	-.475***	-.349**
ACE-III		
- Attention	-.148	-.346*
- Memory	.036	-.217
- Fluency	-.017	-.201
- Language	-.003	-.050
- Visuospatial	-.266	-.169
- Total	-.069	-.300*
Trail Making Test		
- Trails A	-.464***	-.225*
- Trails B	-.266*	-.085
Verbal Fluency		
- Letter	-.087	-.113
- Category	-.226*	-.067
- Switching	-.311**	-.211
- Switching Accuracy	-.264*	-.141
IQCODE (IR)	.633***	

* $p<.05$, ** $p<.01$, *** $p<.001$

Few significant correlations were observed at Time 1, with the IQCODE (SR) only correlating with the ACE-III, and the IQCODE (IR) correlating with the BVMT-R measures and an ACE-III subscale. The two versions of the IQCODE were also significantly correlated. Overall, this demonstrated that the IQCODE demonstrated some convergent validity with a general measure of cognitive decline (the ACE-III), while not strongly correlating with more specific neuropsychological measures. This pattern changed at Time 2, with more significant correlations observed. At Time 2 both IQCODEs were correlated with all four memory measures, with the IQCODE (SR) also correlated with both TMT conditions and three Letter Fluency subscales. At Time 2 the IQCODE (SR) and IQCODE (IR) were

again highly correlated with each other. The IQCODE (IR) was correlated with Trails A and the ACE-III. This pattern of convergent validity with the neuropsychological memory measures was more in line with expectations, given the strong memory focus of the IQCODE.

4.4 Discussion

The current study aimed to explore the relationship between self- and informant-report versions of the IQCODE, with a particular focus on assessing the reliability of these measures over a 12-month period. The IQCODE has been used to look for changes in cognition in older adult populations, and there is emerging evidence that it may have screening utility for detecting MCI (Li et al., 2012). The early detection of cognitive decline is an area where there currently exists a dearth of efficient and reliable screening tools, which has created considerable demand for such procedures to be developed (Ahmed et al., 2012; Cullen et al., 2007). One possible avenue involves collecting self-reports, given that subjective complaints of decline are an explicit diagnostic criterion of MCI (as per the original Peterson criteria). Previous work has looked at using the IQCODE as a self-report measure, but no informant report was collected for comparison, and it has been unclear whether the same or different information can be collected using these as complementary tools (Jansen et al., 2008).

Participants in the current study were categorised as MCI based on the Petersen criteria (Albert et al., 2011; Petersen et al., 1997), including subjective memory complaints along with objective neuropsychological deficits on a standardised memory measure. There were four categories resulting from this: individuals who met criteria for MCI at both Time 1 and Time 2 (MCI-both); those meeting MCI criteria at Time 2 (MCI-single); participants who appeared to revert from MCI to normal cognitive functioning between Time 1 and Time 2

(reverters); and participants that did not meet criteria for MCI (non-MCI). This resulted in 42.9% of the present sample meeting the criteria for MCI at one or both times of testing. This proportion is higher than expected, and outside of most population estimates from previous studies (Hänninen et al., 2002; Lopez et al., 2003; Petersen et al., 2001), but still within some MCI prevalence estimates which have been reported as high as 53.8% amongst adults 65 years and older (Koivisto et al., 1995). However, for the present research looking at the utility of screening measures, inclusive MCI criteria were used in order to maximise the chance of demonstrating the use of self- and informant-report measures to detect declines.

The IQCODE has been used in a number of settings (Jorm & Jacomb, 1989) and with a number of populations to detect cognitive declines (Ehrensperger et al., 2010), including MCI (Li et al., 2012). There is also emerging evidence about the utility of the IQCODE as a self-report measure (Jansen et al., 2008). In the present study differences between scores at Time 1 and Time 2 were initially looked for, and repeated measures *t*-tests of both self- and informant-reports indicated no significant differences between mean scores over time. The lack of significant differences overall supports the idea that both forms of the IQCODE are reliable measures over time. However, despite consistency over time there would be expected differences in scores if declines were occurring, so repeated measures *t*-tests were again conducted after separating the participants based on MCI categorisation. Scores on the IQCODE (SR) were significantly different for those in the MCI-single group, showing that on this measure differences were observed over a 12-month period. However, the direction of this change was not in the expected direction, as the average self-report scores decreased from Time 1 to Time 2, indicating cognitive improvement. It is unclear why this self-reported improvement was seen, particularly given the objective cognitive deficits observed for this group.

The most interesting trend from the *t*-tests was in the MCI-both group, where a fairly large difference between means at Time 1 and Time 2 on the IQCODE (SR) was observed, and it is possible that this would have reached significance had the group been larger. It is likely that this is reflecting ongoing decline in the group who were consistently meeting criteria for MCI over time. Previous research has estimated that the conversion rate of MCI to AD and other dementias is between 5.6% and 41% per year (Geslani et al., 2005; Petersen et al., 1999; Ritchie et al., 2001), and so while none of the participants in the present research met criteria for AD these individuals are likely to be experiencing accelerating cognitive declines.

The group that reverted from MCI to normal cognition appeared to have no difference between Time 1 and Time 2 on the paired *t*-tests. This is unsurprising if something other than cognitive decline led to the initial MCI categorisation, as in this case whatever has affected neuropsychological measures may not have had the same impact on ADLs. It would be unexpected to see a significant improvement in ADLs over time, but objectively this group has improved on the neuropsychological memory measures over a 12-month period. Previous research has identified a number of possible reasons for individuals appearing to revert from MCI including: misdiagnosis using overly liberal criteria (Ganguli et al., 2011); transient cognitive decline due to depression or other psychiatric conditions (Kumar et al., 2006); or poor neuropsychological test performance arising from ill-health or a lack of motivation (Sachdev et al., 2013). It is not clear whether these factors or other uncollected variables contributed to the individuals reverting to normal cognition during the present study.

The coefficient of reliability was high for both versions of the IQCODE, supporting previous evidence of good test-retest reliability on the informant-report measure (Jorm, 2004). However, what has not been demonstrated previously is the test-retest consistency of self-report responses on the IQCODE, and from the current research this appears comparable

to informant-reports. This gives evidence to support the idea that self-reports on cognitive decline are reliable over time. Coefficients of reliability showed a different pattern when participants were grouped by MCI status, and in particular informant-reports were not significantly correlated over time for MCI-both and MCI-single groups. There are a number of possible explanations, but the lack of relationship between Time 1 and Time 2 may be reflecting a range in degrees of decline between individuals in these MCI categories. More work looking specifically at individuals with MCI over time using this measure would be useful to explore, particularly by increasing the sample size, and therefore power, of the present study. IQCODE (SR) test-retest consistency for three groups appear to indicate strong relationships between scores on self-reports over time, with no linear relationship observed from Time 1 to Time 2 for reverters.

The significant intraclass correlations (ICC) supported the use of both measures over time, and indicated that the measurement of cognitive decline over time is reliable. This pattern was repeated when the ICC was recalculated between MCI categories, except for MCI-both on the IQCODE (IR); this had only a weak and nonsignificant ICC, which may indicate there was inconsistency in measurement for this particular group. As mentioned above, it is important to interpret this with caution given the low number in this analysis, with only eight degrees of freedom. Looking at the ICC when participants had been categorised by MCI status showed a slightly different pattern for self-report and informant-report measures. On the self-report measure all groups showed significant ICC values except for the reverters, indicating that those whose cognitive status appeared to improve over time may not have been reliably assessing their functioning. This fits with the idea of an external cause of their difficulty, such as stress or depression at Time 1. The informant-report measures had significant ICCs for the group of reverters, which may indicate that informant-reports are more reliable than self-reports in the case of pseudo-dementia or other transient causes of

cognitive decline. Alternatively, with their objective change in cognitive status it may be that the self-reports were more accurate, and that the ICC should not be significant given the changes that have taken place. The current study was not designed to answer this, but it will be well worth exploring in future research and was both an interesting and unexpected finding.

Item consistency as measured by repeated measures *t*-tests gave some interesting results about consistency over time of individual items, and whether particular items may be sensitive to decline. There was a significant difference on "Remembering where to find things" on the IQCODE (IR), which could indicate a noticeable change in memory functioning. In contrast the self-report items that changed significantly over a one year period were more related to functional ADLs, such as "Handling finances and everyday arithmetic problems". The differences here may reflect that informants noticed memory lapses, whereas participants were more sensitive to noticing practical difficulties in day-to-day life. Several items on each version were not correlated with each other between testing sessions, and again these largely followed the pattern seen in paired *t*-tests, with self-report items predominantly regarding ADLs, and informant-report items more related to difficulties in memory. One possibility for this is that the lack of correlation between these items was due to varying decline over the 12-month period, with particular ADLs being more affected than others.

There was good evidence for content validity as shown by the correlations between the two versions of the IQCODE and the neuropsychological measures administered. The IQCODE (SR) had an unexpected pattern of correlations at Time 1, where the only significant relationships found were with Verbal Fluency and total score on the ACE-III, with no significant correlations with memory measures. A more expected pattern was seen with the IQCODE (IR), which was strongly correlated with both BVMT-R measures, although the correlations with verbal memory measures were not significant. As with the self-report there

was a strong relationship with Verbal Fluency, and it appears that performance on the IQCODE was related to fluency ability for the current sample. At Time 2 both IQCODEs were strongly related to all four memory measures, with the IQCODE (IR) also significantly correlating with the total score on the ACE-III.

The correlation coefficients calculated with the other neuropsychological measures offer some evidence of discriminant validity. At Time 1 neither version of the IQCODE was significantly correlated with Trails A, or Letter or Category Fluency subscales, which was expected given that these measure constructs including visual scanning and verbal communication deficits (Ashendorf et al., 2008; Loonstra, Tarlow, & Sellers, 2001). These subscales are also not as sensitive to cognitive decline in general as the other subscales of the tests, and performance should remain intact on these even in early stages of MCI (Kortte et al., 2002), and so it was not expected that they would correlate strongly with measures estimating decline such as the IQCODE (Murphy, Rich, & Troyer, 2006). However, Trails B and Switching Fluency both measure divided attention and executive functions, and these are expected to be impacted to some degree by MCI, even if early declines are predominantly amnestic (Ashendorf et al., 2008; Nutter-Upham et al., 2008). The correlations between postal and neuropsychological measures at Time 2 showed more significant relationships; in particular the IQCODE (SR) was correlated with both Trails A and B, and with Category Fluency, Switching Fluency, and Switching Accuracy subscales. This may indicate that the IQCODE (SR) was assessing more executive functioning than the informant-report, and could be useful to make predictions about facets of cognitive decline beyond memory, including other aspects of cognition that can be impacted as a part of ongoing cognitive decline.

In the present study a relatively high proportion of individuals appeared to revert to normal cognition from MCI status at Time 1. It is unclear what caused this change, as the

present analyses were not set up to assess the cause of reverters, but the presence of such individuals may have had an impact on the observed results. In particular, measuring the consistency of tests presumes that domains being investigated are relatively consistent, and this may not have been the case for some individuals. It is also important to note that 32.5% of the initial sample did not return for the second stage of this research, and so were unable to be included in analyses. The effect of participant dropout is unclear, but it does reduce the power of the study for detecting a true effect.

The aim of the current study was to assess the relationship between self- and informant-reports in older adults, with a particular focus on the psychometric properties of each version. From the present research both give valuable information about declines and used together are likely to offer greater screening utility than either by itself. In particular, changes in self-reported difficulties over time may relate more to instrumental ADLs, but self-reports are more likely to be influenced by transient difficulties. Informant-reported difficulties appear more likely to indicate changes in memory, but may not reflect the practical changes that cause distress to the individual. The consistency of both self-report and informant-reports was high over a 12-month period, with the only inconsistent results in groups where this would be expected, such as those experiencing increasing declines, and individuals found to have reverted from MCI to normal cognitive functioning. Overall, the present study demonstrated that self-reports demonstrate similar reliability to informant-reports for older adults experiencing early cognitive declines, and that each may offer different important information in predicting subsequent declines.

5. Effectiveness of Multi-Stage Screening Over Time

5.1 Introduction

Age-related cognitive declines represent a growing financial and social cost as increasing life expectancy continues to affect the incidence of neurological declines (M. K. Aronson et al., 1991). The most prevalent of these is mild cognitive impairment (MCI), a progressive neurodegenerative disorder theorised to represent prodromal dementia (Bayer et al., 2014; Bruscoli & Lovestone, 2004). Individuals experiencing MCI often refrain from presenting to primary health clinicians, or underestimate early difficulties caused by neurodegeneration (Löppönen, Räihä, Isoaho, Vahlberg, & Kivelä, 2003). As a result, such individuals are not assessed until declines have progressed and cognitive impairment has a more significant impact on functioning. However, even when individuals present to physicians there are significant limitations in the detection of early cognitive declines in primary healthcare sectors (Cullen et al., 2007). The most common tool used in predicting declines is the MMSE, which is brief and can be administered by a general practitioner, but has shown only limited predictive validity for diagnosing cases of MCI and for identifying those likely to progress to AD (Aggarwal et al., 2005; Ahmed et al., 2012; Petersen, 2003). This has led to a number of brief screening tools being developed and trialled in an attempt to improve the detection of early cognitive impairment (Cullen et al., 2007). The aim of such measures is to offer a way of efficiently and effectively identifying at risk individuals without the necessity of extensive psychometric assessment as a first-line screening methodology (Scharre et al., 2010).

The rate of progression from MCI to dementia tends to be rapid, with conversion estimates between 5.6% (Ritchie et al., 2001) and 41% (Geslani et al., 2005) per annum, considerably higher than the approximately 1% of cognitively intact older adults expected to

develop dementia over a period of 12 months (Petersen et al., 1999). Another complicating factor in assessing continuing declines are individuals who have been termed *reverters*. These individuals appear to revert to normal cognition over a period of time, having previously met criteria for MCI (Ganguli et al., 2011). A number of reasons have been suggested for why some individuals' cognition appears to improve, including psychiatric disorders such as depression appearing as pseudo-dementia (Kumar et al., 2006), or test taking behaviours and anxiety impacting initial measurement (Sachdev et al., 2013). Despite a lack of clarity around why some individuals revert, such reports are ubiquitous in the literature, and rates of reverting are typically reported between 4.5% (Nordlund et al., 2010) and 53% (Ganguli et al., 2011), with one study reporting that 92% of participants reverted or changed diagnostic categories over time (Ritchie et al., 2001). Overall, inconsistencies in diagnosis and prognosis for cases of MCI have led to a situation where despite the knowledge that individuals with MCI represent those most at risk of progressive cognitive declines, it is difficult to briefly and accurately identify these individuals.

Collectively these challenges with the detection and diagnosis of MCI, along with the unreliability of the diagnostic category, limit the detection of cases, and the possible impact that early intervention may offer. One solution may lie in improving the detection of early declines, and determining whether particular characteristics indicate those most likely to revert to normal cognition instead of progressively declining. Several attempts at multi-stage screening for cognitive decline have been attempted, but have been restricted by methodological limitations. One possible way to improve the efficiency of cognitive screening involves using postal questionnaires as a first-line screening approach, and following this with neuropsychological testing where indicated. A multiple-stage screening, such as this would allow testing to be targeted at individuals most likely to meet criteria for decline, as well as allowing the possibility of identifying individuals in the community

experiencing early cognitive declines who would be unlikely to present to primary health physicians (Alessi et al., 2003).

Limitations in previous attempts at developing postal screening have included testing self-report measures without a meaningful comparison (Jansen et al., 2008), postal tools only being measured against the MMSE (Lonie et al., 2009), and only offering neuropsychological testing to those presenting as MCI on the postal screen (van Uffelen et al., 2007). These significantly limit the conclusions that can be drawn from the respective studies; as a multi-stage MCI screening needs to demonstrate that those identified via screening as likely MCI are also likely to meet more stringent criteria on standardised gold-standard testing.

While self-reported memory difficulties are a key diagnostic consideration of the most commonly used MCI criteria (Petersen et al., 1997) there is limited but encouraging evidence that by also considering informant-report information the individuals who are likely to revert to normal cognition over time can be identified (Sachdev et al., 2013). The updated MCI criteria reflect the benefit of self- or informant-reported difficulties, allowing either to be considered for diagnosis (Albert et al., 2011). Postal screening offers a simple and straightforward means of collecting such self-report and informant-report data. Moreover, individuals who revert to normal cognition demonstrate less functional decline, so utilising well validated questionnaires measuring changes in ADLs through multi-stage screening may offer utility for differentiating individuals expected to cognitively decline from those likely to be experiencing transient cognitive difficulties (Li et al., 2012).

The present study aimed to explore the utility of a multi-stage screening approach to assess cognitive changes over time. Postal screening was used a first-line screening approach, and this included collecting self- and informant-reports in order to predict subsequent cognitive declines. Specifically, the goals were to 1) Assess the predictive validity of postal

screening tools for identifying cases of MCI; 2) Explore changes in cognition over time to see how screening measures reflect objective cognitive changes; and 3) Assess whether self- and informant-reports add reliability to the diagnosis of MCI. This was accomplished by administering postal screening tools followed by a neuropsychological battery, and then repeating this process 12 months later.

5.2 Method

5.2.1 Participants

Participants were recruited through multiple means from the local community. Community groups with older adult members, such as Rotary and Probus Clubs, were contacted and in turn passed on project information to members. An advertisement was placed in *Age Concern*, a free local newsletter with an older adult target population. The remainder of the sample were recruited through the NZBRI's volunteer database from a list of 1,300 older adults who were cognitively and physically healthy at the last point of contact. This list was randomised before recruitment began, with the only inclusion criteria being 65 years or older at the point of first contact. From these approaches 114 individuals were recruited and participated in the initial postal screening, with 78 taking part in both stages of testing, meaning a retention rate of 68.4% across both of the postal and neuropsychological sessions. However, only 77 participants returned the necessary responses for the present analyses.

The only exclusionary criteria used were that participants were not to have a diagnosis of AD, so that the sample would reflect the community and be as representative as possible. All participants provided verbal followed by written consent, and ethical approval was obtained from the University of Canterbury Human Ethics Committee.

5.2.2 Instruments

5.2.2.1 Postal Screening Measures

Three questionnaires were used in postal screening in the present study. These were selected to gather a range of information, which is crucial for identifying likely cases of MCI. The SAGE examines a range of cognitive functions including, memory, executive functions, orientation, and visuospatial manipulation (Scharre et al., 2010). It is comprised of 11 questions with a maximum score of 22, and the summed score is used to differentiate individuals with MCI from those with dementia, as well as cognitively intact older adults. For the present study an adapted version of the SAGE was used, with demographic and ethnicity questions appropriate for New Zealand, and modifications between USA and NZ terminology for money calculation items.

The IQCODE includes 16 items assessing change in memory and ADLs over the last ten years (e.g., handling finances or learning to use a new gadget around the house) (Jorm, 1994). Each item is scored on a five-point Likert scale from *Much Improved* to *Much Worse*, with higher average scores indicating more impairment. The IQCODE has been extensively used as a screening tool to look for cognitive changes after a range of disorders including AD (Cullen et al., 2007), VaD (Jorm & Jacomb, 1989), and to assess post-stroke damage (Jorm, 1994). Informants are often relied upon in the detection of early cognitive changes (Cullen et al., 2007) but self-reports of decline are of equal importance. SMCs are one of the Petersen criteria, so it stands to reason that self-reports and/or informant-reports should be collected in any MCI screening process, and there is emerging evidence that the IQCODE has good reliability and validity as a self-report measure as well as an informant-report measure (Refer to chapter 2 & 3; (Jansen et al., 2008)). For the present study two versions of the IQCODE were used, with the same questions, but modified instructions for the self-report version.

5.2.2.2 Neuropsychological Measures

A battery of neuropsychological tests was administered to objectively measure aspects of cognition, and to give a criterion measure of decline in order to assess how well the screening tools were able to detect and predict cognitive deficits. The BVMT-R (Benedict, 1997) measures visual memory and includes delayed and recall conditions to assess visual encoding and retrieval deficits. This test was developed to address a lack of visual memory measures appropriate for multiple administrations, and the six alternate forms allow retesting with reduced practice effects. Test-retest reliability is reported at .63 to .92 for total recall and delayed recall conditions, and inter-rater reliability is given at .97, indicating that this a reliable memory measure (Benedict et al., 1996).

The RAVLT (Rey, 1964) assesses verbal delayed memory, and also contains a recognition trial. Test-retest reliability is reported at .51 to .86 across all the trials, and content validity appears to be high with strong correlations between the RAVLT and other verbal memory tests such as the CVLT (Delaney et al., 1992). The most common early signs of cognitive decline are in the areas of visual and verbal delayed memory, and these two neuropsychological memory measures are able to detect these early changes (Luis et al., 2011; Small et al., 1995).

The TMT (Reitan, 1958) was included in the neuropsychological battery as it offers a measure of executive functions, as well as divided attention and processing speed. The TMT is less reliant on working memory than many other tests, so it is somewhat resistant to amnestic cognitive declines, and performance should not be significantly impaired by discrete early memory difficulties (Kortte et al., 2002). The TMT correlates fairly highly with other visual searching tasks (e.g., Digit Symbol from the WAIS-III, .63; (Sanchez-Cubillo et al., 2009)), and tends to have reliability coefficients of .65 and higher reported (Lezak, 2004).

Verbal Fluency from the D-KEFS, including Letter Fluency, Category Fluency, Switching Fluency, and Switching Accuracy, gives another measure of executive functions and divided attention, as well as semantic ability (Delis et al., 2001). In older adults test-retest reliability is reported at .70 or greater for letter and category conditions, which are most resistant to decline (Snow et al., 1988). The Verbal Fluency conditions are also only modestly correlated with memory measures (.17 to .22 with Wechsler Memory Scales and the Selective Reminding Test), giving another test that should be relatively unaffected by amnestic decline (Ruff et al., 1997).

Finally, the ACE-III (Hsieh et al., 2013; Mioshi et al., 2006) was administered. This test was developed as a standalone screening tool of cognitive functioning, and provides a brief measure of memory, orientation, visuospatial ability, and verbal fluency (Hsieh et al., 2013). Collectively these areas are those most likely to be affected throughout early stages of cognitive decline, and so this test offers some utility to screen for MCI (Aggarwal et al., 2005; Busse et al., 2006).

5.2.3 Procedure

The SAGE and both versions of the IQCODE were mailed out to all participants who had indicated interest in the study at the initial phone contact, along with project information and consent forms. Following these postal questionnaires all participants took part in a brief neuropsychological testing session assessing current cognitive functioning. Implied consent was initially given over the phone, with written consent obtained at the testing session. Test administration occurred in the same order for all participants, and they were administered by a clinical psychology PhD student trained in the use of these measures.

After 12 months all participants who completed the research at Time 1 were contacted again and were offered participation in the second stage of the research looking for changes

over time. The testing procedure was repeated, with alternate forms administered where possible. Neuropsychological administration was by the same researcher, and all participants consented to their involvement at the second stage as well as the first.

5.2.4 Data Analysis

Initially ANCOVA were used to look for differences over time on the measures used. Change scores were then calculated based on these differences and the correlations with postal and neuropsychological measures were computed. Analysis of Variance (ANOVA) and multiple regression analyses were used to explore between-group differences and the degree to which individual tests contributed to predicting cases of MCI. Finally, Receiver Operating Characteristics (ROC) curves were used to measure the predictive validity for MCI of the postal questionnaires and MCI status over time, and Odds Ratios (OR) calculated for each statistically significant ROC curve using logistic regression. Given the exploratory nature of the present analyses, and a lack of prior evidence as to cut-offs, single optimal cut-offs are reported from ROC analyses for each measure.

5.3 Results

5.3.1 Participants

During the initial recruitment and testing 70 females and 44 males completed the postal screening and neuropsychological testing, with an age range of 65-93 (M=75.04, SD=5.88). At Time 1 there were 34 individuals categorised as MCI based on Petersen's criteria (Albert et al., 2011; Petersen et al., 1997), including subjective memory complaints and objective memory deficits observed on the neuropsychological measures. Included in this group were 20 females (28.6%) and 14 males (31.8%), and the individuals in this group were significantly older than the non-MCI participants (M=77.62, SD=5.26 vs. M=73.95, SD=5.82, t(112)=3.16, p=.002, d=.66).

At Time 2 (12 months after initial testing), 78 participants agreed to take part in the second stage of the research, giving a total response rate of 68.4%. Of these 77 returned the necessary responses and so are included in the present analyses. This group was aged between 65 and 86 (*M*=74.90, *SD*=5.42); in total 48 females and 29 males participated in both stages of the research. Their ethnicity was not dissimilar to recent census data from the Canterbury DHB (Statistics New Zealand, 2013), with 94.9% NZ European/Pakeha, 1.3% Maori, and 3.8% other.

5.3.1.1 Returners and Non-returners

ANCOVA were used to compare participants depending on whether they agreed to be tested at Time 2, based on their Time 1 responses, with age and gender considered as covariates. In total 36 participants did not take part at Time 2, and one did not provide postal responses. There was no significant difference between these groups on postal scores, although the SAGE was trending towards significance, F(1, 110)=3.03, *p*=.085 (Returners *M*=19.60, *SD*=1.98, Non-returners *M*=18.58, *SD*=3.84).

Scores on the neuropsychological measures were converted to age-adjusted standardised scores based on established norms (Population *M*=100, *SD*=15). There were significant differences observed on both conditions of the RAVLT between those who returned and those who did not, with RAVLT Delayed Recall F(1, 110)=4.83, *p*=.030 (Returners *M*=113.0, *SD*=18.54, Non-returners *M*=103.75, *SD*=21.71), and Total Recall F(1,110)=4.68, *p*=.033 (Returners *M*=119.89, *SD*=17.25, Non-returners *M*=111.52, *SD*=20.58) showing that those who did not return had lower age-adjusted standard scores on average at Time 1 for measures of verbal memory. There was also a difference observed on the ACE-III raw scores indicating a possible difference in current cognitive functioning, F(1, 110)=14.36, *p*<.001 (Returners *M*=90.03, *SD*=5.46, Non-returners *M*=84.94, *SD*=8.59). Of the 36 participants who did not return, 15 met MCI criteria, meaning that while 31.5% of

participants elected not to return, 44.1% of those identified as experiencing cognitive declines at Time 1 chose not to return. The difference in MCI proportion between those who returned and those who did not approached significance, χ^2=3.53, p=.06, φ=-.176. Subsequent analyses are based on participants who completed both phases of data collection (n=77).

5.3.2 MCI Categorisation

Twenty-four individuals met MCI criteria at Time 2 (13 females (27.1%) and 11 males (37.9%)). Overall this meant 42.9% of the present sample were classified as MCI at one or both testing points. Participants were categorised into four groups based on MCI status: individuals who met MCI criteria at both Time 1 and Time 2 (MCI-both); individuals meeting MCI criteria at only Time 2 (MCI-single); individuals who did not meet criteria for MCI (non-MCI); and participants who appeared to revert from MCI to normal cognition between Time 1 and Time 2 (Reverters). In total 10 participants were classified as MCI-both, 14 MCI-single, 44 non-MCI, and 9 reverters. The participants that appeared to revert to normal cognition all scored at least 1.5 standard deviations below age-adjusted norms on neuropsychological memory measures at Time 1, but did not score below this cut-off at Time 2. There were no significant differences between the ages of individuals in the four MCI groups (MCI-both M=77.50, MCI-single M=76.21, Reverters M=76.11, Non-MCI M=73.52), F(3,73)=2.24, p=.091, η^2=.08.

Paired t-tests were initially used to look for differences over time on postal measures. Neither version of the IQCODE differed significantly over the 12 months, t(72)=-1.70, p=.094 for the IQCODE (SR) and t(66)=.049, p=.961 for IQCODE (IR). In contrast, there was a significant difference observed on the SAGE, with decreased average scores indicating more difficulty on this measure over time, t(76)=2.86, p=.006, d=.15 (Time 1 M=19.58, SD=1.99, Time 2 M=18.86, SD=2.38). Paired t-tests were then used to look for differences between Time 1 and Time 2 on the postal measures after splitting the participant group based

on MCI category, and these are shown in Table 11. The SAGE and IQCODE (SR) showed significant differences over time for MCI-single participants, with both representing a larger degree of cognitive decline. There were no significant differences observed for the other MCI groups over time, including for reverters.

Table 11
Paired t-tests for Postal Measures from Time 1 to Time 2 for each MCI Group

	IQCODE(SR)			IQCODE (IR)			SAGE		
	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*
MCI-both	-.305	-2.07	.654	-.079	-.36	.121	1.40	1.58	.500
MCI-single	.096	2.26*	.628	-.103	-1.21	.334	1.43	2.22*	.593
Reverter	-.102	-.732	.269	-.047	-.78	.275	1.00	1.25	.417
Non-MCI	-.034	-1.23	.190	.069	1.83	.300	.295	.994	.015

* $p<.05$

Changes on the neuropsychological measures for the overall sample were assessed using paired *t*-tests. The only tests showing significant differences between Time 1 and Time 2 were Switching Fluency and Switching Accuracy on the Verbal Fluency test, with both scores increasing over time, $t(76)=-2.83$, $p=.006$, $d=.080$ (Time 1 $M=11.30$, $SD=2.92$, Time 2 $M=12.60$, $SD=4.13$) and $t(76)=-5.37$, $p<.001$, $d=.174$ (Time 1 $M=10.97$, $SD=2.95$, Time 2 $M=13.13$, $SD=3.30$) respectively. Differences on neuropsychological measures for each MCI group were then explored in the same way, with memory test comparisons shown on Table 12, and the remaining neuropsychological measures on Table 13. MCI-single participants showed a large and significant decrease in average Total Recall BVMT-R scores, while reverters significantly improved on this measure over time. All groups except reverters also significantly improved in Switching Accuracy performance over time.

Table 12

Paired t-tests of Neuropsychological Memory Measures for each MCI group

	BVMT-R Delayed			BVMT-R Total			RAVLT Delayed			RAVLT Total			ACE-III		
	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*
MCI-both	1.95	-.47	.01	5.70	-1.88	.06	7.50	1.05	.02	6.80	1.41	.03	1.20	.66	.04
MCI-single	23.36	6.12***	.11	19.93	6.76***	.16	5.27	1.90	.05	2.86	.89	.02	-.93	-.84	.06
Reverters	-14.83	-2.48*	.05	-21.47	-2.77*	.04	-6.97	-.78	.01	-2.50	-.62	.02	1.56	.95	.06
Non-MCI	2.07	1.13	.01	-1.28	-.75	.01	2.30	-1.35	.02	-1.60	-.87	.01	-.21	-.39	.02

* $p<.05$, ** $p<.01$, ***$p<.001$

Table 13

Paired t-tests of Executive Functioning and Verbal Ability Neuropsychological Measures for each MCI group

	Trails B			Letter Fluency			Category Fluency			Switching Fluency			Switching Accuracy		
	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*	M_{Diff}	*t*	*d*
MCI-both	0.00	0.00	0.0	.40	.25	.02	4.30	1.46	.05	-.30	-.20	.01	-1.90	-2.39*	.30
MCI-single	1.07	1.48	.15	.50	.59	.05	-.07	-.09	.00	-2.64	-3.44**	.32	-2.64	-3.35**	.30
Reverters	.67	.52	.05	-.22	-.37	.07	-.44	-.74	.14	-.89	-.546	.04	-1.22	-.97	.09
Non-MCI	-.16	-.35	.02	-.09	-.31	.02	-.11	-.22	.01	-1.18	-1.96	.07	-2.25	-3.85**	.15

* $p<.05$, ** $p<.01$

Change scores were generated for the neuropsychological measures by calculating the difference between Time 1 and Time 2, such that positive scores indicated an improvement over time. Correlations between the Time 1 postal questionnaires and neuropsychological change scores indicate the relationship between initial postal questions and change over time. These correlations are presented in Table 14. Moderate correlations are seen between IQCODE (SR) and both BVMT-R and RAVLT Delayed Recall, indicating a negative relationship between IQCODE (SR) memory difficulties and delayed verbal recall. The IQCODE (IR) was negatively correlated with both Delayed Recall and Total Recall on the RAVLT, as well as positively correlated with Trails A. Finally, the SAGE was negatively correlated with both Verbal Switching measures and with the ACE-III, indicating a relationship with this screening tool and measures of executive functioning. The negative correlations between IQCODE measures and neuropsychological test scores indicate that as individuals reported more current difficulties they tended to show decreased performance on the neuropsychological memory measures.

Table 14

Correlations Between Time 1 Postal Questionnaires and Neuropsychological Change Scores

	IQCODE (SR)	IQCODE (IR)	SAGE
BVMT-R			
- Delayed Recall	-.265*	-.036	-.087
- Total Recall	-.085	.036	-.122
RAVLT			
- Delayed Recall	-.390**	-.311*	.000
- Total Recall	-.299	-.309*	-.099
TMT			
- Trails A	.132	.241*	-.190
- Trails B	.060	.029	-.125
Verbal Fluency			
- Letter Fluency	.029	.092	.077
- Category Fluency	.070	.114	-.202
- Switching Fluency	.051	.070	-.333**
- Switching Accuracy	.007	-.040	-.252*
ACE-III	.126	.071	-.243*

* $p<.05$, ** $p<.01$

Given that the MCI categorisation was based on neuropsychological scores below age-adjusted norms, an overall change score was calculated as a criterion of decline by averaging change from Time 1 to Time 2 on the four memory age-adjusted standard scores collected (BVMT-R and RAVLT) which represent standardised measures normed so that *M*=100, *SD*=15. The overall change score for the sample had a mean of -3.08, 95% *CI* (-12.15, 5.98) and *SD*=39.94. The sample was separated according to diagnostic category, which showed the average change was relatively small for MCI-both and non-MCI groups, while as expected, the MCI-single and reverter groups showed large changes over time (MCI-both *M*=-6.65, *SD*=36.3; MCI-single *M*=-51.41, *SD*=28.06; reverters *M*=45.78, *SD*=29.68; and non-MCI *M*=3.11, *SD*=28.96). Between group differences were tested using a one-way ANCOVA again controlling for age and sex, $F(3,71)=20.38$, $p<.001$, $\eta^2=.46$.

A multiple regression was conducted to look at whether the postal measures at Time 1 were able to predict decline at Time 2. The neuropsychological change score was used as the

dependent variable, with both Time 1 IQCODEs and the SAGE as independent variables. These screening measures statistically significantly predicted change in neuropsychological scores over time $F(3,59)=3.73$, $p=.016$, $R^2=.16$ with Beta weights of IQCODE (SR)= -.326 ($p=.042$), IQCODE (IR) = -.080 ($p=.623$), and the SAGE=-.181 ($p=.152$). However, only the IQCODE (SR) added significantly to the prediction model and predicted unique variance in the change score, $\hat{Y}=-40.70X+228.33$, $p=.031$.

A further regression was calculated using the IQCODE (SR) and age to explore any relationship between age and self-report scores. This analysis indicated that age did not have a main or interaction effect on predicting memory change over time. Analysing the predictive relationship between the IQCODE (SR) and memory change showed a significant result in the absence of the other postal measures $F(1,71)=11.77$, $p=.001$, $R^2=.142$ with a regression equation of $\hat{Y}=-44.35X+136.83$ and Beta weight=-.377. As IQCODE (SR) scores increase a decrease in memory change scores can be seen, demonstrating that increasing self-reported memory difficulties are able to predict impaired performance on standardised neuropsychological memory measures.

The regression equation was used to estimate the memory change of non-returners based on Time 1 IQCODE (SR) scores, and this showed a predicted average memory change of -4.64. This did not represent a significant difference from the measured average change of returners ($p=.589$).

5.3.3 MCI Prediction

ROC curves were calculated for each of the three postal measures to predict MCI categorisation at Time 1, Time 2, and an overall diagnostic classification. At Time 1 the IQCODE (IR) had an optimal cut-off of 3.30, giving sensitivity of 53% and specificity of 88%, with an area under the curve (AUC) of .698 ($p=.015$), OR = 8.76, 95% CI (1.17, 65.52).

The other two postal measures did not have significant AUCs when making predictions at Time 1, with IQCODE (SR) AUC=.574, *p*=.347, and SAGE AUC=.562, *p*=.418. This implies that only informant-reports demonstrated predictive utility at rates higher than chance.

ROC curves for the three postal measures were again calculated for Time 2 postal measures against Time 2 MCI categorisation. The IQCODE (IR) was again significant, AUC=.686, *p*=.009, OR = 16.38, 95% CI (2.13, 126.10) with an optimal cut-off of 3.03 which gave sensitivity of 75% and specificity of 53%. The IQCODE (SR) was not significant for the Time 2 comparison, but the trend was in the expected direction with AUC=.638, *p*=.054. The SAGE was significant, AUC=.676, *p*=.014, OR = 1.27, 95% CI (1.03, 1.57) with an optimal cut-off at 20.5 which gave sensitivity of 92% and specificity of 44%. Predictive utility was therefore demonstrated by both the IQCODE (IR) and the SAGE, which were able to predict cases of MCI at Time 2.

Finally, the predictive ability of the postal measures at Time 1 was explored by calculating ROC curves using Time 2 MCI categorisation as the outcome variable. The IQCODE (IR) again had a statistically significant ROC curve, AUC=.677, *p*=.019, OR = 6.07, 95% CI (0.95, 38.88) with an optimal cut-off at 3.26 which gave 54% sensitivity and 84% specificity. The AUC for the IQCODE (SR) was also statistically significant, AUC=.711, *p*=.004, OR = 9.93, 95% CI (1.06, 93.53) with the cut-off at 3.34 giving 52% sensitivity and 90% specificity. This implies the IQCODE (SR) may be more useful for predicting subsequent declines than the previous ROC statistics indicated, given that it was able to predict future declines at statistically significant rates. The predictive ability of the IQCODE (IR) was also demonstrated over time. The Time 1 SAGE was not able to make predictions at Time 2 better than chance, AUC=.547, *p*=.509. The AUC for these ROC curves are shown in Table 15.

Table 15
AUC of Postal Measures Predicting Dichotomous MCI Classification

	MCI Status (Time 1)	MCI Status (Time 2)
IQCODE (SR) Time 1	.574	.711**
IQCODE (IR) Time 1	.698*	.677*
SAGE Time 1	.562	.547
IQCODE (SR) Time 2		.683
IQCODE (IR) Time 2		.686**
SAGE Time 2		.670*

* $p<.05$, ** $p<.01$

5.4 Discussion

The present focus of inquiry aimed to explore the relationship between postal screening tools and cognitive changes over time. In particular, it was hoped that brief screening tools would offer utility for predicting subsequent declines over time between testing sessions. MCI represents an area of interest in research focused on age-related cognitive declines, given that these individuals appear to be more at risk of experiencing progressive impairment, such as AD, than older adults in general. If older adults experiencing the first stages of cognitive decline could be identified effectively then interventions aimed at slowing or halting such declines could be trialled and implemented, but to date difficulties in making such identification has limited potential interventions. Three postal measures were included in the present research, which allowed a variety of information to be collected, and also reduced some of the limitations present in previous work testing multi-stage MCI screening.

Participants were categorised as having MCI based on the criteria suggested by Petersen and updated by the NIA (Albert et al., 2011; Petersen et al., 1997) and this led to four groups over the two testing sessions: those consistently meeting MCI criteria; those

experiencing decline over time to meet criteria at Time 2; individuals who did not meet MCI criteria; and participants who appeared to revert to normal cognition between Time 1 and Time 2. Overall this led to 42.9% of the present sample meeting MCI criteria at some point across the study, including those who reverted over time. This proportion was higher than expected, and outside of many estimates of prevalence (Hänninen et al., 2002; Petersen et al., 2001), however, estimates have been reported as high as 53.8% (Koivisto et al., 1995). There are several possible reasons for such observed discrepancies between studies, and in particular the use of different MCI diagnostic criteria, or different criterions of decline are likely to have an impact (Hänninen et al., 2002). Inclusive MCI criteria were used for the present study in order to provide the best opportunity to demonstrate screening utility of the measures used. Given the serious nature of MCI and subsequent declines it can be useful to use liberal criteria in order to ensure a reasonable sensitivity is achieved. The other interesting group were the nine participants who appeared to revert from impaired to healthy cognition in the 12 months between testing sessions. The present study was not set up to explore the reasons behind reverters, but some possible reasons why this pattern occurs have been suggested previously, including psychiatric conditions or initial test-taking difficulties (Kumar et al., 2006; Sachdev et al., 2013). While reverters do not comfortably fit into the idea of a linear pattern from early impairment to progressive decline, these individuals are ubiquitous in the research area, often in high proportions (Busse et al., 2006; Ganguli et al., 2011; Gauthier et al., 2006).

The proportion of participants who chose not to take part in the second stage of the present research was higher than expected, and represents a potential bias due to the decreased data at Time 2. However, several characteristics of the sample limit this potential issue. In particular, those who did not return were considerably more likely to have been classified as MCI at Time 1, and therefore are likely to have been experiencing more age-

related declines. The conversion rate of MCI to dementia is estimated at between 5.6% (Ritchie et al., 2001) and 41% (Geslani et al., 2005) and so it is possible that those falling into this category would be less likely to be able or willing to participate in further research. A related possibility involves health more generally, whereby a number of participants contacted indicated interest in taking part, but were unable to due to physical health, injury, or scheduled surgery. It is unclear whether these individuals' cognitive status may have been related to physical difficulties or illness, but these were clear barriers to participation, and there are strong links between physical health and age-related cognitive decline (Etgen et al., 2010; Heyn et al., 2004). It is therefore not necessarily problematic to have participant attrition this high, and these individuals not taking part at Time 2 does not invalidate the present results, due to the increased likelihood that they may have declined further, which would have supported the current findings.

Self- and informant-report postal measures tended not to change over time, with both versions of the IQCODE showing no significant differences. This was to be expected given that the informant version has high reported test-retest reliability (Jorm, 1994), and the self-report version appears to have similar psychometric properties (Chapter 3). In contrast the SAGE did demonstrate a significant decrease in average score over time, indicating that overall individuals had more cognitive difficulties at Time 2 than Time 1. When pairwise comparisons over time were made for each MCI category the only statistically significant differences were observed among participants categorised as MCI-single on the IQCODE (SR) and the SAGE. This was particularly interesting given the nature of the MCI groups, and in particular reverters demonstrated an improvement across standardised cognitive tests over time, yet did not demonstrate a significant improvement on the SAGE, which is a cognitive screening tool. Moreover, the reverters also did not demonstrate significant change over time on either self- or informant-reports. The changes seen on the SAGE, but not either

IQCODE, could be due to the different areas that each are assessing, and while the present study was not set up to explore such a finding it will be interesting to explore in future research. It is also possible that self- and informant-reports remain unaffected by transient cognitive declines that result in variable neuropsychological performances, which may have resulted in some false positives by the screening tool that can then be clarified with full neuropsychological batteries. However, it is important to note that for screening tools at least, it appears more beneficial for higher sensitivity with false positives, than to potentially miss some individuals and limit any possible early intervention efforts to ameliorate or halt further decline.

The only overall significant differences on neuropsychological measures over the 12-month period were Switching Fluency and Switching Accuracy from Verbal Fluency. The lack of change in memory scores was somewhat explained when the MCI groups were looked at separately, where differences between MCI-single and reverters were seen. Diagnosis of MCI was made using a memory criterion, so those meeting MCI at Time 2 but not Time 1 performed more poorly on memory measures during the second testing session; in particular decreased performance on the two BVMT-R scales appeared to indicate difficulty. In contrast the reverters appeared to improve on this measure, which accounted for them not meeting MCI diagnostic criteria at Time 2. It was interesting that changes on the verbal memory measures were much smaller, with none approaching statistical significance.

On the other neuropsychological measures there were differences seen on the Switching Accuracy scale from Verbal Fluency, where three of the four groups changed over 12 months. There was also a large mean difference between scaled scores on Category Fluency for participants in the MCI-both group, although this did not reach significance, which was likely due to a large standard deviation among participants. Despite differences

being observed on Switching Accuracy no significant differences were seen on Trails B, which is interesting given the overlap in executive functioning that both measure.

It was expected that the three postal measures used in the present study would be positively correlated with the neuropsychological memory change scores, given that these are purported to assess cognitive change with a particular focus on early memory difficulties. The correlations for Time 1 postal scores against neuropsychological change scores indicated that there were significant negative correlations between the IQCODE (IR) and both RAVLT conditions, while the IQCODE (SR) was negatively correlated with changes on delayed recall conditions from both the RAVLT and the BVMT-R. Higher IQCODE scores indicate increasing memory and ADL impairment, and so it was expected that these scores would increase as BVMT-R and RAVLT scores decreased. Delayed recall is likely to be the best predictor of decline, as this is often the first sign of age-related cognitive decline (Small et al., 1995). The lack of significant correlations between the SAGE and changes on memory measures was unexpected, although the SAGE was significantly correlated with changes on the ACE-III, which is a more comprehensive measure of a similar range of cognitive processes to the SAGE. This may indicate that the SAGE is related to cognitive change more generally than the IQCODEs are, while these are better specific predictors of memory changes.

There were significant differences between MCI groups based on an average neuropsychological memory change score, but more interesting was that only the IQCODE (SR) added to the prediction when regression analyses was conducted. Overall the regression indicated that 16% of the variance in neuropsychological memory change scores were accounted for by these tests. Given the aim of the present study was to look at making predictions of decline from brief screening, as an indication for using multi-stage cognitive screening, this is an encouraging finding. In particular, this result demonstrates that

informant-reports of memory decline and difficulties with ADL are predictive of declines on age-adjusted standardised measures that are strongly associated with MCI. Interestingly, adding age to the regression analysis did not increase the predictive ability. Age has long been established as strongly linked to dementia and cognitive decline, with increasing prevalence of all forms of dementia as age increases (M. K. Aronson et al., 1991; Wimo, Jonsson, & Winblad, 2006). It was therefore interesting that age was not a factor in the present study, with no significant difference in age observed between the four MCI groups. One possibility is that a combination of the sample size and the relatively restricted age range resulted in no significant effect of age being observed. The average age of 75.04 was also fairly high, which may have reduced the statistical impact that age had on differentiating cases of MCI from cognitively healthy older adults.

The predictive utility of the postal screening tools was assessed through the use of ROC curves to see how well these tools could indicate likely cases of MCI. At the Time 1 testing only the IQCODE (IR) had a statistically significant AUC, indicating that through using this test 69.8% of cases could be correctly identified. While ideally a screening tool would have a better predictive rate than this, it still represents a predictive accuracy significantly better than chance, and fulfils the aim of identifying individuals most at risk in order to inform more extensive testing. The cut-off of 3.30, which maximised the sensitivity and specificity of the measure, was similar to previous research using the IQCODE to identify MCI, where a cut-off of 3.19 was optimal (Li et al., 2012). The difference between these two values could be due to the different response format, where in the present study this was used as a postal tool, instead of being administered face-to-face. It would be interesting in future to directly compare the response format and determine whether this does have an impact on scores.

Predictions using the postal screening tools at Time 2 indicated more predictive validity than at Time 1. The IQCODE (IR) again demonstrated a significant result, with 68.6% of cases being correctly identified based on the AUC, although the optimal cut-off based on this analysis was 3.03. The optimal cut-off is found by maximising sensitivity and specificity, but because the purpose of screening measures is to identify likely cases the sensitivity is more important, and so while a cut-off of 3.03 is close to the expected score of non-impaired individuals, it gave a sensitivity of 75%. The IQCODE (SR) did not statistically significantly predict cases of MCI, but was trending in the right direction with an AUC of .638 and a *p*-value of .054, meaning that this would likely reach significance had the sample size been larger. The SAGE had a cut-off of 20.5, which is considerably higher than the cut-off given by the test development study at 16 (Scharre et al., 2010). As with the IQCODE it would be interesting to assess whether the response format has had an impact on scores on this test, given that it has not been utilised as a postal screening tool previously. There were also a number of participants who indicated that they did not follow the instructions when completing this tool. In particular, several participants volunteered that they had checked the date on a calendar before responding. Recall of the current date is a good standalone measure of memory and orientation (O'Keeffe et al., 2011), and so it is unclear how much of an impact it has if this is not being answered appropriately, particularly given that this accounts for 4 of the 22 points possible on the SAGE.

The third set of ROC curve analyses explored the possibility that screening responses at Time 1 could predict MCI cases at the 12-month follow-up, and both versions of the IQCODE demonstrated utility for predicting future declines. In particular, despite not meeting significance in the previous comparisons, the self-report version correctly identified 71.1% of MCI cases with a cut-off of 3.34. This was similar to the cut-off suggested by the informant-report, at 3.26. Overall, these results are encouraging, and give evidence to support

the use of postal screening to indicate individuals likely to have MCI, and also to predict individuals likely to experience decline from healthy cognition to MCI over a 12-month period.

The present study aimed to explore the use of postal screening measures to indicate likely cases of MCI, and to predict incident cases over a 12-month period. This was undertaken through the use of three postal screening tools, and administering a neuropsychological battery of tests to all participants assessing the most common areas of early cognitive decline. The results supported the idea that postal screening tools have utility for predicting decline, and offer evidence that cognitive screening can be undertaken without the large time and financial costs that have typically been associated with this. As predictions are able to be made based on postal measures, the use of these as a first-line screening modality is therefore supported from the present results. More work is needed to explore differences based on response format of the postal measures used, and in particular whether the SAGE remains as useful a test as previous research shows, despite some individuals not following all instructions for the measure. Yet despite possible limitations the results show the potential benefits of multi-stage screening, and the use of such measures for predicting subsequent declines over a 12-month period.

6. Effect of Life-Course Participation in Stimulating Activities

6.1 Introduction

Age-related cognitive declines, and specifically MCI, represent an increasing health concern for older adults across industrialised nations and the developing world (Anderson & Hussey, 2000; Kalaria et al., 2008). MCI is a neurodegenerative condition representing a stage of cognitive decline beyond normal aging but not meeting full diagnostic criteria for dementia (Ritchie & Touchon, 2000). Individuals experiencing early cognitive declines are a heterogeneous group, and it has typically been difficult to identify such individuals for research or treatment. There have been significant variations in reported prevalence rates of MCI, along with diagnostic instability and many individuals appearing to revert back to normal cognition, having previously been identified as cognitively impaired. Moreover, there is significant variation in the rates with which individuals with MCI progress to dementia, with the conversion rate of MCI to dementia estimated at between 5.6% (Ritchie et al., 2001) and 41% (Geslani et al., 2005) per year; significantly higher than the 1 to 2% of cognitively intact older adults expected to develop AD over 12 months (Petersen et al., 1999).

One hypothesis for differences in the rate individuals' progress to dementia is the theory that staying cognitively and physically active may protect against future declines and help maintain cognitive functioning (Podewils et al., 2005). There is an established relationship between decreasing engagement in cognitively and physically stimulating activities and incident cognitive decline (Fratiglioni, Paillard-Borg, & Winblad, 2004; Verghese et al., 2006), but the causal direction of this has not yet been established. It is currently unclear whether increasing cognitive decline leads to withdrawal from activities (James et al., 2011) or that continued engagement offers some protection from incident declines (Rovio et al., 2005; Wilson et al., 2002b). Current thinking appears to favour the

latter via the neural reserve hypothesis (Stern, 2002), where staying cognitively, physically, and socially active helps maintain cognition even in the presence of neuropathology (Wilson et al., 2005). Research linking frequency of engagement with each of these activity types consistently demonstrates a protective effect from developing cognitive impairment over time, as well as promoting physical health, which also has a beneficial impact on cognition in old age (Heyn et al., 2004; Lautenschlager et al., 2008).

Wilson (e.g., (Wilson et al., 2005; Wilson et al., 2000; Wilson et al., 2013)) has expanded further on the concept of neural reserve, by exploring how cognitively stimulating activity over the life-span may increase neural reserve and offer protection from cognitive decline. In particular, involvement in leisure activities with cognitive, social, and physical components during mid-life and adulthood have been linked to improved memory functioning (Christensen & Mackinnon, 1993), and a decreased likelihood of dementia in old age (Whitmer et al., 2005). One of the ways this may occur is through increased synaptogenesis associated with cognitive and physical activity across the lifespan (Churchill et al., 2002). Post-mortem studies have demonstrated variable levels of impairment between older adults despite neuropathology associated with Alzheimer's disease (AD) that would be expected to cause significant cognitive impairment (Boyle et al., 2013; Riley et al., 2002; Satz, 1993). It is therefore possible that lifestyle factors may contribute to the resilience of the brain, meaning that more extensive neuropathological changes need to occur before an observable impact is seen (Kempermann, 2008).

Given the observed difficulties in reliably identifying individuals at risk of age-related cognitive declines, and the unreliability of such diagnoses, the inclusion of information regarding current frequency of activity participation may improve the diagnostic processes. In particular the rate of disease progression from MCI to dementia is an important consideration in research aiming to slow or halt declines, but this rate appears variable based on protective

factors that are often not measured (Hultsch, Hertzog, Small, & Dixon, 1999). Given that research showing late-life leisure activity having an impact on the disease expression of MCI is widespread, it is important to consider the impact of cognitive reserve on the prognosis of MCI, and the expected heterogeneity of rates of change between individuals. While some of the variation is likely due to methodological and sampling differences, it is also possible that some of this variation may be due to engagement in stimulating activities, and therefore may be able to be quantified in screening.

The present study aimed to explore whether late-life engagement with cognitive, physical, and social activities offered protection from cognitive decline over a 12-month period. Specifically, it was expected that more frequent participation in activities would be related to a reduced degree of decline over a one-year period, compared to individuals with less frequent activity. It was hypothesised that more frequent cognitive, physical, and social engagement would mitigate decline over time, and keep at risk individuals cognitively intact. Frequency of cognitive activity across the lifespan was also assessed, and it was hypothesised that a higher frequency of cognitive activity would be related to decreased cognitive impairment. Furthermore, engagement in cognitive, social, and physical leisure activities were explored through the use of a postal questionnaire, with the view to exploring whether such information is useful for improving the prediction of MCI in a community sample. It is possible that the reliability of MCI diagnosis could be improved by factoring in the protective effects of cognitive, physical, and social activity on neural health, as well as these factors contributing to estimations of ongoing cognitive decline.

6.2 Method

6.2.1 Participants

Participant recruitment was undertaken through visiting local community groups with

older adult members in Christchurch, NZ (e.g., Rotary and Probus clubs), who in turn passed on project information to their members. An advertisement was placed in *Age Concern*, a free newsletter with an older adult target population. Individuals were also contacted from the NZBRI volunteer database, which contained contact information for 1,300 individuals who were cognitively healthy at the last point of contact. In total 145 individuals indicated interest in taking part in the research, with 114 completing stage one and 78 taking part at Time 1 and Time 2. However due to the specific analyses being utilised only the 78 who completed both stages were included in the present analyses. The only inclusion criterion for the present study was that participants were 65 years or older at recruitment. The only exclusion criterion was that individuals did not meet diagnostic criteria for dementia at first contact, so that the sample would be representative of the community. All participants gave informed consent before taking part, and were fully informed about the purpose and nature of the study. Ethical approval for this research was obtained from the University of Canterbury Human Ethics Committee.

6.2.2 Instruments

Four questionnaires were administered as part of the initial postal screening in order to collect a variety of information, in particular any change from previous levels of functioning, along with early signs of cognitive deficits. Specifically, self-report and informant-report versions of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), and the Self-administered Gerocognitive Examination (SAGE) were posted to all participants. Furthermore, information about past and current engagement in cognitive, physical, and social activities was also collected via the General Activities Questionnaire (GAQ), discussed below. Neuropsychological tests assessing a range of cognitive areas, including memory, executive functioning, verbal fluency, and orientation were then completed to help quantify the information provided by the postal screens.

6.2.2.1 Postal Screening Measures

The SAGE is a recently developed tool to screen for MCI and AD, and examines a variety of cognitive areas including: memory, executive functions, and visuospatial manipulation (Scharre et al., 2010). The SAGE contains 11 questions that are summed to give a total possible score of 22, which has some evidence for differentiating individuals with MCI from both healthy controls, and individuals with AD. We used an adapted version of the SAGE, with demographic questions that were appropriate for NZ, and modifications between USA and NZ terminology for money calculation questions.

The IQCODE includes 16 items asking about memory changes over time, as well as any changes in instrumental ADLs, such as handling finances or driving (Jorm & Jacomb, 1989). The IQCODE has been used extensively as a screening instrument to look at cognitive changes in disorders including AD, VaD, and post-stroke damage (Cullen et al., 2007; Jorm, 1994). There is also emerging evidence for the use of the IQCODE in detecting changes associated with MCI (Li et al., 2012). Each IQCODE item is scored on a five-point scale from *Much Improved* to *Much Worse*, and the average score is taken from the 16 questions (Jorm, 2004). Participants were sent two versions of the IQCODE in the present study, an informant report (to be completed by someone who had known them at least 10 years), and a self-report. Despite the questionnaire being developed for an informant to answer, there is some evidence that self-reports may be useful in detecting early cognitive decline (Jansen et al., 2008), and this measure may facilitate collecting this type of data (Chapter 2 & 3).

The General Activities Questionnaire (GAQ; Appendix E) was adapted for the present study based upon a semi-structured interview template used by Wilson in research looking at engagement in stimulating activities over the life-span and activity during late-life (e.g., (Wilson et al., 2005; Wilson et al., 2013; Wilson et al., 2002b)). The questionnaire has items assessing the frequency of cognitively stimulating activities at four approximate points in

development, childhood (6 years), teenage (12 years), young adult (18 years), and adulthood (35-40). Participants were asked to answer as accurately as they could for those stages of life, but that specific recollection of the age in question was less important than themes during those stages. There were three questions at childhood, and seven for each of the other three time points, with each item answered on a 4-point scale assessing frequency, from *Every day or almost every day* to *Several times a year/rarely*. Scores were averaged for each time point to give a measure of cognitive activity, with higher scores indicating less frequent activity. Questions assessing present-time activities were more varied, and included items assessing cognitive, physical, and social activities. In total there were 27 items regarding how participants spend their time at present; of these 20 had a cognitive component, 6 physical, and 7 social. As per item development (Wilson et al., 2005) items could load on multiple elements (e.g., During the last year how often did you participate in political or cultural group activities was considered to have both cognitive and social components (Karp et al., 2006)). Each of these items had the same four scale options as the previous life-stage questions, and average scores were calculated for the three types of activity. Given that this measure was developed as part of the present research the psychometric properties are unclear, however the semi-structured interview used by Wilson has demonstrated reasonable psychometric properties across a number of studies (Wilson et al., 2005; Wilson et al., 2013).

6.2.2.2 Neuropsychological Measures

The BVMT-R (Benedict, 1997) is a measure of delayed and recognition visual memory. There are six alternate forms of the visual stimulus on the BVMT-R, which allows for the measure to be useful over time, and for multiple administrations. Unlike other similar measures of visual memory there is less possibility of practice effects due to the multiple equivalent forms (Benedict et al., 1996). Test-retest reliability is reported at .63 to .92 for delayed and total recall conditions, with an inter-rater reliability of .97 (Benedict, 1997). This

measure also appears to have good construct validity, correlating strongly (.62 to .77) with other memory and visuospatial construction measures (e.g., the Hopkins Verbal Learning Test and the ROCF), and only weakly correlating with tests of language ability (.25 to .30; e.g., Boston naming test and Verbal Fluency) (Benedict et al., 1996).

The RAVLT (Rey, 1964) offers a measure of delayed verbal memory, as well as a recognition memory task. It has been used extensively over time to assess memory difficulties, and has reported test-retest reliability of .51 to .72 for the delayed and recognition trials (Delaney et al., 1992). It also correlated well with other verbal learning and memory tasks such as the CVLT at .33 to .47 and the Verbal Selective Reminding Test at .58 to .69 (Crossen & Wiens, 1994; Macartney-Filgate & Vriezen, 1988).

The TMT (Reitan, 1958) offers measurement of executive functioning, processing speed, and visual scanning. This test tends to correlate fairly highly with other visual searching tasks (e.g., Digit Symbol from the WAIS-III of .63) (Lezak, 2004; Sanchez-Cubillo et al., 2009). The TMT is also less reliant on working memory than other measures used, and so is likely to be less affected by memory decline (Kortte et al., 2002).

Four Verbal Fluency subscales (Letter Fluency, Category Fluency, Switching Fluency, and Switching Accuracy from the D-KEFS (Delis et al., 2001)) were assessed as a further measure of executive functioning, as well as divided attention and verbal fluency ability (Gomez & White, 2006). In older adults Verbal Fluency has a reported test-retest reliability of .70 or greater (Snow et al., 1988), and only has modest correlations with memory measures, meaning discretely memory difficulties should not impact upon performance on this test (Ruff et al., 1997).

The ACE-III (Noone, 2015) is a brief tool used to detect likely cases of MCI by assessing a range of cognitive areas including: orientation, memory, visuospatial ability, and

verbal fluency. The ACE-III subscales correlate strongly with the tests of the constructs they claim to measure, meaning this test has good content validity, and overall correlated strongly with the ACE-R (.99) indicating that the many validation studies completed on the previous version are likely to remain valid (Hsieh et al., 2013). Together these neuropsychological tests briefly measure the cognitive areas most likely to demonstrate early cognitive deficits, and have been shown to be sensitive to detecting MCI and early AD (Aggarwal et al., 2005; Busse et al., 2006).

6.2.3 Procedure

The screening measures were initially mailed to all consenting participants. Three questionnaires (the SAGE and both versions of the IQCODE) were sent to screen cognitive functioning. The fourth, the GAQ, asked about previous and current levels of activity. Implied consent was obtained by telephone, and written consent was then collected when participants attended the neuropsychological testing session. Test administration was in the same order for all participants, and was conducted by a clinical psychology PhD student trained in their administration. The testing took between 50-80 minutes for each participant.

After 12 months all participants who completed the first stage of the research were again contacted and offered participation in the second stage of the research. For those who chose to take part postal measures were again sent out. This was followed by neuropsychological testing using the same tests, but with alternate forms where available.

6.2.4 MCI Categorisation

Following the neuropsychological testing participants were classified as MCI or non-MCI at both time points. Classification was based on the Petersen criteria (Albert et al., 2011; Petersen et al., 1997) including subjective memory complaints identified through self-report or informant-report; objective memory deficits of 1.5 standard deviations below age-adjusted

norms on neuropsychological measures; relatively intact ADLs; generally intact cognitive functioning; and not meeting diagnostic criteria for dementia. This led to four MCI categories: non-MCI who did not meet MCI criteria at either time point; MCI-single who appeared to decline from Time 1 by meeting MCI criteria at Time 2; MCI-both who met criteria at both time points; and Reverters, who met criteria at Time 1 but appeared to revert to normal cognitive functioning by Time 2.

6.2.5 Data Analysis

Initially descriptive statistics for postal measures were calculated, along with Analysis of Covariance (ANCOVA) to test for changes on these measures over time with Time 1 as a covariate, time 2 scores as the dependent variable, and MCI category as a factor. A discriminant analysis was then calculated to assess whether MCI groups differed on a linear combination of variables including all postal screening tools, age, and sex. Following this, ANCOVA were conducted for the neuropsychological measures, looking at patterns in responding and for changes over time, these were again used so that age and sex could be treated as covariates. Between-group differences of the four MCI categories were also conducted. Finally, multiple regressions were used to look for potential moderating effects of current cognitive activities on change in neuropsychological measures.

6.3 Results

6.3.1 Participants

Participants (n=78; 49 females and 29 males) were aged between 65 and 83 years at the time of testing (M=74.79; SD=5.39). In total 10 participants met MCI criteria at both testing points (MCI-both), 15 at just Time 2 (MCI-single), 9 reverted from MCI to normal cognition (reverters), and 44 did not meet MCI criteria (non-MCI). The ages of participants in these four groups were not significantly different, $F(3,74)=2.147$, p=.102. The ethnicities of

participants were similar to the expected distribution for older adults in Canterbury based on District Health Board Data from the 2013 census, with 94.9% NZ European, 1.3% Maori, and 3.8% other (Statistics New Zealand, 2013).

6.3.2 Postal Measures Analyses

Descriptive statistics for each of the postal measures were calculated for Time 1 and Time 2, and are shown in Table 16, along with the mean scores for the historical activities. The mean scores of the SAGE and IQCODE (IR) were lower at Time 2, while the IQCODE (SR) was higher, indicating greater cognitive impairment. Lower scores on the SAGE indicate increased cognitive difficulty, while higher scores on the IQCODEs indicate a higher degree of memory and ADL difficulty. Of the current GAQ items, physical activity was the most frequently reported, although it had the largest variation at both Time 1 and Time 2. Social activities were reported the least frequently. During teenage years there was the lowest average frequency of cognitive activity reported, and the highest frequency was reported during adulthood. The largest amount of variation was seen in cognitive activity during childhood. Dependent *t*-tests were calculated to determine whether significant change occurred on these postal measures for the sample as a whole. Scores on the SAGE were significantly different over time, with a lower average at Time 2 indicating increased cognitive difficulty, $t(77)=2.91$, $p=.005$. Frequency of physical activity also decreased significantly, $t(77)=-4.60$, $p<.001$. The other comparisons were not significantly different, although frequency of social activities approached significance, with a decrease in activity reported $t(77)=-1.921$, $p=.058$.

Table 16
Descriptive Statistics for Postal Questionnaires at Time 1 and Time 2

	Time 1		Time 2	
	Mean	SD	Mean	SD
SAGE	19.603	1.983	18.872*	2.371
IQCODE (SR)	3.150	.3444	3.200	.285
IQCODE (IR)	3.137	.331	3.130	.373
GAQ				
- Cognitive	1.066	.325	1.031	.293
- Physical	1.555	.587	1.390***	.5389
- Social	.797	.345	.736	.412
Historical Activities				
- Child	1.154	.828		
- Teenager	.958	.560		
- Young Adult	1.030	.573		
- Adult	1.280	.509		

* $p<.05$, ** $p<.01$, *** $p<.001$

To test whether changes in the postal measures occurred similarly across groups, ANCOVAs were calculated, with Time 2 scores as the dependent variable, Time 1 scores as a covariate, and MCI category as a factor (including all four MCI groups mentioned previously). These were calculated for each of the postal questionnaires, and are presented in Table 17. The only significant change over time was between IQCODE (SR) scores with the average score increasing significantly, indicating a greater degree of impairment. Although the SAGE and IQCODE (IR) did not reach significance both were trending in the anticipated direction, with a higher average IQCODE (IR) and lower average SAGE indicating more difficulty. No significant changes over time were observed for GAQ items.

Table 17
ANCOVA Change Scores for Postal Questionnaires

	F	*df*	$_p\eta^2$
SAGE	2.118	3, 73	.087
IQCODE (SR)	12.792***	3, 68	.565
IQCODE (IR)	2.781	3, 62	.135
GAQ (Cognitive)	1.143	3, 73	.047
GAQ (Physical)	.083	3, 73	.003
GAQ (Social)	.090	3, 73	.004

* $p<.05$, ** $p<.01$, *** $p<.001$

The participant sample was then divided according to MCI category and paired *t*-tests for the postal questionnaires were calculated looking for differences over time as post-hoc analyses of these group data. These t-tests are presented in Table 18. Significant changes were seen on the SAGE and IQCODE (SR) for MCI-single participants, with decreasing SAGE and increasing IQCODE (SR) indicating increasing impairment. There was also a significant decrease in physical activity for non-MCI participants. No change over time was seen in MCI-both and Reverter groups. Correlations of each of the paired samples are presented in Table 19, where all groups showed significant positive correlations for cognitive, physical, and social activities. Screening measures for non-MCI participants were all significantly correlated, but only the IQCODE (SR) for MCI-both and MCI-single, and the IQCODE (IR) for reverters showed significant correlations.

Table 18

Paired Sample t-tests for Postal Questionnaires for each MCI Category

	SAGE		IQCODE (SR)		IQCODE (IR)		GAQ (Cognitive)		GAQ (Physical)		GAQ (Social)	
	t	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*
MCI-Both	1.583	.148	-2.067	.069	-.364	.725	-1.387	.199	-1.094	.302	-.476	.646
MCI-Single	2.333	.035*	2.264	.043*	-1.205	.251	-.616	.548	-2.145	.050	-.432	.672
Reverters	1.251	.246	-.732	.488	-.778	.462	.010	.993	-1.492	.174	-1.414	.195
Non-MCI	.994	.326	-1.232	.225	1.826	.076	-1.251	.218	-3.706	.001**	-1.592	.119

* $p<.05$, ** $p<.01$

Table 19

Paired Sample correlations for Postal Questionnaires for each MCI Category

	SAGE		IQCODE (SR)		IQCODE (IR)		GAQ (Cognitive)		GAQ (Physical)		GAQ (Social)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
MCI-Both	.514	.129	.719	.019*	.038	.923	.849	.002**	.753	.012*	.835	.003**
MCI-Single	.187	.505	.709	.007**	.339	.258	.857	<.001***	.877	<.001***	.702	.004**
Reverters	.083	.832	.088	.837	.744	.034*	.886	.001**	.930	<.001***	.908	.001**
Non-MCI	.589	<.001***	.673	<.001***	.746	<.001***	.830	<.001***	.829	<.001***	.686	<.001***

* $p<.05$, ** $p<.01$, *** $p<.001$

6.3.3 Discriminant Analysis

It had been hypothesised that cognitive screening tools and participants' frequency of lifetime cognitive activity would be related to cognitive decline, and so a discriminant analysis was run to test whether the four MCI groups differed significantly on these variables. This analysis contained 11 independent variables collected at Time 1 (Age, SAGE, IQCODE (SR), IQCODE (IR), GAQ historic: Child, Teenager, Young Adult, Adult, and GAQ present: Cognitive, Physical, Social). Discriminant analysis tests whether groups differ on a linear combination of predictor variables, and in the present analysis none of the variables statistically significantly discriminated between groups. The best result involved a 3-function solution, using 3 factors based on linear combinations of the input variables that was somewhat able to statistically discriminate between the four groups. However, while trending towards significance this was not a significant result, Wilks λ=.413, χ^2= 45.564, *df*=33, Canonical correlation=.642, *p*=.071.

A stepwise discriminant analysis was then calculated to look for individual significant predictors of group differences. Due to the large number of potential predictors in the initial calculation, a stepwise follow-up allows individual variables to be looked at in regard to their linear predictive value on the four groups. The IQCODE (IR) was the only statistically significant variable in the equation, Wilks λ=.792, χ^2= 13.16, *df*=3, Canonical correlation=.456 *p*=.004. This result indicates that IQCODE (IR) scores are able to discriminate between MCI groups and that clear between-group differences can be seen based on this measure.

6.3.4 Neuropsychological Measures Analyses

Scores for change over time on the neuropsychological memory measures were calculated for individual participants between Time 1 and Time 2, and descriptive statistics

and paired t-tests for each of these are presented in Table 20. Overall, these show that BVMT-R Delayed Recall scores decreased over time while Total Recall increased. The opposite was seen for the RAVLT, with a positive average change score on Delayed Recall but negative change on Total Recall. However, none of the changes over time were statistically significant for the overall sample.

Table 20
Descriptive Statistics of Neuropsychological Change Over Time

	Mean	SD	*t*	Minimum	Maximum
BVMT-R Delayed Recall	-3.571	16.997	1.856	-48.00	46.50
BVMT-R Total Recall	.2942	16.996	-.153	-39.00	57.00
RAVLT Delayed Recall	.1154	15.689	-.065	-50.00	75
RAVLT Total Recall	-.1945	12.648	.136	-30.00	32.48

ANCOVA were used to look for change over time on neuropsychological measures in order to determine whether change was detected across these from Time 1 to Time 2. As above, these were calculated with Time 2 scores as the dependent variable, Time 1 as a covariate, and MCI as the independent variable. The results of these analyses are shown in Table 21, and indicated significant differences on all four memory measures, but not for the ACE-III.

Table 21
ANCOVA Scores for Neuropsychological Memory Measures over Time

	F	η^2
BVMT-R Delayed Recall	25.975***	1.07
BVMT-R Total Recall	29.331***	1.21
RAVLT Delayed Recall	5.864**	.241
RAVLT Total Recall	4.269**	.175
ACE-III Total	1.661	.068

* $p<.05$, ** $p<.01$, *** $p<.001$

Finally, correlations were used to look for linear relationships between postal measures and the neuropsychological change score. The results of these correlations are

presented in Table 22 and show that late-life activities were not significantly related with other postal measures, or with cognitive change scores. There was a significant negative correlation observed between the IQCODE (SR) and the neuropsychological change score, indicating that as IQCODE (SR) scores increased performance on neuropsychological memory measures decreased.

Table 22
Correlations of Time 1 Postal Measures and Neuropsychological Change Score

	Cognitive		Physical		Social		Change Score	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
SAGE	.104	.364	.095	.407	-.048	.676	-.125	.275
IQCODE (SR)	-.104	.379	-.099	.404	.024	.843	-.377	.001**
IQCODE (IR)	-.152	.217	-.146	.236	-.063	.612	-.206	.091
Change Score	-.003	.979	.154	.178	.067	.557		

* $p<.05$, ** $p<.01$, *** $p<.001$

6.3.5 Moderation Analyses

Moderation analyses were conducted between Time 1 postal measures and Time 1 participation in activities to assess the possible interaction of activity on subsequent cognitive declines. Activity was hypothesised to moderate the rate of change, where individuals with higher frequency of stimulating activity would demonstrate less cognitive decline over the 12-month period. GAQ engagement in activities and postal screening measures were used as predictor variables, with the mean neurological change score, from the standardised memory measures, used as an outcome measure. Analyses were conducted using hierarchical regressions, with predictors entered in the first step and the interaction term based on centred predictors in the second step. The results of these two-step regression analyses are shown in Table 23.

Table 23
Two-Step Regression Interaction Effects

Predictors	R^2 Change	*F*	*df*
SAGE x Cognitive	.002	.017	1,74
SAGE x Physical	.046	3.75	1,74
SAGE x Social	0.00	0.00	1,74
IQCODE (IR) x Cognitive	.085	6.28*	1,64
IQCODE (IR) x Physical	.007	0.49	1,64
IQCODE (IR) x Social	.044	3.12	1,64
IQCODE (SR) x Cognitive	.061	5.29*	1,69
IQCODE (SR) x Physical	.001	0.06	1,69
IQCODE (SR) x Social	.059	5.18*	1,69

* $p<.05$

A significant moderation was seen between the IQCODE (IR) and GAQ current cognitive activities, R^2change=.085, (*F* 1,64)=6.279, *p*=.015 where those participating in cognitively stimulating activities showed a positive change over the 12 months, while those with low reported frequency of activity had negative change and demonstrated worse performance on the neuropsychological measures. A similar trend was shown between the IQCODE (SR) and current cognitive activities, R^2change=.061, (*F* 1,69)=5.294, *p*=.024, with more frequent cognitive activity appearing to be protective. The IQCODE (SR) also demonstrated a significant moderation relationship with social activities, R^2change=.059, (*F* 1,69)=5.182, *p*=.026 where more frequent social engagement also appeared to be protective. The interaction between the IQCODE (IR) and social activities was approaching significance, R^2change=.044, (*F* 1,64)=3.119, *p*=.082, with a clear similarity to the previous moderations in the observed trend. The only interaction approaching significance from the SAGE was with physical activities, which was interesting given that physical activities did not approach a significant effect from the other measures, R^2change=.046, (*F* 1,74)=3.754, *p*=.057. The three significant moderations are displayed on Figure 6. For all three moderations lower frequency of activities was associated with more significant cognitive decline (positive

change), while higher frequency of activity was associated with less cognitive decline or even cognitive improvement over time.

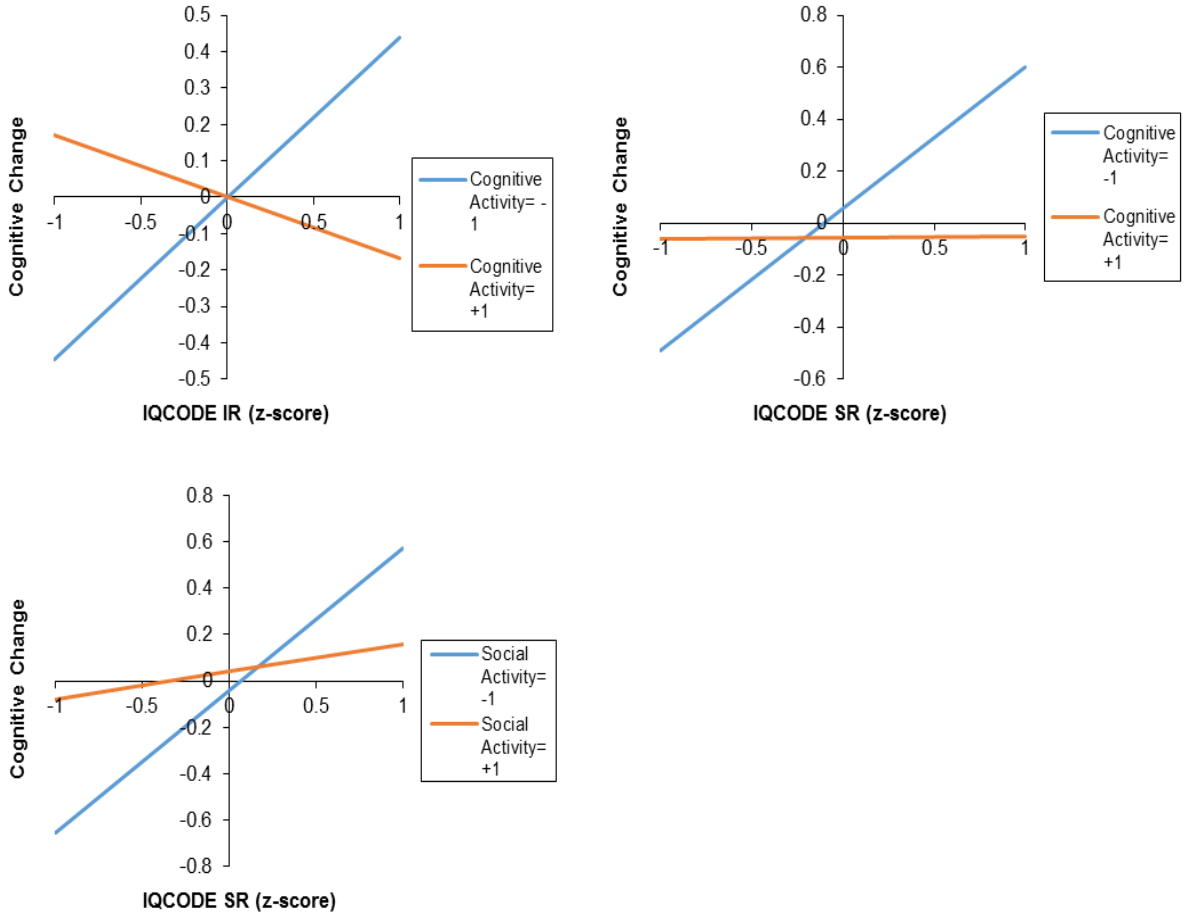

Figure 6. Interaction effects demonstrating the moderation of stimulating activity on cognitive decline.

6.4 Discussion

The present research was designed to explore the relationship between cognitive decline and engagement with cognitively, physically, and socially stimulating activities. It was hypothesised that more involvement with such activities would protect individuals against cognitive declines over a 12-month period. There is ongoing debate about the impact that staying cognitively, physically, and socially active in late-life can have on preventing or slowing declines (James et al., 2011; Rovio et al., 2005; Wilson et al., 2002b), but emerging

data supports the theory of neural reserve and the possibility that staying active may offer protection from cognitive decline (Perani & Abutalebi, 2015; Stern, 2002). Furthermore, it has been hypothesised that cognitive activity throughout life may offer late-life protection from declines (Wilson et al., 2013). AD and other age-related cognitive declines are an increasing health and social burden due to ageing populations, yet difficulty remains in identifying individuals most at risk of developing such conditions, and by extension being able to offer interventions for slowing or halting such decline (Acevedo & Loewenstein, 2007). Consequently, there is great need for accurately identifying individuals in early stages of decline, and the present study aimed to demonstrate the utility of considering frequency of stimulating activities in making predictions about declines.

Comparison of postal screening measures over time for all participants indicated that only the IQCODE (SR) was significantly different between testing sessions, whereas the other screening measures were trending in the expected direction but did not reach significance. This was unexpected given that 15 participants appeared to decline from normal cognition to MCI over the course of the 12 months. One possibility from this is that over a relatively short space of time individuals may be more sensitive to detecting changes than those who know them well, particularly if they are able to compensate for some of these difficulties. This trend was further supported when looking at paired sample *t*-tests between testing periods for each of the postal measures, with significant changes only being seen on the SAGE and the IQCODE (SR) for MCI-single participants, and for physical activities of non-MCI participants. However, given that participants in the MCI-single group had demonstrated an objective decline it was expected that this would be reflected in scores on the postal measures. Moreover, it was expected that informants would notice such changes over the one-year period and this would be reflected on the IQCODE (IR). There did appear to be a trend approaching significance for physical activity in this group (p=.05), which

would support the idea that participation in physically stimulating activity decreases as cognitive declines present. It is possible that with a larger sample size in each group more results may have reached significance.

Given that the Reverter group appeared to improve from mildly impaired to normal cognition it was expected that this group would also show significant differences on postal measures over time. One possibility explaining the lack of significant differences for this group is that the postal screening measures were giving an accurate portrayal on the individual at Time 1, which then did not change, so whatever had caused the discrepancy (e.g., depression, stress, or test-taking behaviours) was not reflected in postal screening measures. This would offer support for the concept of using screening tools such as these for identifying the most at risk individuals, even in the case of other factors impacting a given presentation. Future research exploring this possibility would be useful to clarify whether or not measures like the SAGE and the IQCODE are resistant to transient cognitive decline. The idea of reverters is ubiquitous in research on MCI and age-related decline, but it is not entirely clear why this pattern is consistently seen (Ganguli et al., 2011; Sachdev et al., 2013). Ongoing work exploring the difference between this group and those who continue to decline will be important to establish in future, and in particular establishing whether these individuals present differently on some tests that would allow for differentiation from older adults likely to progress to dementia.

A disparate pattern was seen in the correlations of each measure over time, particularly in the Reverter group. There was only a very weak relationship between scores at Time 1 and Time 2 for the SAGE and the IQCODE (SR), whereas the IQCODE (IR) had a strong relationship. This could indicate a lack of consistency between responding, but again given the cognitive changes observed in this group, and the small sample, this needs to be interpreted with caution.

Following these comparisons, a discriminant analysis was conducted to assess whether any of the variables from the postal screens were able to discriminate between the four MCI groups. Overall, there was no linear function that significantly discriminated the groups, although a trend towards significant between-group differences on this measure was encouraging. It was unclear why the groups were not able to be discriminated using these variables, as it was expected that the current frequency of activities, self- and informant-reported memory and daily functioning, and age, would all be different between these groups. One possibility for why between group differences were not observed is the heterogeneity of older adults and limited power of the sample in the present study, and it is possible that with a larger sample size more definitive results would have been observed.

The stepwise discriminant analysis indicated that only informant-reports of decline were consistently discriminating between groups, but what was more interesting was that age did not significantly discriminate between MCI groups. This was surprising given the extensive evidence for the impact of age in late-life cognitive decline (Ott et al., 1995; Petersen et al., 2001; Petersen et al., 1997). However, it is possible that the relatively high average age (74.79 years) may have had an impact on this, whereby a high proportion of old but cognitively intact participants may have skewed this result compared to previous epidemiological studies. Such a sampling artefact is unfortunate, but difficult to prevent when assessing community samples requiring volunteers. Future research expanding on the present findings by stratified sampling may be useful for determining whether this finding disappears with a larger range of older adults.

The observed interaction between activity participation and incident cognitive decline was as hypothesised, although less significant relationships than expected were seen between screening measures and frequency of activity. Higher frequencies of cognitive and socially stimulating activities appear to be related to reduced rates of cognitive decline over a

12-month period, with individuals reporting higher frequency of engagement with these less likely to demonstrate objective cognitive decline. However, the expected impact of physical activity was not observed in the present analyses, and it is unclear why this was not seen. One possibility is in the measure used, which was more strongly aimed at cognitive activity participation, and so may have missed some of the range of physically stimulating activity that older adults engage in. What to include in such measures varies widely between studies, with differences in reported frequency based on how many response options were available and how complex the screening tool is (Sofi et al., 2011). Repeating the present analyses with a more comprehensive measure of physical activity would be useful to determine whether a true effect exists that was not measured, or whether the impact of socially and cognitively stimulating activities is more significant for preventing incident cognitive decline.

Despite the significant interaction effects there were no significant differences in reported activity between groups over time for the MCI groups. Furthermore, there was no significant relationship between participants' frequency of activity and neuropsychological change scores. Given previous findings of decreasing likelihood of cognitive impairment with increasing activity, the lack of a linear relationship between activities and neuropsychological change scores was unexpected. One possible explanation for this is that the particular individuals who volunteer for research such as this are more likely than the population in general to engage in stimulating activities. In particular, several of the present sample were recruited through community groups such as Rotary, which present social and cognitively stimulating opportunities to older adult members. Looking at this relationship again in future work with a sample recruited from more diverse sources may change the observed trend. Moreover, it is possible that 12 months was too short a follow-up period to detect changes in activity participation, and that a longer follow-up would help to detect the impact of continued engagement in stimulating activities.

Differences observed in the present research from Wilson's work on stimulating activities may reflect differences in response format (e.g., (Wilson et al., 2005; Wilson et al., 2002a; Wilson et al., 2002b)). In particular, reducing the number of response options may have led to less variation in responding than in previous research. This point was raised by several participants, who wanted a *Never* response in addition to what was available, and if this was added there would have been more variation possible amongst respondents. Trialling the GAQ as a postal screening tool with a fifth option would be useful to determine whether this measure can add information above what was identified in the present research. It would also be useful to collect information about activities via a semi-structured interview alongside the postal GAQ to test whether response format or social desirability was having an impact on the frequency of reported engagement with particular activities. The present study was not set up to measure socially desirable responding, nor to test whether the response format impacted on reported activity.

The present study identified a number of patterns of decline in a representative community group, including some evidence for the use of both informant- and self-reports in identifying those at risk of cognitive declines. It was expected that the level of engagement with cognitively, physically, and socially stimulating activities would have an impact on decline over a 12-month period, and some evidence of this was shown. Repeating these measures over further time-points would be useful to see whether ongoing high levels of activity offer any protection against incident cognitive decline, and what impact physical activity has over a longer follow-up.

7. Exploring Subtypes of MCI Using Cluster Analysis

7.1 Introduction

Mild cognitive impairment (MCI) represents a stage of decline beyond normal aging, but not meeting full diagnostic criteria for dementia. There have been a number of attempts to operationally define diagnostic criteria for MCI, but yet there remains a lack of a universally recognised definition. However, the most common diagnostic criteria of MCI are those proposed by Petersen (Petersen et al., 1997) and expanded on by the NIA (Albert et al., 2011), and include: subjective reports of memory impairment; quantifiable deficits on a standardised neuropsychological test; relatively intact ADLs; otherwise normal cognition; and the absence of dementia. MCI is theorised to represent prodromal dementia, which is supported by epidemiological studies reporting the annual conversion rate of MCI to AD between 5.6% (Ritchie et al., 2001) and 41% (Geslani et al., 2005), which is significantly higher than the approximately 1 to 2% expected annually for cognitively intact older adults (Petersen et al., 1999).

As the concept of and research into MCI has progressed it has been hypothesised that the initial operational definition of MCI was deficient, and that considering primarily memory deficits precludes identifying prodromal cases of dementias other than AD (Petersen et al., 2001). Resultantly, subcategories of MCI have been theorised as likely to have varied outcomes, with amnestic MCI likely to develop to AD, non-amnestic MCI to develop into FTD, and multiple-domain deficits developing to VaD (Busse et al., 2003; Petersen et al., 2001; Rasquin et al., 2005; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006). However, there remain difficulties with these multiple diagnostic categories, and in particular the number of cognitive domains assessed has led to different findings between studies, with little agreement in how many domains need to be included (Busse et al., 2006). Moreover, there has been a lack of distinction observed between different MCI diagnostic groups, and

significant movement between MCI subgroups over time (Busse et al., 2003). Overall, current evidence indicates that outcomes are worse for individuals diagnosed with amnestic MCI, and their conversion to all types of dementia is higher than those diagnosed with non-amnestic MCI (Busse et al., 2006; Matthews et al., 2008).

The cognitive deficits first noticed tend to vary somewhat between dementia diagnoses, with memory declines seen first in AD, and executive functioning decline preceding FTD (Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010; Stopford et al., 2012). This presents a challenge in assessing for early cognitive decline, as taking amnestic, non-amnestic, and multiple-domain MCI into consideration creates a larger burden on testing, and leads to difficulties in assessing the accuracy of screening (B. C. Stephan, Kurth, Matthews, Brayne, & Dufouil, 2010). Moreover, once multiple domains are impaired the difference between MCI and dementia becomes blurred, and it becomes challenging to differentiate these. It is also unclear at present whether the trajectory of decline necessarily follows these subcategories of MCI, with evidence that individuals classified as amnestic MCI tend to develop dementia of all types at higher rates than other subcategories (Busse et al., 2006). This raises the question of whether subcategories of MCI are actually separate presentations, or whether such differences are just part of the heterogeneity of older adults experiencing declines.

One method of assessing differences among individuals with data from a range of cognitive instruments is to cluster participants based on their scores using latent class analysis (LCA). LCA assumes that categorical indicators are flawed measures of an underlying and unobserved construct, which can be validated using statistical techniques (Rindskopf & Rindskopf, 1986). The observed relationships between variables within each cluster grouping are occurring with the combination of that class, meaning that the class explains the observed variation (Vermunt & Magidson, 2002). By utilising cluster analysis similarities and

discrepancies between groups can be calculated in such a way so as to indicate the most similar cases, and therefore demonstrate whether individuals with diverse early cognitive declines are statistically separate from cognitively intact older adults (Fraley & Raftery, 1998). If these groups are distinct across a range of cognitive measures this would support the idea of categorically distinct subgroups of MCI, which is expected if amnestic, non-amnestic, and multiple-domain MCI represent prodromal forms of different dementias. In contrast it may be useful to consider early declines more generally, and attempt to screen for early difficulties before trying to differentiate the likely trajectories of decline.

One further diagnostic challenge regarding MCI is in the fundamental difficulty of applying categorical criteria to a continuous disorder. Because cognitive declines are progressive it is difficult to accurately decide where cut-offs should be, and some of the epidemiological disagreement in previous research has involved whether 1.0 (Busse et al., 2006; Ritchie et al., 2001) or 1.5 (Geslani et al., 2005; Petersen et al., 1999) standard deviations below age-adjusted norms represent objective cognitive deficits. Using LCA offers a further advantage given that it is an atheoretical analysis, meaning the clustering is made independently of cut-offs or diagnostic thresholds. If discernible differences exist between cognitively intact individuals and those suffering MCI then these should be represented in the cluster solution irrespective of whether the individuals meet diagnostic cut-offs on tests.

The current study aimed to: 1) Use LCA to cluster individuals using a range of neuropsychological information, and to determine the optimal number and distribution of clusters; 2) Assess diagnostic reliability by comparing and contrasting the clustering results with diagnostic MCI cut-offs; and 3) Explore whether subcategories of MCI aid first-line screening in a representative New Zealand sample. This was explored through the use of postal screening and standardised neuropsychological measures administered twice, with 12 months between testing sessions.

7.2 Method

7.2.1 Participants

Participants were recruited by a variety of means from older adults in Canterbury, NZ. Initially local community groups with older adult members, such as Rotary and Probus, were contacted and in turn passed project information on to interested individuals. An advertisement was also placed in *Age Concern*, a free local newsletter with an older adult target population. Finally, participants were recruited from the NZBRI volunteer database, which contained contact information for 1,300 older adults who were physically and cognitively healthy at the last point of contact. The volunteer list was randomised before recruitment to prevent particular demographic variables being over-represented.

From these collection methods, 114 participants took part in the first stage of testing, including postal screening and a neuropsychological examination. After 12 months these participants were again contacted and offered participation in the second stage of research, looking for any changes over time. In total 78 participants completed both stages of the research. The only exclusion criteria applied to the current sample was that participants had not received a diagnosis of dementia, in order that they represent the local older adult community as closely as possible. The only inclusion criteria for the present research was that participants were 65 years or older at the first point of contact. All participants gave implied consent at first contact, and written informed consent at the neuropsychological testing session. All participants were fully informed about the nature of the study. Ethical approval for this research was obtained from the University of Canterbury Human Ethics Committee.

7.2.2 Instruments

A range of instruments were used to collect a variety of information about current functioning, and any changes in functioning over time. In particular, measurement of

cognitive areas including memory, executive functions, orientation, and attention were collected (Beversdorf et al., 2007; Fischer et al., 2007).

7.2.2.1 Postal Screening Measures

The SAGE (Scharre et al., 2010) is a recently developed standalone screening measure developed to detect early cognitive deficits by briefly assessing a range of cognitive constructs. The SAGE contains 11 questions worth differing amounts adding to a maximum score of 22, with the total score showing some utility in differentiating individuals with MCI from both healthy individuals and those with dementia (Scharre et al., 2010). Included in the 11 items are questions assessing memory, orientation, executive functions, and visuospatial manipulation. For the present study, an adapted version of the SAGE was used, with modified demographic options reflecting the New Zealand population, and adjustments made to terminology for money calculation questions.

The IQCODE (Jorm, 1994) was used to assess changes over time in memory and instrumental activities of daily living, such as handling finances. The IQCODE involves an informant answering 16 questions about any observed changes in daily functioning and everyday memory tasks over the preceding 10 years. Responses are scored on a five-point Likert scale, from *Much Improved* to *Much Worse*, with the average taken of the 16 items, and higher scores indicating greater impairment. The IQCODE has been used in assessment for a range of cognitive disorders, including AD, VaD, and post-stroke damage (Cullen et al., 2007; Jorm & Jacomb, 1989). This tool has also been used in a variety of formats including face-to-face interviews, telephone interviews, and pen-and-paper completion, all of which appear to have similar psychometric properties (Jorm, 2004). While the IQCODE was developed as an informant report there is emerging evidence of the psychometric properties of using this as a self-report measure, so a version with modified instructions was used to assess self-reported difficulties in memory and ADLs (Li et al., 2012)(Chapter 3).

The GAQ was developed for the present research based upon a semi-structured interview template used by Wilson in research exploring the relationship between stimulating activities over the lifespan and cognitive decline (e.g., (Wilson et al., 2005; Wilson et al., 2000; Wilson et al., 2002b)). This questionnaire assesses the frequency of cognitively stimulating activities including reading, writing, and playing games such as checkers or crosswords. Frequencies of cognitive activity were asked about at four approximate developmental points, childhood (6 years), teenage (12 years), young adulthood (18 years), and adulthood (35-40). At each stage participants were asked to respond as accurately as they could, but that specific ages were less important than the trend they experienced during these stages. Each question was answered on a 4-point Likert scale assessing frequency, with options from *Every day or almost every day* to *Several times a year/rarely*. The measure of cognitive activity was taken by using the average at each age-point. Questions assessing engagement in current activities were more extensive, and 27 items were used to explore current activities, including items exploring the frequency of participation in cognitive, physical, and social activities. Each item could contribute towards multiple elements, given that many activities cannot be narrowed down to only representing one such factor (Karp et al., 2006; Wilson et al., 2005). Of the 27 items 20 contained a cognitive component, 7 a social component, and 6 a physical component. Each of the present activity questions had the same 4-point frequency scale as the historical questions, and average scores were calculated for cognitive, social, and physical activities respectively.

7.2.2.2 Neuropsychological Measures

A brief neuropsychological battery was administered to all participants, in order to briefly measure a wide range of aspects of cognition. The BVMT-R (Benedict, 1997) was developed to provide a brief and reliable measure of visual working and delayed memory, as well as providing the opportunity for retesting with six equivalent versions (Benedict et al.,

1996). Test-retest reliability for the delayed and total memory conditions is reported at .63 to .92, with high inter-rater reliability, and convergent validity with other measures of delayed visual memory (Benedict, 1997).

The RAVLT (Rey, 1964) provides a second memory measure, and assesses working and delayed verbal memory. The RAVLT has high reported test-retest reliability, ranging from .51 to .86 across learning trials and delayed memory, as well as correlating highly with other verbal learning tests such as the CVLT (.33 to .47) (Delaney et al., 1992; Macartney-Filgate & Vriezen, 1988). Collectively, visual and verbal delayed memory are the most common aspect of cognition to demonstrate early decline, and so the BVMT-R and RAVLT are likely to detect signs of amnestic MCI (Small et al., 1995).

The TMT (Reitan, 1958) provides a measure of executive functioning, along with processing speed and some indication of motor speed. Trails A and B have also shown some utility for detecting early executive functioning declines (Ashendorf et al., 2008). The TMT correlates highly with other visual searching tasks (e.g., Digit Symbol from the WAIS-III at .63) (Lezak, 2004), and performance is relatively resistant to early memory declines (Kortte et al., 2002).

Verbal Fluency from the D-KEFS (Delis et al., 2001) provides another measure of executive functions and divided attention, particularly through Switching Fluency and Switching Accuracy subscales. Letter Fluency and Category Fluency subscales also offer insight into verbal ability and processing speed, while all four subscales are relatively resistant to early amnestic declines (Ruff et al., 1997). Test-retest reliability for Verbal Fluency is reported at .70 for older adults, and is appropriate for repeated administration with equivalent alternate forms (Snow et al., 1988).

The ACE-III (Noone, 2015) is the latest iteration of the Addenbrooke Cognitive Examination, which was designed as a standalone measure of cognitive decline. The ACE-III assesses a range of cognitive constructs, including orientation, attention, memory, visuospatial construction, and verbal fluency. Subscales of these constructs have been shown to be valid, and the ACE-III is correlated highly (.99) with the ACE-R, indicating that the validation studies and reliability coefficients for this test remain valid (Hsieh et al., 2013). Collectively these areas represent those most likely to decline in MCI, and the ACE-III has shown some diagnostic utility for detecting early deficits (Aggarwal et al., 2005; Busse et al., 2006).

7.2.3 Procedure

Participants were initially mailed postal questionnaires (SAGE, GAQ, and both informant-report and self-report versions of the IQCODE) along with project information and consent forms. Once these had been completed participants were again contacted and completed a face-to-face neuropsychological testing session. When contacted, participants were reminded to bring hearing and visual aids as needed for the testing. The neuropsychological tests were administered in the same order for all participants, and were presented by a clinical psychology student trained in their administration. The neuropsychological testing took approximately one hour for each participant.

After 12 months all participants that completed the first stage of the research were contacted again and were offered participation in the follow-up study looking for changes in cognition over time, along with the consistency of responses on the measures used. The postal and neuropsychological procedure was repeated, with alternate forms administered where possible. Informed consent was obtained at the follow-up testing appointment, and the same researcher administered the tests.

7.3 Results

7.3.1 Participants

Participants were aged between 65 and 83 years when they were initially recruited (*M*=74.79; *SD*=5.39), with 49 females and 29 males taking part. MCI categorisation based on the Petersen criteria (Albert et al., 2011; Petersen et al., 1997) was conducted at both Time 1 and Time 2 testing.

7.3.2 MCI Categorisation

Amnestic MCI was diagnosed based on the four memory scales (Delayed and Total Memory from both the BVMT-R and RAVLT). Secondly, non-amnestic MCI was diagnosed based on measures assessing executive functioning (Switching Fluency, Switching Accuracy, and Trails B), given that this is a common early cognitive deficit in FTD. Finally, multiple domain MCI was operationally defined by participants meeting cognitive impairment criteria on each of the memory and executive functioning neuropsychological measures, or on the ACE-III, which examines a range of cognitive aspects. For each MCI subtype, a deficit of 1.5 standard deviations below age-adjusted norms on a neuropsychological measure indicated impairment.

Table 24 shows the number of participants diagnosed in each MCI subtype, as well as those meeting criteria during at least one testing session. Amnestic MCI was the most common diagnosis observed, with non-amnestic the least common having only 7 participants meeting criteria across both testing sessions. MCI diagnosis was made independently for Time 1 and Time 2. Overall, 29 (37.2%) participants met the diagnostic criteria for MCI at Time 1 and 30 (38.5%) at Time 2.

Table 24
Number of Participants Identified Using Each MCI Subtype Criteria

	Amnestic	Non-amnestic	Multi-domain
Time 1	11	6	12
Time 2	19	5	6
Overall	21	7	15

The ages of participants in the three MCI subtypes, as well as those not showing impairment, did not differ significantly $F(3,74)=2.641$, $p=.056$, $\eta^2=.096$, (amnestic: $M=76.38$, $SD=5.45$; non-amnestic: $M= 73.29$, $SD=4.92$; Multi-domain: $M=77.0$, $SD=5.08$; Non-MCI: $M=73.31$, $SD=5.21$). Participants' ethnicities were similar to what was expected based on Canterbury DHB data from the 2013 census, with 94.5% NZ European, 1.3% Maori, and 3.8% other (Statistics New Zealand, 2013).

7.3.3 Reliability of Diagnoses

Cohen's Kappa was calculated for each MCI diagnostic group to assess the reliability of the Petersen diagnoses over a 12-month period. Amnestic ($\kappa=.026$) and non-amnestic ($\kappa=.12$) subtypes both showed a lack of consistency over time and were not statistically significant, while multiple-domain MCI demonstrated only fair consistency $\kappa=.28$, $p=.009$. Calculating Cohen's kappa for an overall MCI diagnosis also had only fair consistency, $\kappa=.29$, $p=.011$.

One possible factor affecting the reliability of MCI diagnostic categories were those appearing to revert from impaired to healthy cognition over the 12-month period between testing. Cross-tabulation of MCI diagnosis over time indicated that a large proportion of individuals reverted in two of the three MCI subtypes, with 7 of 11 (63.6%) amnestic MCI cases, 4 of 6 (66.7%) non-amnestic MCI cases, and 1 of 12 (8.3%) multiple-domain MCI appearing to revert to normal cognition. This large reversion rate indicates that the MCI subtype diagnoses based on the tools used to identify these in the present study are not

consistent over time, and that most of the initially-impaired individuals were experiencing transient declines rather than age-related cognitive decline. However, nine individuals (32.1%) moved between MCI subtypes, meaning their neuropsychological profiles were inconsistent, while still showing deficits on some measures. This indicates further unreliability of the diagnostic subtyping of MCI amongst the present sample, and in the case of two participants who moved to multiple-domain MCI this may represent further cognitive decline.

7.3.4 Cluster Analysis using LCA

Model-based clustering using LCA was used to assess and identify heterogeneity in the data, and as an alternative means to the Petersen criteria of categorising participants. This also allowed an exploration of whether individuals meeting diagnostic cut-offs would appear different from older adults in general, and be identifiable without *a priori* considerations being used to separate classes within the sample. Model-based clustering was run using the Mclust package in R using data collected at Time 1, (Fraley, Raftery, & Scrucca, 2012; Team R Core, 2014). All variables were standardised prior to analysis and included: Current cognitive, physical, and social activity frequency; BVMT-R Total and Delayed Recall; RAVLT Total and Relayed Recall; Letter, Category, and Switching Fluency and Switching Accuracy; Trails A and B; and the ACE-III Total score. Results from the Mclust algorithm showed that the optimal solution included two clusters, and subsequently K-means clustering was used to determine cluster membership for individual cases.

Figure 7 displays the average z-scores for both clusters on the neuropsychological measures and the GAQ current activities. The average scores for cluster 1 are consistently higher than cluster 2, and all are significantly different between groups, except on Trails A (p=.126). There were 48 participants in cluster 1 (61.5%) and 30 in cluster 2 (38.5%).

Participants were significantly older in cluster 2 (*M*=76.67, *SD*=4.96) than cluster 1 (*M*=73.63, *SD*=5.37), *t*(76)=-2.50, *p*=.014, *d*=0.58.

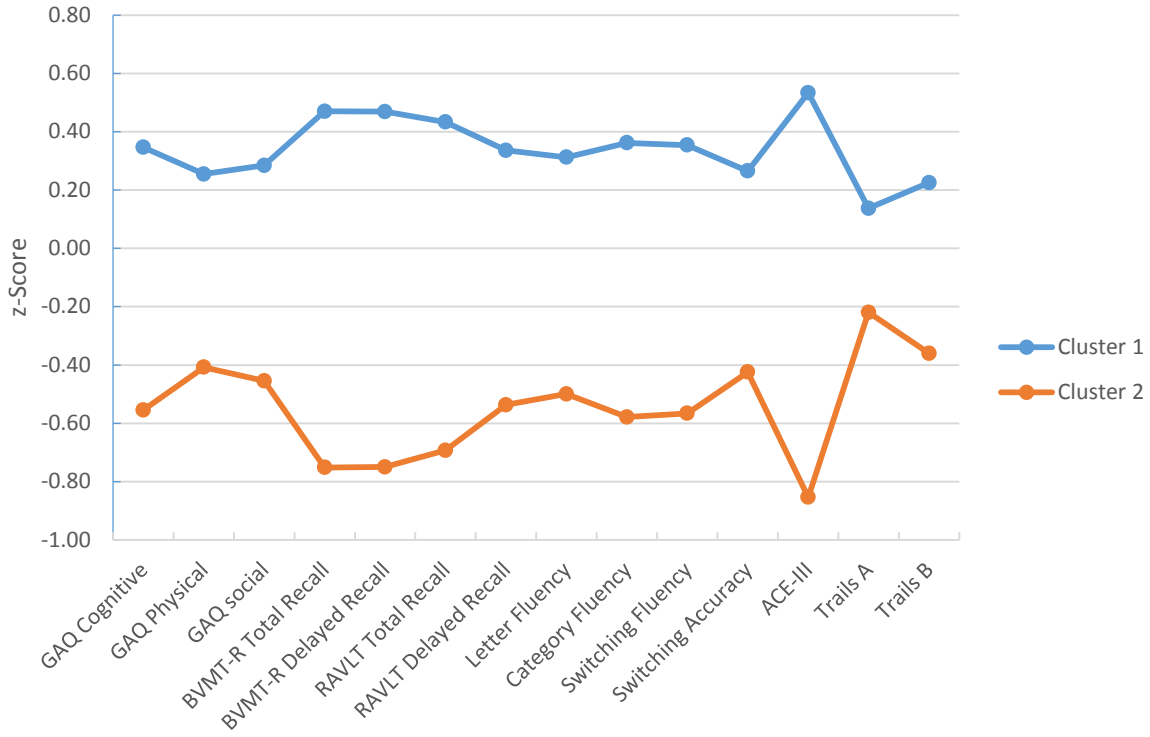

Figure 7. Mean neuropsychological test z-scores for each cluster group at Time 1.

Scores across the neuropsychological measures and GAQ activity frequency were then plotted for data collected at Time 2 based on the clustering results, and these are shown in figure 8. All tests were significantly different between cluster 1 and cluster 2 at Time 2, indicating that the cluster solution remained valid using the second testing data.

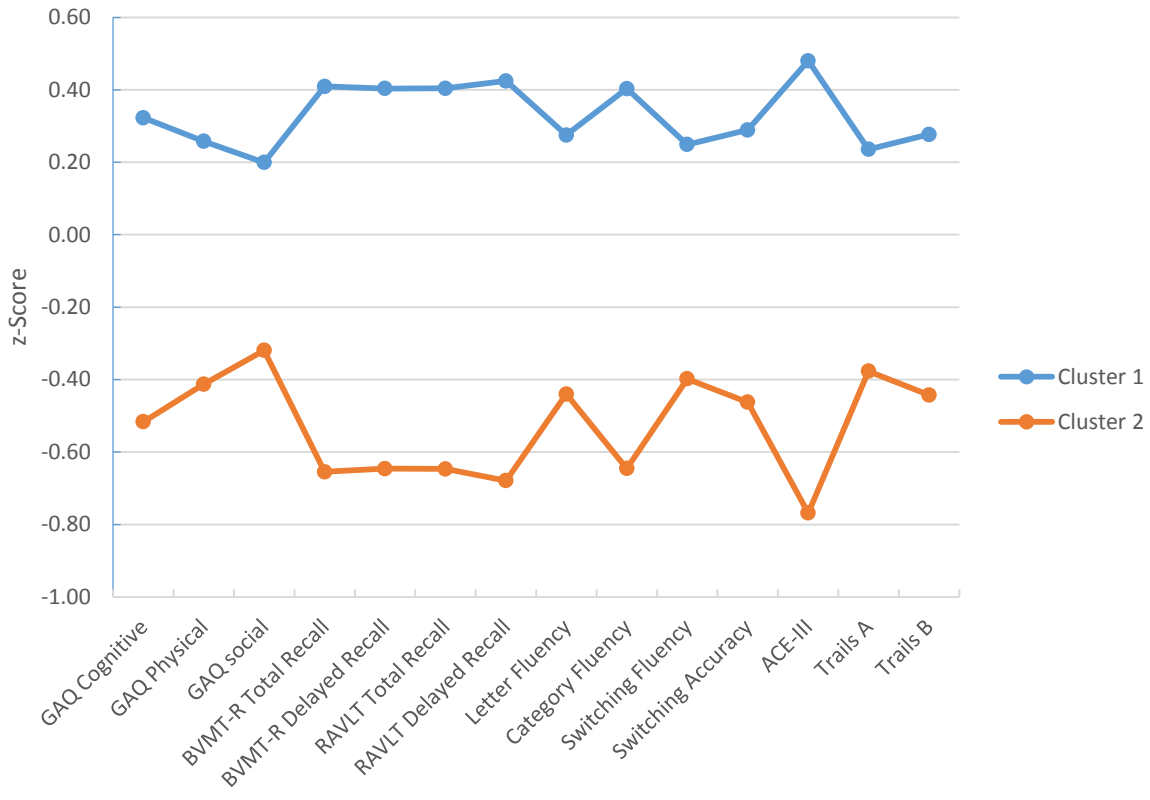

Figure 8. Mean neuropsychological test z-scores for each cluster group at Time 2.

Based on the similar distribution of scores between Time 1 and Time 2 a second cluster analysis was conducted using Time 2 data. The cluster solutions were then compared using Cohen's Kappa, which demonstrated a very high level of agreement κ=.748, p<.001. This indicates that despite some change over time in those showing cognitive decline and those reverting to normal cognition there were two clear and consistent groups observed. As with the initial cluster solutions these groups were then graphed for Time 1 and Time 2, displayed on Figure 10 and Figure 11 respectively. Both figures indicate the clear observed differences between the two cluster groups based on standardised neuropsychological and current activity z-scores.

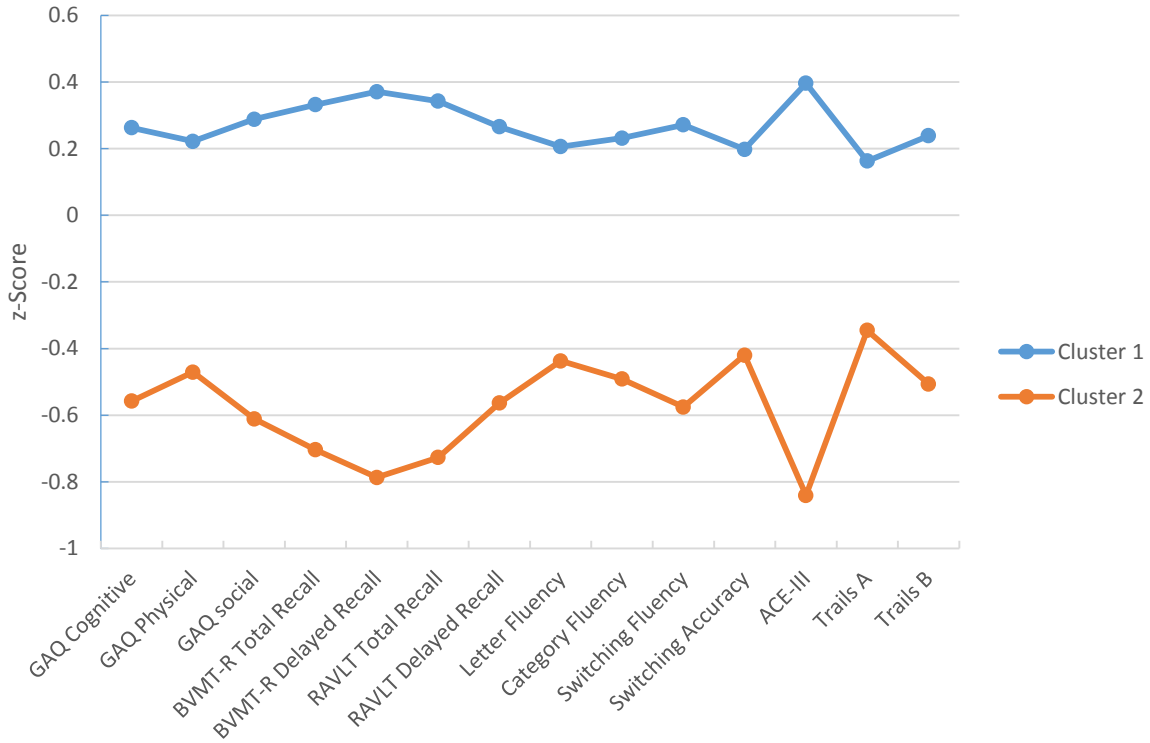

Figure 9. Mean neuropsychological test z-scores for the second cluster solution (Time 2 data) at Time 1.

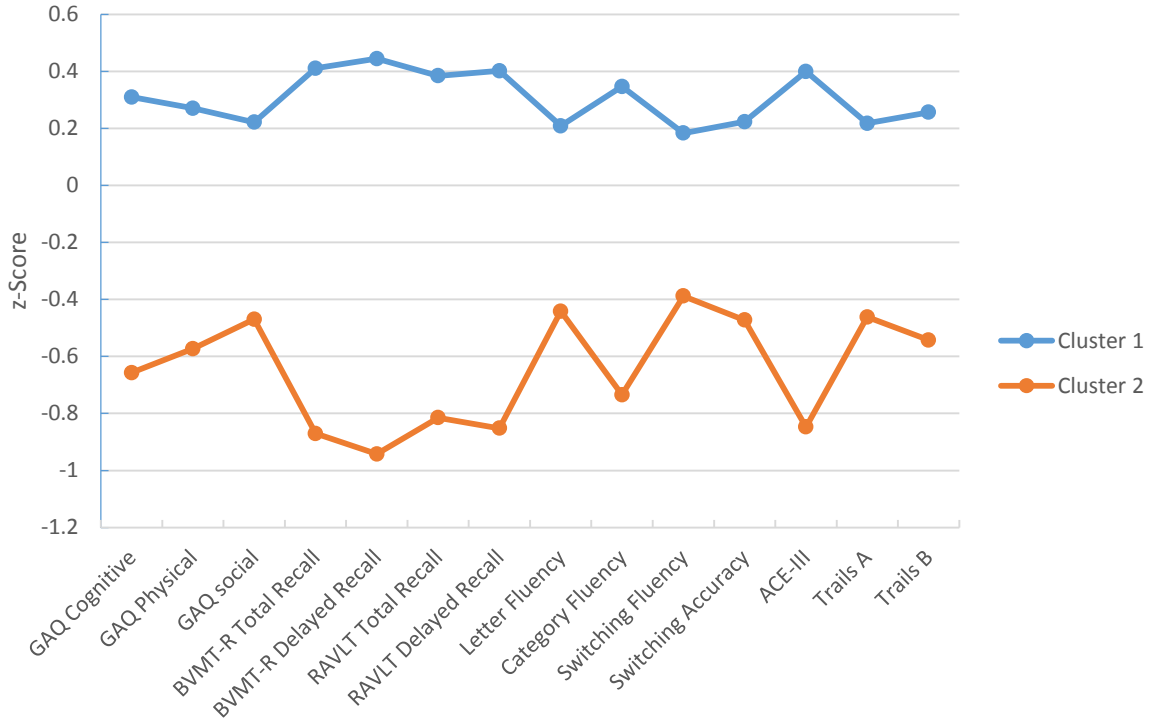

Figure 10. Mean neuropsychological test z-scores for the second cluster solution (Time 2 data) at Time 2.

Repeated measures ANOVA were then calculated to look for differing rates of change over time between participants in the two groups. None of these demonstrated a significant interaction effect between difference over time and cluster group participation. The only significant main effect was seen on Switching Accuracy, $F(1,76)=5.346$, $p=.023$, ${}_p\eta^2= .066$. This demonstrates that on average rates of change were generally similar between groups over time.

Independent *t*-tests were used to calculate the differences between the two cluster groups on historical cognitive activities, and these are presented in Table 25. Each comparison indicates that there was a significant difference in the frequency of cognitive activity between individuals in cluster 1 and cluster 2 during childhood, teenage, young adulthood, and adulthood. In each case those in cluster 1 demonstrated a higher frequency of cognitive activity than those in cluster two. These results provide an external validation of the differences between clusters, as historic activities were not included in the clustering model but were hypothesised to be related to cognitive impairment.

Table 25
t-Test Results for Frequency of Lifespan Cognitive Activity.

	t	*p*	*d*	*Mean Difference*
Child	2.26	.027	.53	.428
Teen	4.84	<.001	1.13	.555
Young Adult	3.25	.002	.75	.414
Adult	3.16	.002	.74	.355

7.3.5 Relationship Between Cluster Group and Diagnostic Group

Given the reliance on diagnostic criteria for determining individuals demonstrating characteristics of age-related cognitive decline, these were compared to the result of model-based clustering. Diagnostic criteria such as those proposed by Petersen (Petersen et al., 1997) apply categorical rules to continuous cognitive phenomena, whereas cluster analysis

separates individuals into a number of groups that maximise distances between clusters. Therefore, it is useful to explore the similarity between these two methods of differentiating individuals for consistency in identifying those with impaired cognitive performance. Table 26 shows the number of participants with each MCI subtype diagnosis that were in cluster group 1 and cluster group 2 based on the Time 1 clustering solution. The most interesting finding was that more individuals in the non-amnestic MCI group were in the higher performing cluster, whereas the expected pattern was seen for amnestic and multiple-domain MCI, with most cases in cluster group 2.

Table 26
Cross-Tabulation between Cluster Groups and MCI Diagnostic Subtypes

	Cluster Group 1	Cluster Group 2
Time 1		
- Amnestic MCI	2	9
- Non-amnestic MCI	4	2
- Multiple domain MCI	1	10
Time 2		
- Amnestic MCI	7	12
- Non-amnestic MCI	4	1
- Multiple domain MCI	0	6

Fisher's exact test was used to quantify the relationship between cluster group and MCI diagnostic categories by comparing each of these separately. Amnestic MCI demonstrated significant differences from the expected frequencies, indicating a strong relationship between cluster grouping and diagnostic criteria at Time 1 (p=.002) and Time 2 (p=.012). Multiple-domain MCI likewise showed significant results at Time 1 (p<.001) and Time 2 (p=.002). Non-amnestic MCI did not show a significant relationship at either Time 1 (p=.577) or Time 2 (p=.358). This indicates that the results of the cluster analysis were broadly similar to the groups based on Petersen diagnostic criteria, except for non-amnestic MCI.

7.3.6 Clinically Significant and Reliable Changes

A further means of assessing the reliability of changes from Time 1 to Time 2 involves calculating reliable and Clinically Significant Change (CSC). Memory measures were used, given their particular use in detecting subsequent declines and the sensitivity of the BVMT-R and RAVLT for this purpose (Small et al., 1995; Trivedi et al., 2006). Change scores were calculated for the four memory measures, Total and Delayed Recall on the RAVLT and the BVMT-R. For each participant CSC was noted if the changes in age-adjusted normative scores were greater than 1.5 standard deviations, or alternatively if participants' scores decreased enough for them to meet the cut-off for MCI. The descriptive statistics for these change scores and the frequency of CSCs can be seen in Table 27, and indicate a large amount of variation across these measures, while the means remain close to zero overall. Negative values indicate a decrease in score between Time 1 and Time 2.

Table 27
Descriptive Statistics and Clinically Significant Change Frequency for Memory Tests

	Mean	SD	Minimum	Maximum	CSC
BVMT-R					
- Total Recall	0.294	17.00	-39.00	57.00	25
- Delayed Recall	-3.57	17.00	-48.00	46.50	27
RAVLT					
- Total Recall	-0.19	12.64	-30.00	32.48	20
- Delayed Recall	0.12	15.69	-50.00	75.00	13

Reliable change was then calculated based on criteria proposed by Jacobson and Truax (Jacobson & Truax, 1991) where:

$$\frac{Change}{SD \times \left(\sqrt{2 \times \left(\sqrt{1 - test\ retest\ reliability}\right)}\right)}$$

Test-retest reliability values used were previously established through normative studies, with BVMT-R Total Recall = .92, Delayed Recall = .63 and RAVLT Total Recall = .78, Delayed Recall = .51 (Benedict, 1997; Delaney et al., 1992; Schmidt, 1996).

Initially all reliable changes were looked at, including those who appeared to decline and those appearing to improve over the 12-month period. This resulted in 11 (14.1%) individuals on the BVMT-R Total Recall, 4 (5.1%) on Delayed Recall, 3 (3.8%) of RAVLT Total Recall, and 3 (3.8%) of RAVLT Delayed Recall scores showing reliable changes. Clinically significant and reliable changes over time were then compared using Fisher's exact test, which indicated a high level of agreement between these dichotomous categorisations for each of the four comparisons (BVMT-R Total Recall $p<.001$, Delayed Recall $p=.012$; RAVLT Total Recall $p=.013$, Delayed Recall $p=.004$). Of the reliable changes observed 5 of the 11 BVMT-R Total observations represented a reliable decrease, meaning over half of these changes were participants significantly improving on this measure over 12 months. A similar pattern was observed across the other three memory measures, with 1/4 on the BVMT-R Delayed Recall, 1/3 RAVLT Total Recall, and 2/3 RAVLT Delayed Recall observations also representing declining performances over 12 months. From this it can be seen that approximately half of the reliable changes represented individuals improving on these standardised psychometric measures. There was no significant difference in age between those who reverted to normal cognition and those who declined over the intervening period $t(16)=.557$, $p=.585$ (Reverters $M=74.7$, SD=6.40; Impaired $M=76.13$, $SD=3.72$).

7.4 Discussion

The present study aimed to explore the distribution of cognitive difficulties amongst a representative community sample of older adults aged 65 years and over. Specifically, LCA was utilised in an attempt to identify the optimal statistical grouping of these older adults

based on a range of neuropsychological information. Diagnostic reliability of MCI subtypes was also assessed by comparing and contrasting diagnostic criteria with the cluster analysis solution. Finally, clinical significance in cognitive changes was explored, and the appropriateness of diagnosis and labelling reviewed in relation to the degree of impairment seen in individuals.

One of the difficulties for ongoing research into early signs of dementia is in accurately diagnosing the prodromal stages of the disease processes. A number of ways of defining this have been suggested, but the most commonly accepted is MCI, and more specifically MCI as defined by Petersen (Petersen et al., 1997). Issues have arisen with this operational definition of prodromal dementia, given the focus on discretely memory difficulties (Petersen et al., 2001), which has led to theorising that a different presentation could be indicative of FTD and VaD (Yaffe et al., 2006). However, these subtypes of MCI have only been differentiated in clinical settings (Rasquin et al., 2005), and often with difficulties separating MCI groups apart (Busse et al., 2003; Klekociuk & Summers, 2014). In the present research a randomly selected community sample were tested in order to ascertain whether these distinct MCI subgroups were observed, and whether separating individuals into these categories made sense in the context of a range of neuropsychological data. By collecting a range of cognitive information and utilising cluster analysis algorithms to cluster data without *a priori* theoretical considerations any common elements between individuals can be looked for, and if subtypes of MCI are distinct then these should be clear when clustering occurs.

Three subtypes of MCI were explored in the present research, and in total 21 participants met criteria for amnestic MCI, 7 for non-amnestic, and 15 multiple-domain. This meant that during across both testing sessions 43 participants (55.1%) met criteria for MCI; whilst high, this is not outside of inclusive prevalence estimates for cognitive decline

amongst older adults (Koivisto et al., 1995). It is also possible that the age of participants contributed to this high rate of MCI, given that the incidence of cognitive decline increases with age (M. K. Aronson et al., 1991), and the average age of participants in the present study was 74.79 years. The ages of participants in each MCI group were not significantly different, nor were these different from those that did not meet MCI criteria. The three MCI diagnostic subtypes were not consistent over time, and there was a large amount of variation within and between subtypes, with the diagnostic grouping shifting, as well as individuals appearing to revert to normal cognition over the 12 months between testing. By grouping all MCI cases together the consistency improved somewhat, and was statistically significant. This finding provides evidence for the view that subtyping MCI may not be a helpful way of conceptualising variation in cognitive declines, given that outcomes appear unrelated to the subtype diagnosed (Busse et al., 2003; Fischer et al., 2007). In particular, it may be more useful to consider cases of MCI more generally, and use a broad diagnostic consideration to identify cognitive changes rather than to attempt to make predictions about eventual prognosis and type of incident dementia.

Reverters are a ubiquitous group within research on cognitive decline and MCI (e.g., (Ganguli et al., 2011; Nordlund et al., 2010; Ritchie et al., 2001)), and the same was seen in the present results with 11 participants reverting between Time 1 and Time 2 across the MCI subgroups. A number of possibilities for reversion to healthy cognition have previously been offered, and some of these have been discussed previously in Chapters 3 and 4. The present analyses did not explore this further, but reverters continue to be a limitation on research into cognitive decline, and add to the complexity of assessing diagnostic stability.

Using cluster analysis to determine whether meaningful subgroups are present in the data allows exploration of whether participants with different MCI subtype diagnoses are significantly different across a range of neuropsychological measures (Fraley & Raftery,

1998). Moreover, clustering can demonstrate whether a brief screening battery would allow these individuals to be differentiated from cognitively intact older adults. The initial clustering solution was made based on the range of neuropsychological data collected at Time 1, including: measures of memory; executive functioning (including divided and sustained attention, task switching, and mental flexibility); visuospatial ability; and orientation. This analysis provided clear evidence that the participant sample formed two distinct clusters, with significant differences between the means of standardised scores on the neuropsychological measures and frequency of activity participation. The differences between these two groups were then maintained over time, despite individuals within each cluster group who declined or reverted over time. This provides further evidence for a more general conceptualisation of early cognitive decline, where the overall neuropsychological pattern supports the idea of those experiencing cognitive difficulties and those who are cognitively intact, rather than particular distributions reflecting MCI subtypes as meaningful and discrete entities. Cluster analysis results based on Time 2 data largely agreed with the optimal cluster solution from Time 1, with a high level of agreement between these classifications, although this cluster solution did not completely separate cognitively impaired and cognitively intact individuals.

Of particular interest was the difference between cluster groups on the frequency of lifetime cognitive activity, with significantly higher rates of activity seen at each age-point for those in the cognitively intact cluster group. This finding is in line with previous work on the importance of life-course cognitive activity for late life cognitive health (e.g., (Wilson et al., 2005; Wilson et al., 2013)), where those who have engaged throughout life are less likely to meet diagnostic criteria for MCI. This also provides external validation for the cluster analysis as a meaningful way of separating the participant sample into those who are experiencing cognitive impairment versus those who appear to be cognitively healthy; as

clear between-group differences were observed on a variable expected to converge with late-life cognitive health. It must be noted that a possible limitation to this finding is that the differences between these groups may be due to an external variable such as intelligence, which was not measured in the present study, and so could not be controlled for.

The two groups identified on the basis of the clustering solution were further compared with categorical diagnostic groups based on the Petersen MCI criteria, with the adaptation for varied change in cognition leading to the MCI subtypes (Busse et al., 2003; Petersen et al., 1997). Due to the small expected frequency of MCI cases Fisher's exact test was used, which demonstrated that amnestic and multi-domain declines lined up with the cluster solution at rates higher than chance. While applying categorical classification criteria to continuous cognitive variables is inherently problematic, this still demonstrates that the diagnostic criteria are able to identify the same individuals as a cluster solution using the full range of neuropsychological data available. The importance of this is in supporting the ongoing use of diagnostic cut-offs when identifying likely cases of MCI, despite the varied psychometrics that may be used in making such a diagnostic decision. If a range of aspects of cognition and varied tests collectively identify those most likely to be experiencing decline, then it is also possible that the particular tests used may not have a significant impact on the decision of who is likely to meet such criteria for decline. Future research into what impact varying the psychometrics used would have on subsequent cluster analysis results and diagnostic classification would be useful.

An additional consideration regarding individuals who appear to have experienced cognitive decline over time is the actual impact that any changes in cognition may have had. To this end, clinically significant and reliable changes were assessed amongst the participant sample. Given the reliance on 1.5 standard deviations below age-adjusted norms to indicate cognitive impairment this was used as the cut-off to indicate CSC; this is less than the 2

standard deviations initially suggested as a cut-off for assessing CSC (Jacobson, Follette, & Revenstorf, 1984). Practically, this meant that if individuals had a high baseline performance they could still demonstrate a clinically significant decline, even without meeting the diagnostic threshold. A significant limitation of using diagnostic cut-offs that rely on age-adjusted norms is that high functioning individuals need to decline a lot further than those in the average range in order to be 1.5 standard deviations below age-adjusted norms. The present results indicated that a large number of participants demonstrated CSC from Time 1 to Time 2, although the sample means demonstrated that overall the scores stayed fairly constant.

As well as assessing whether changes were clinically significant it is also important to establish whether changes are greater than would be expected based on simple measurement unreliability (Jacobson & Truax, 1991). Fewer individuals demonstrated reliable changes than CSC, lending some evidence to the possibility that the variation on the neuropsychological measures presents a possible limitation in confidently diagnosing cognitive decline. Older adults represent a heterogeneous group with large within-group variation expected, even before factoring in the impact of cognitive decline. However, in practice making a diagnosis of cognitive decline does not rely on a specific change, instead cut-offs are used to diagnose. Comparing the CSC and reliable changes using cross-tabulation indicated that reliable changes were seen amongst both reverters and participants experiencing cognitive decline. This is a useful validation of the changes over time detected in the present analyses, where significant improvement and decline on neuropsychological measures were reliable and greater than the expected variation of the measures used.

A number of limitations are important considerations in the present analyses. In particular, the diagnosis of MCI subgroups was only able to be completed using limited neuropsychological data, and such diagnoses would likely be more reliable if additional

evidence was available. In future, additional testing should be conducted to improve the diagnostic reliability of MCI subgroups, and therefore to see if this has an effect on the stability of such groups over time. The sample size in the present research was also relatively small for detecting meaningful differences in diagnostic categories, and it is not clear whether true between-group differences were being observed for MCI subtypes. Future work exploring such diagnostic groups would benefit from significantly larger sample sizes within each group, and this would allow for more confidence in generalising from findings.

The present study assessed the use of LCA to cluster participants into groups based on a variety of neuropsychological information, and to compare and contrast such groups with established diagnostic cut-offs. The results supported the use of cluster analysis as a meaningful way of identifying older adults experiencing cognitive decline, and demonstrated a high level of agreement between statistical clustering approaches and the Petersen diagnostic criteria. However, from the present analyses there was less utility in differentiating subtypes of MCI, as these groups were inconsistent over time, and there was a large amount of movement between these subtypes. The results support a more general conceptualisation of early cognitive decline, where specific impaired aspects of cognition may not be helpful for making prognostic predictions, but determining early cognitive decline in general may be the more useful process for determining older adults most likely to progress to dementia.

8. Overall Discussion and Conclusions

8.1 Discussion

The current research explored the utility of a multi-stage screening approach for the detection of MCI. Specifically, postal screening tools collecting self-reports, informant-reports, cognitive screening, and frequency of stimulating activities were all used to aid in this first-line detection of cognitive decline. Neuropsychological measures were used to validate this screening approach, and tools assessing attention, orientation, executive functioning, and both visual and verbal delayed memory were administered.

It was hypothesised that the variables collected through postal screening would be useful for making predictions about likely cases of MCI, and this was supported in the findings. In particular, the IQCODE (IR) and SAGE both demonstrated predictive rates at well above chance levels during the initial testing. Interestingly at the Time 1 data collection self-reports did not predict MCI cases to a statistically significant level. This was unexpected given the diagnostic requirement of self-identified cognitive decline in the original Petersen MCI criteria (Petersen et al., 1997), and the usefulness of considering self-reports in the diagnosis of MCI (B. C. M. Stephan et al., 2013). There was no difference in mean scores for MCI and non-MCI groups on the IQCODE (SR), although after assessing internal consistency of the measure it appeared that by removing several items the predictive accuracy improved substantially. It is unclear from the present analyses whether removing those particular items from self-report questionnaires like the IQCODE would improve their diagnostic utility, but this was an interesting finding. The items removed tended to assess changes to ADLs rather than in memory, which may mean focusing solely on subjective changes in memory functioning would provide a better scope for future screening. Clear differences were seen in mean IQCODE (IR) scores of participants in MCI and non-MCI groups from the initial collection of data, which was an interesting finding when the same

was not seen on self-reports. A possible explanation for this finding is that informants are more sensitive to initial changes in memory and ADL functioning than the individuals experiencing a decline in cognition. In contrast, comparing Time 1 and Time 2 responses on the IQCODE (SR) showed that individuals in the MCI-single group who had demonstrated an objective cognitive decline over the 12-month follow-up period did have significantly different scores on this measure. There was also a difference trending towards significance over time for those participants meeting criteria for MCI at both Time 1 and Time 2; this is likely to reflect that ongoing declines were being picked up by the measure, and so using the IQCODE (SR) as a tool for measuring the trajectory of decline would be interesting to explore in future research.

8.1.1 Screening Utility of Postal Measures

The informant-report IQCODE demonstrated the highest accuracy for making predictions about MCI of the measures trialled in the current research. ROC curve analyses consistently found significant results, demonstrating that the IQCODE (IR) was able to differentiate cognitively intact individuals from those with MCI. This pattern was seen using Time 1 data, and combined Time 1 and Time 2 data (without responses from participants who did not return for the second stage of the study). This finding was further supported using stepwise discriminant analysis, which showed that the IQCODE (IR) was the only variable to statistically discriminate between participant groups by itself. This is an important finding, as it lends support to the hypothesis that informant-reports can aid in the detection of early cognitive declines, and that these can be considered interchangeable with self-reports for detecting SMCs. Previous findings have indicated that IQCODE scores can be predictive of subsequent institutionalisation, as well as making predictions about individuals who will progress to dementia within two years (Jorm & Jacomb, 1989; Louis et al., 1999). The current research findings add to this, by demonstrating that IQCODE scores are related to

cases of MCI, as well as providing further evidence about IQCODE scores continuing to reflect ongoing decline as cognitive deterioration progresses. Following a sample group like the one in the current study in which some individuals progress to dementia would allow this relationship to be explored further.

The SAGE is a recently developed cognitive screening tool for assessing a range of aspects of cognition, which has demonstrated good psychometric properties and predictive validity for MCI (Scharre et al., 2010). It was hypothesised that this screening utility would extend to using the measure as a postal screening tool. The present results supported the use of the SAGE in this manner, and demonstrated that adapting it for a New Zealand population did not detract from the measure's appropriateness or applicability. One large difference in the present results compared to those published previously was the cut-off that gave the best sensitivity and specificity. The present results indicated that a total score of 20.5 represented the optimal cut-off score, considerably higher than the 16 reported during test development. It was interesting that further analyses using Time 2 data reduced the diagnostic utility of the SAGE, and in particular this was seen when repeating the ROC curve calculations after removing the participants who did not take part in Time 2. There are several possibilities for why this was found, but the most likely reason is that the individuals who did not return and take part at Time 2 were more likely to be experiencing cognitive declines that those who did return, therefore removing them from the overall analyses reduced the frequency and severity of MCI for detection. This was supported by exploring the Time 1 scores of those who returned and those who did not, where a higher proportion of participants with MCI did not take part at Time 2.

The SAGE demonstrated good test-retest reliability, and had reasonable convergent and divergent validity with the neuropsychological battery administered during the present research. Given the recency of test development this is a useful finding, and supports the

ongoing use of the SAGE for the detection of early cognitive declines. While showing good reliability, there was a significant change over time, likely reflecting the increasing cognitive impairment amongst the sample population over a 12-month period. Moreover, amongst the participants in the MCI-single group, who demonstrated cognitive decline over the intervening 12-month period, the SAGE did show a significant difference over time. It is important that a screening tool like the SAGE demonstrates high test-retest reliability, given that the measure should be stable over time, but conversely when a quantitative change has occurred the measure needs to pick this up. It was therefore interesting that those in the reverter group did not have a significant change over time on the measure; particularly given that this group demonstrated significant changes on the more comprehensive neuropsychological battery. It will continue to be of interest in future work on MCI to establish a more comprehensive profile of the individuals who revert, and to see whether those likely to revert have a different psychometric presentation across screening or neuropsychological measures.

8.1.2 Impact of Engagement in Stimulating Activities

Cognitively enriching activities have been theorised to lead to improved cognitive outcomes in later life, including lower incidence of dementia, and reduced disease presentation in the presence of neuropathology. The colloquial phrase, *use it or lose it,* has extensive epidemiological research demonstrating that older adults' neural health is promoted by maintaining cognitive, physical, and social activity. The present research expanded on the work of Robert Wilson (e.g., (Wilson et al., 2005; Wilson et al., 2002a; Wilson et al., 2013) by including a consideration of life-span and late-life activity frequency in the screening approach for detecting cognitive decline. While in the past the relationship between such activities and declines has been established, whether measuring ongoing activity engagement can add to predictive models for MCI had not been studied. Of particular interest were the

clear differences between the cluster analysis groups on historic cognitive activities. These cluster groups were based on current cognitive performance, and were divided into cognitively impaired and cognitively intact groups, yet for data collected for all four life-stages the between-group difference was significant. This finding supports previous findings into the life-course impact of cognitive activity, as well as demonstrating that this information could be used in screening for possible declines.

Current engagement in stimulating activities was hypothesised to have a protective effect through reducing incident cognitive declines. A 12-month follow-up period is a relatively short duration for this effect to be seen, but the present results revealed three significant moderation effects. For all three, higher levels of activity were associated with less cognitive decline. A number of other moderations calculated were trending in the same direction, and may have reached significance if the sample size was larger, or at a later follow-up. The significant moderation effects involved cognitive and social activities, while ongoing engagement in physical activity did not demonstrate any protective ability. The lack of statistically significant moderations from engagement in physical activity is interesting and unexpected, as ongoing physical activity has previously been strongly linked to improved cognitive health and decreased incidence of MCI (Churchill et al., 2002; Heyn et al., 2004; Lautenschlager et al., 2008). One possible reason for this lack of statistical significance was that a significant decrease in the frequency of physical activity was reported by participants in the non-MCI group. There is no clear reason why the group of cognitively intact participants had a large decrease in physical activity, but it is possible that there was inconsistent reporting of physical activity at Time 1, leading to these unexpected findings at Time 2 and among the overall data analyses. It is also possible that the current sample group have high levels of physical activity participation, above what would be expected for a representative community sample (discussed further below).

There are several important implications from the findings between life-span cognitive activity and incident cognitive decline at late-life. Firstly, the present results support the hypothesis that higher frequencies of cognitive activity across all developmental stages have significant benefits later in life, and in particular are related to lower incidence of MCI. Secondly, assessment of the current frequency of activity participation demonstrated strong links with cognitive decline over the 12-month follow-up. In particular, assessing current cognitive and social frequency of activity may be useful in determining older adults most at risk of subsequent declines. While the current research was concerned with exploring the relationship between frequency of activity and cognitive decline, future work should assess the predictive validity of including this information in predicting outcomes over time for those most at risk of decline.

8.1.3 Reliability of MCI Diagnoses

As discussed previously, MCI diagnoses have often been unreliable, with significant proportions of individuals identified as having MCI later appearing to revert to normal cognition. Furthermore, once subtypes of MCI are considered, the reliability of diagnoses decreases further, with many individuals appearing to move between subtypes. The present research aimed to explore whether considering subtypes of MCI in a community sample increased the predictive utility of screening, and whether this contributed meaningfully to a screening approach. Multiple-domain MCI was the only subtype to demonstrate significant consistency over time, with inconsistent amnestic and non-amnestic MCI subgroup diagnoses. Diagnostic consistency was further improved when the subtypes were combined, and an overall diagnostic consistency was calculated. This likely occurred because of movement between MCI subtypes for the participants experiencing decline, providing evidence that while their diagnostic grouping was inconsistent, their overall cognitive difficulties had been identified and were ongoing. This was an interesting finding, as

disagreement over diagnostic criteria, and whether subtypes of MCI should be considered separately, has been an ongoing argument (Busse et al., 2003; Busse et al., 2006). The present results support assessing for cognitive decline generally, with limited benefit seen from attempting to differentiate subtypes of MCI early in the process of decline. A more specific cognitive profile is likely to be helpful once declines begin progressing, in order to inform specific cognitive interventions. These non-pharmacological interventions either aim to compensate for a declining aspect of cognition via cognitive training (e.g., using mnemonics and semantic elaboration techniques to mitigate declines in working memory) or to support cognitive functions that remain intact via cognitive rehabilitation (e.g., rote learning social skills to overcome executive function deficits that cause decreased behavioural inhibition). Determining a specific cognitive profile is necessary for informing such interventions, and differentiating a subtype of MCI may add to this, but based on the current results this should follow a generalised determination of the presence of cognitive decline.

MCI subtypes were further considered in relation to participant clusters generated using LCA. The advantage of utilising cluster analysis with a broad range of data is that the resultant clusters represent the most similar individuals, with no theoretical underpinning. Therefore, if subtypes of MCI represented discrete and orthogonal groups then these would be expected to be seen on cluster analysis, given the disparate neuropsychological profile of each subtype. The present analyses demonstrated two clear groups based on the range of neuropsychological data and the current frequency of activity participation. The clustering solution that minimised variation within groups included one group who appeared to be cognitively impaired, and a cognitively intact group. This was an interesting and unexpected finding, given that participants did demonstrate cognitive declines in line with disparate MCI subtypes. However, given the unreliability of the MCI subtypes over time the statistical clustering solution appears to provide a more stable differentiation of cognitively impaired

and cognitively intact participants. It is possible that with a larger sample size more groups would be seen, but the present results were curious given how consistent the cluster groups were, especially when looking for differences between cluster groups on Time 2 neuropsychological scores. A number of participants in the cognitively intact cluster group at Time 1 experienced declines, and met diagnostic criteria for MCI at Time 2, similarly a number of cognitively impaired participants reverted to normal cognition at Time 2. Despite this, the between-group differences seen in the cluster solution remained at Time 2. As with previous findings, the cluster analysis results support the idea of assessing for generalised cognitive decline. The current research suggests collecting a range of neuropsychological information and looking across tests to determine who may be experiencing decline appears to be more useful than relying on measures of discrete aspects of cognition, such as memory or executive functioning.

8.2 Limitations and Future Research

One major limitation that arose in the current research was through participants inconsistently following instructions on the postal measures. As previously discussed, a number of participants noted that they had checked the date before answering this question, which accounts for 4 of the 22 points on the SAGE. Given the usefulness of assessing the date for gathering information on orientation and memory, this presents a significant limitation in the present results. The SAGE included an instruction about not checking the date while answering this question, but it is possible that with more explicit instructions participants would be more likely to follow this. Given the benefit of asking participants the date, it would be useful to explore this in any future research using the SAGE as a postal screening tool. Overall, the screening utility of the SAGE was resistant to participants not following the instructions of the questionnaire with a statistically significant AUC from the ROC curve; a beneficial characteristic of the postal questionnaire, given the lack of

supervision possible while individuals complete the measure. However, this deviation from the instructions is likely to have accounted for some of the reason the calculated cut-off score was higher than expected, with overall scores having been inflated by fewer participants incorrectly recalling the date. It would be interesting to assess a sample group such as the present one with face-to-face and postal versions of the SAGE using alternate forms, in order to explore the impact of response format. There were several unusual responses on both versions of the IQCODE that also may reflect issues with responding to the measure, and in particular several participants reported a large improvement over the last ten years. It is unlikely, but possible, that older adults experience a marked improvement in memory and ADL functioning, and so it is unclear whether these responses indicated response errors or not.

A further limitation of the postal screening was a number of missing responses, where participants only returned one version of the IQCODE. When these participants attended the testing session they were all prompted about returning the second response. Additionally, some participants required further explanation about why both self-report and informant-report responses were required, and this was given at the neuropsychological testing session. Despite this prompting, a number of participants did not return the missing IQCODE, which led to the variation in the number of participants included across the calculated statistics. Increasing the response rate among those included in the study would likely have improved the results, although the total impact of the missing questionnaires is unclear, given that significant trends were seen on these measures across many of the statistics calculated.

A similar limitation lay in the number of individuals who dropped out of the study between Time 1 and Time 2, with 31.5% of the participant group electing not to return. There are a number of reasons why these individuals did not, or could not, take part in both stages of research, but the most common reason given when contacted was that their current health

was preventing them from participating. There were also several participants who could not be reached, and did not respond to a follow-up postal invitation to take part in the second stage of the research. It is unclear why these individuals could not be contacted after attempts over a period of several months, but among them were some of the oldest participants in the sample (>90 years of age). Despite the response rate, the present research still maintained an above average response to research involving postal questionnaires, with a meta-analysis concluding that among New Zealand studies the average response rate is 51% (J. V. Cook, Dickinson, & Eccles, 2009); the response rates of the present research were 78.6% and 68.4% at Time 1 and Time 2 respectively. Response rates across research involving postal elements also tends to only improve if incentives are offered to participants, which was not the case with the present study (Edwards et al., 2002; Nakash, Hutton, Jørstad-Stein, Gates, & Lamb, 2006). It is possible that individuals identified as MCI at Time 1 who chose not to return may represent those with the most significant decline over time, which in turn may have precluded them from ongoing participation. There is also a possible limitation caused by contamination of the sample with individuals in the early stages of dementia. As discussed previously, there are significant difficulties in applying categorical criteria to continuous processes, and so it is likely that by using different tests and operational criteria some individuals included could instead have been considered as meeting criteria for dementia. This represents a common difficulty in assessing early declines, and the point at which MCI becomes dementia is contentious.

The present research used a relatively brief neuropsychological battery, taking between 50-80 minutes per participant. More comprehensive testing results in a larger range of cognitive constructs with which to make conclusions about aspects of current cognitive functioning, but is increasingly time consuming and can be aversive for participants. The implication from this is that measuring constructs like multiple-domain MCI may have been

improved through the use of more comprehensive testing. Repeating the current statistical clustering using more comprehensive neuropsychological testing in future would be useful to expand on the present findings, and to assess whether this makes any substantial difference to the observed results.

The measurement of ADLs in the present studies may also represent a limitation. Significant disagreement exists in the literature regarding the best way to assess this impairment, and the degree to which functional impairment is indicative of MCI, as opposed to dementia. For the present research, self-reports during the neuropsychological testing sessions, and responses on IQCODE questions that included instrumental ADLs, such as handling finances and learning to use new gadgets around the house, were used to assess current ADL functioning. This measurement is a possible limitation as it was not tightly controlled, and significant variation may have occurred based on participant reporting. Measurement of ADLs are also impacted by comorbidity, particularly physical health complaints. For the present study ADL difficulty due to comorbidities was not differentiated from ADL deficits due to cognitive decline; this likely overestimated the amount and frequency of impairment present in the reported results, but also represents a fair estimation of such difficulties within a community sample.

Intelligence was not assessed or estimated in the present study, and this represents a further limitation. Intelligence is strongly correlated with memory (Conway, Kane, & Engle, 2003; Oberauer, Schulze, Wilhelm, & Süß, 2005), and moderately correlated with executive functioning (Ardila, Pineda, & Rosselli, 2000; Roca et al., 2009). Not having this information is therefore a limitation, as individuals with lower intelligence are more likely to score below average on standardised neuropsychological measures. There is therefore a risk that such individuals are incorrectly classified as MCI, and inflate the false positive rate. Furthermore, individuals with high intelligence are likely to score well on memory measures, and so

deficits may not be detected early. Including a measure of intelligence in future research would overcome this limitation, and allow estimations of cognitive decline to take intelligence into account. Similarly, emotional disorders such as anxiety and depression can have an impact on test taking performance and on memory functioning, and no data were collected on this in the present research (Kumar et al., 2006; Sachdev et al., 2013; Zandi, 2004). The GAQ postal questionnaire asked about emotional disorders, but this was not responded to accurately and so represented a further limitation. This limitation could be reduced in future by including clinical measures of anxiety and depression such as the Geriatric Anxiety Scale and the Geriatric Depression Scale. This would then improve the detection of emotional disorders presenting as cognitive decline, and reduce this potential source of false positives. Such individuals also possibly make up some of the reverter group, as over time if their emotional disorders resolve the related cognitive difficulties may also improve.

A final possible limitation also exists in the sample group involved in the present research. While all participants were recruited from the community, a number who volunteered were members of Rotary and Probus clubs. These organisations offer opportunities for social and cognitive activity, and so may be unrepresentative of many older adults in the community who lack such social support. While this group did not make up the majority of the sample, this might have led to an over-estimation of the rate of current cognitive and social activity. Similarly, a significant proportion of community dwelling older adults are likely to have debilitating physical health conditions, which would then impact on their ability to participate in research such as this. Therefore, it is likely that those who were willing and able to take part in the present research represent a group of physically healthy older adults, which may have led to an overly high rate of current physical activity. Exploring the possibility of these sampling limitations in future would be interesting, as the impact of

these is unclear from the present results. The sample were predominantly NZ European, which limits the generalisability of the present results to the wider New Zealand population where there is more ethnic diversity. While the current sample was relatively representative of Canterbury, it would be worthwhile trialling the measures used with a more diverse and nationally-representative population. In particular, it would be beneficial to gather further data on the applicability of SAGE to more diverse ethnic groups, as this measure has not been used in New Zealand before. Furthermore, it would be useful to assess whether the participation in stimulating activities and the types of activities are similar between ethnic groups.

8.3 Summary

The present research demonstrated a multi-stage screening approach for the detection of early cognitive declines in older adults. Utilising postal cognitive screening and a combination of self-reports and informant-reports this screening modality demonstrated reasonable predictive validity for individuals meeting diagnostic criteria for MCI. The dual inclusion of self- and informant-reports to assess subjective declines in memory and ADLs has not been validated previously, yet both forms of reporting have demonstrated usefulness in assessing changes in cognition. The postal screening approach was followed with a neuropsychological battery for all participants. Previous research looking at multi-stage screening has neglected to validate the screening approach fully, by only testing individuals likely to support the screening tools (i.e., those identified as likely to have MCI), whereas this limitation was not present in the current research. Furthermore, the consideration of life-course and late-life activity participation has not been explored in relation to diagnosis and adding to cognitive screening information. This information led to clear between-group differences for those experiencing cognitive decline and those who were not.

The present results provide a platform for demonstrating the utility of postal screening to identify likely cases of MCI amongst community dwelling older adults, and that such an approach can be used to inform testing for individuals most likely to need it. By removing the initial face-to-face contact, multi-stage screening may also allow individuals who are less willing to present to primary health professionals to still receive cognitive screening. Given the increasing prevalence of MCI and dementia, such a screening approach could reduce the time and costs associated with early identification. Ongoing development of interventions aimed at reducing the impact of cognitive decline relies on early identification of MCI, and novel approaches to detection will need to continue to be developed to cope with the increasing demand on services. The present study demonstrates the feasibility of multi-stage screening using postal measures as a reliable and valid method of cognitive screening, and for detecting cases of MCI in a community sample.

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Appendix A

HUMAN ETHICS COMMITTEE

Secretary, Lynda Griffioen
Email: human-ethics@canterbury.ac.nz

Ref: HEC 2014/148

1 December 2014

Jonathan Hackney
Department of Psychology
UNIVERSITY OF CANTERBURY

Dear Jonathan

The Human Ethics Committee advises that your research proposal "Screening and predicting mild cognitive impairment" has been considered and approved.

Please note that this approval is subject to the incorporation of the amendments you have provided in your email of 26 November 2014.

Best wishes for your project.

Yours sincerely

Lindsey MacDonald
Chair
University of Canterbury Human Ethics Committee

Appendix B

Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)

Please give this version of the IQCODE to somebody who knows you well (e.g., spouse, relative, or friend) and ask them to fill it in about you.

Name (who the questionnaire is for): _____

Date of Birth: _____

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 2004. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same, or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered 'Hasn't changed much'. Please indicate the changes you have observed by circling the appropriate answer.

Compared with 10 years ago how is this person at:

	1	2	3	4	5
1. Remembering things about family and friends e.g. occupations, birthdays, addresses	Much improved	A bit improved	Not much change	A bit worse	Much worse
2. Remembering things that have happened recently	Much improved	A bit improved	Not much change	A bit worse	Much worse
3. Recalling conversations a few days later	Much improved	A bit improved	Not much change	A bit worse	Much worse
4. Remembering his/her address and telephone number	Much improved	A bit improved	Not much change	A bit worse	Much worse
5. Remembering what day and month it is	Much improved	A bit improved	Not much change	A bit worse	Much worse

6. Remembering where things are usually kept	Much improved	A bit improved	Not much change	A bit worse	Much worse
7. Remembering where to find things which have been put in a different place from usual	Much improved	A bit improved	Not much change	A bit worse	Much worse
8. Knowing how to work familiar machines around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
9. Learning to use a new gadget or machine around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
10. Learning new things in general	Much improved	A bit improved	Not much change	A bit worse	Much worse
11. Following a story in a book or on TV	Much improved	A bit improved	Not much change	A bit worse	Much worse
12. Making decisions on everyday matters	Much improved	A bit improved	Not much change	A bit worse	Much worse
13. Handling money for shopping	Much improved	A bit improved	Not much change	A bit worse	Much worse
14. Handling financial matters, e.g. the pension, dealing with the bank	Much improved	A bit improved	Not much change	A bit worse	Much worse
15. Handling other everyday arithmetic problems, e.g. knowing how much food to buy, knowing how long between visits from family or friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
16. Using his/her intelligence to understand what's going on and to reason things through	Much improved	A bit improved	Not much change	A bit worse	Much worse

Appendix C

Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)

Please fill in this version of the IQCODE about yourself, remembering what you have been like now compared to 10 years ago.

Name: _____

Date of Birth: _____

Now we want you to remember what you were like 10 years ago and to compare it with what you are like now. 10 years ago was in 2004. Below are situations where you had to use your memory or intelligence and we want you to indicate whether this has improved, stayed the same, or got worse in that situation over the past 10 years. Note the importance of comparing your present performance with 10 years ago. So if 10 years ago you always forgot where you had left things, and you still do, then this would be considered 'Hasn't changed much'. Please indicate the changes you have observed by circling the appropriate answer.

Compared with 10 years ago how are you at:

	1	2	3	4	5
1. Remembering things about family and friends e.g. occupations, birthdays, addresses	Much improved	A bit improved	Not much change	A bit worse	Much worse
2. Remembering things that have happened recently	Much improved	A bit improved	Not much change	A bit worse	Much worse
3. Recalling conversations a few days later	Much improved	A bit improved	Not much change	A bit worse	Much worse
4. Remembering his/her address and telephone number	Much improved	A bit improved	Not much change	A bit worse	Much worse
5. Remembering what day and month it is	Much improved	A bit improved	Not much change	A bit worse	Much worse
6. Remembering where things are usually kept	Much improved	A bit improved	Not much change	A bit worse	Much worse

7. Remembering where to find things which have been put in a different place from usual	Much improved	A bit improved	Not much change	A bit worse	Much worse
8. Knowing how to work familiar machines around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
9. Learning to use a new gadget or machine around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
10. Learning new things in general	Much improved	A bit improved	Not much change	A bit worse	Much worse
11. Following a story in a book or on TV	Much improved	A bit improved	Not much change	A bit worse	Much worse
12. Making decisions on everyday matters	Much improved	A bit improved	Not much change	A bit worse	Much worse
13. Handling money for shopping	Much improved	A bit improved	Not much change	A bit worse	Much worse
14. Handling financial matters, e.g. the pension, dealing with the bank	Much improved	A bit improved	Not much change	A bit worse	Much worse
15. Handling other everyday arithmetic problems, e.g. knowing how much food to buy, knowing how long between visits from family or friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
16. Using your intelligence to understand what's going on and to reason things through	Much improved	A bit improved	Not much change	A bit worse	Much worse

How Well Are You Thinking?

Please complete this form in ink **without** the assistance of others.

Name_____ Date of Birth _____/_____/_____

How far did you get in school? _____ I am a Man_____ Woman_____

I am NZ European_____Māori _____Pacific Islander_____ Asian_____ Other_____

Have you had any problems with memory or thinking? Yes_____ Only Occasionally_____ No_____

Have you had any blood relatives that have had problems with memory or thinking? Yes_____ No_____

Do you have balance problems? Yes_____ No_____

If yes, do you know the cause? Yes (specify reason)_____ No_____

Have you ever had a major stroke? Yes_____ No_____ A minor or mini-stroke? Yes_____ No_____

Do you currently feel sad or depressed? Yes_____ Only Occasionally_____ No_____

Have you had any change in your personality? Yes (specify changes)_____ No_____

Do you have more difficulties doing everyday activities due to thinking problems? Yes_____ No_____

1. What is today's date? (from memory – no cheating!) Month_____ Date_____ Year_____

2. Name the following pictures (don't worry about spelling):

_____ _____

Answer these questions:

3. How are a watch and a ruler similar? Write down how they are alike. They both are… what?

_____

4. How many 20 cent pieces are in $2.40? _____

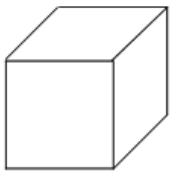
5. You are buying $13.40 of groceries. How much change would you receive back from a $20 note?

_____

6. Memory Test (memorize these instructions). Do later only after completing this entire test:

At the bottom of the very last page: Write "I am done" on the blank line provided.

7. Copy this picture:



8. Drawing test

- Draw a large face of a clock and place in the numbers
- Position the hands for 5 minutes after 11 o'clock
- On your clock, label "L" for the long hand and "S" for the short hand

9. Write down the names of 12 different animals (don't worry about spelling):

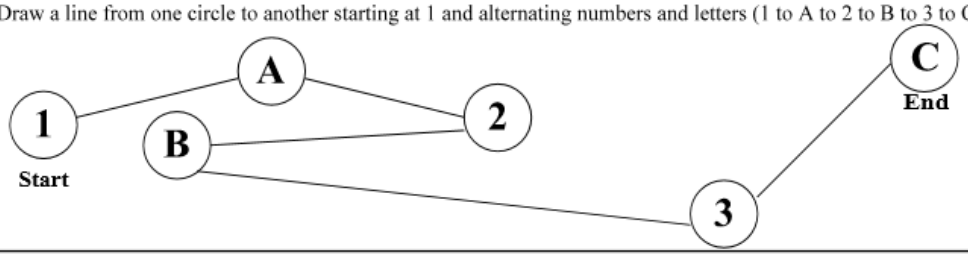
_____ _____ _____ _____

_____ _____ _____ _____

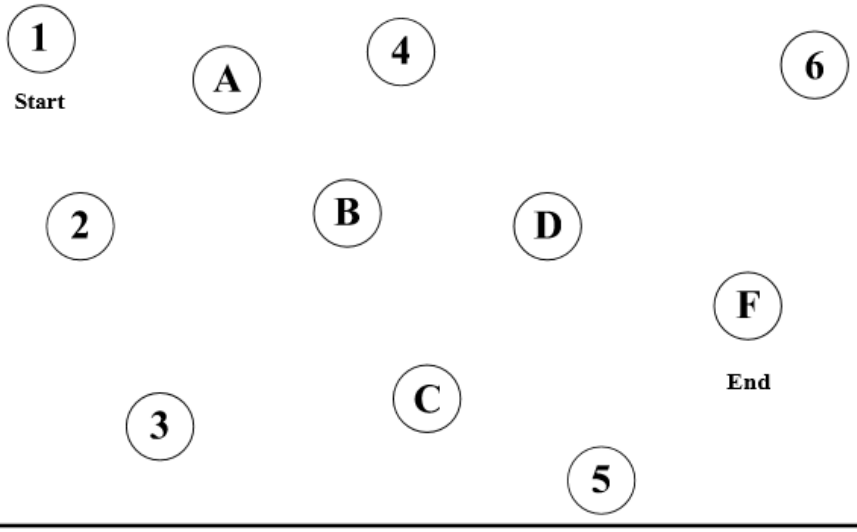
_____ _____ _____ _____

Review this example (this first one is done for you) then go to question 10 below:

Draw a line from one circle to another starting at 1 and alternating numbers and letters (1 to A to 2 to B to 3 to C).

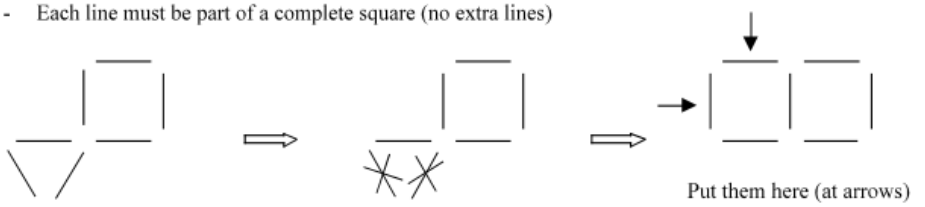


10. Do the following: Draw a line from one circle to another starting at 1 and alternating numbers and letters in order before ending at F (1 to A to 2 to B and so on).



Review this example (this first one is done for you) then answer question 11 below:

- Beginning with 1 triangle and 1 square
- Move 2 lines (marked with an X)
- To make 2 squares and no triangle
- Each line must be part of a complete square (no extra lines)



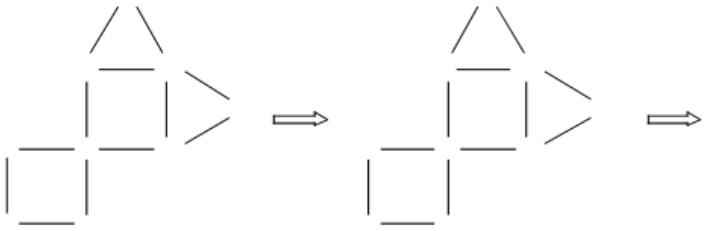
Put them here (at arrows)

1 triangle, 1 square | Move these 2 lines | Makes 2 squares (answer)

(Example) **(Example)** **(Example)**

11. Solve the following problem:

- Beginning with 2 squares and 2 triangles
- Move 4 lines (mark with an X)
- To make 4 squares and no triangles
- Each line must be part of a complete square (no extra lines)



2 squares, 2 triangles | Move 4 lines | **Draw answer here**

Mark with an X **4 squares**

12. Have you finished? _____

Appendix E

General Activities Questionnaire

On the following pages are brief questions about general activities at various points in your life. They cover: childhood (around 6 years old), Teenage (12 years old), Young adulthood (18 years old), Adulthood (round 40 years), and more recent times.

Quickly answer each question by circling the number representing how often you participated in the activity. Answer quickly but accurately, using the age in years to guide what activities you were involved in at those points in your life.

Just do your best across the questions, and give you best guess if you are unsure. Please complete this page first.

Your Name: _____ Date of Birth:_____ Gender: Male/Female

Highest level of education (e.g., high school, Technical or other qualification, Bachelor's degree, other degree?):_____

Age when you left school:_____

What was your major occupation (e.g., homemaker, teacher, mechanic, dentist, salesperson, lawyer, etc):

_____

What is the maximum number of adults you have ever been in charge of or supervised during midlife (30-65 years) – circle one option:

None
1-5
6-10
More than 10

The following are some questions about things that may have happened to you during your life. Please circle the answer that best applies to you.

1. Have you ever suffered a head injury during which you lost consciousness for 20 minutes or more?
   Yes No

2. Have you ever been diagnosed with epilepsy?
   Yes No

3. Do you suffer from multiple sclerosis?
   Yes No

4. Do you suffer from any other neurological disorder?
   Yes No
   If yes please specify _____

5. Have you ever suffered a stroke that required hospital treatment?
   Yes No

6. Have you ever been diagnosed with a psychiatric illness?
   Yes No
   If yes please specify _____

General Activities in Childhood - Age 6

The first questions are about when you were 6 years old, or thereabouts. Please give your best recollection and circle one or the options for each.

1. When you were 6, how often did you play games like tic-tac-toe, checkers, or other board games, cards, or word games?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

2. How often did someone in your home read to you when you were 6?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

3. How often did someone in your home tell you stories when you were 6?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year

GO TO NEXT PAGE

General Activities in Teens - Age 12

The next questions are about when you were 12 years old, or thereabouts. Please give your best recollection and circle one or the options for each.

1. When you were 12, about how much time did you spend reading each day?
   1 None
   2 Less than one hour
   3 One to less than two hours
   4 Two to less than three hours
   5 Three or more hours

2. When you were 12, how often did you read books?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

3. When you were 12, how often did you visit a library?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

4. When you were 12, how often did you read newspapers?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

5. When you were 12, how often did you read magazines?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

6. When you were 12, how often did you write letters?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

7 When you were 12, how often did play games like checkers or other board games, cards, puzzles, word games, crosswords, or any other similar games?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

GO TO NEXT PAGE

General Activities in Young Adulthood - Age 18

The next questions are about when you were 18 years old, or thereabouts. Please give your best recollection and circle one or the options for each.

1. When you were 18, about how much time did you spend reading each day?
   1 None
   2 Less than one hour
   3 One to less than two hours
   4 Two to less than three hours
   5 Three or more hours

2. When you were 18, how often did you read books?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

3. When you were 18, how often did you visit a library?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

4. When you were 18, how often did you read newspapers?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

5. When you were 18, how often did you read magazines?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

6. When you were 18, how often did you write letters?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

7. When you were 18, how often did play games like checkers or other board games, cards, puzzles, word games, crosswords, or any other similar games?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

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General Activities in Adulthood - Age 40 (35-45)

The next questions are about when you were 40 years old, or thereabouts. Please give your best recollection and circle one or the 4 options for each.

1. When you were 40, about how much time did you spend reading each day?
   1 None
   2 Less than one hour
   3 One to less than two hours
   4 Two to less than three hours
   5 Three or more hours

2. When you were 40, how often did you visit a library?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

3. When you were 40, how often did you read newspapers?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

4. When you were 40, how often did you read magazines?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

5. When you were 40, how often did you read books?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

6. When you were 40, how often did you write a paragraph or more by letter or email?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

7. When you were 40, how often did you play games like checkers or other board games, cards, puzzles, word games, crosswords, or any other similar games?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

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General Activities in Present Time / Recently

The following are some questions about how you spend your time presently, or how you have spent your time recently. Circle one or the options for each.

1. About how much time do you spend reading each day?
   1 None
   2 Less than one hour
   3 One to less than two hours
   4 Two to less than three hours
   5 Three or more hours

2. In the last ten years, did you ever keep a diary or journal?
   1 Yes
   2 No

   If Yes, roughly for how many years? ____

3. In the last year, how many times did you visit a museum or an exhibition?
   1 Never
   2 1-2 times
   3 3-9 times
   4 10-19 times
   5 More than 20 times

4. In the last year, how many times did you attend a concert, play, or musical?
   1 Never
   2 1-2 times
   3 3-9 times
   4 10-19 times
   5 More than 20 times

5. In the last year, how often did you visit a library?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

6. During the last year, how often did you read newspapers?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

7. During the past year, how often did you read magazines?
   1 Every day or almost every day
   2 Several times a week
   3 Several times a month
   4 Several times a year / rarely

GO TO NEXT PAGE

8. During the last year, how often did you read books?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 Several times a year / rarely

9. During the last year, how often did you write letters?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 Several times a year / rarely

10. During the last year, how often did you play games like checkers or other board games, cards, puzzles, word games, crosswords, or any other similar games?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 Several times a year / rarely

11. During the last year, how often did you do handicrafts like needlework, weaving, or knitting?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

12. During the last year, how often did participate in political or cultural group activities?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

13. During the last year, how often did you participate in courses or learning of some type, including community education or discussion groups?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

14. During the last year, how often did participate in sporting activities or play golf?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

15. During the last year, how often did you meet up with friends or participate in group activities?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

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16. During the last year, how often did you exercise by walking?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

17. During the last year, how often did you listen to the radio?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

18. During the last year, how often did you do gardening, or arrange flowers?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

19. During the last year, how often have you taken part in artistic activities such as painting, drawing, or photography?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

20. During the last year, how often have you spent time helping out family, or working for charity?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

21. During the last year, how often did you participate in any outdoors activities?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

22. During the last year, how often did spend time collecting stamps or other items?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

23. During the last year, how often did tend to cook?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

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24. During the last year, how often did you do chores or housework?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

25. During the last year, how often did you attend church or religious services?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

26. During the last year, how often did you play music or sing?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

27. During the last year, how often did you follow the stock market?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

28. During the last year, how often did you play bingo, or anything similar?
1 Every day or almost every day
2 Several times a week
3 Several times a month
4 several times a year / rarely

END of questions