Depressive Symptoms, Positive and Negative Affect and Progression to Cognitive Disorders: The PATH Through Life Project

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A thesis submitted for the degree of Doctor of Psychology - Clinical (DPsych)
of The Australian National University

Revised and submitted 8th March 2016

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Statement of Originality

This thesis is submitted to The Australian National University in fulfilment of the Doctor of Psychology - Clinical (DPsych) degree. The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution. The thesis is less than 40,000 words in length, exclusive of tables, figures and bibliographies.

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Caroline Frances Brodrick  Date
Acknowledgements

I would like to express my very great appreciation to my research supervisor Professor Kaarin Anstey for her constant support, guidance and constructive feedback throughout my post graduate degree. Her knowledge and expertise were invaluable and I have learnt so much from her over the past three years. I would like to thank my wonderful research panel including Dr. Richard Burns, Dr. Richard O’Kearney and Dr. Moyra Mortby for their guidance and feedback. I would like to thank all of the persons involved in the collection of the data for the PATH study and for permission to include these data in my research. I would also like to thank Dr. Alex Bahar-Fuchs for providing me with the opportunity to complete my research practicum.

I would like to thank Freddy for proof reading my thesis and Saranne, Annie, Anna and JD for their love, support and laughter throughout my post graduate degree and beyond. I would also like to thank Scott for his constant love and support throughout this process. I look forward to starting the next chapter of my life with you as your wife. Italy here we come!

Finally, I would like to acknowledge my parents for their generosity, patience, encouragement, and love throughout my undergraduate and postgraduate degrees. I would not be where I am today without you and I am so very grateful and lucky to have you both. Thank you.
Abstract

Dementia is an increasing health concern for Australia with rates of diagnoses of dementia predicted to rise within our ageing population (Prince, Albanese, Guerchet, & Prina, 2014). The potential effects are widespread not only at the individual level but at a socioeconomic level with associated medical costs (Cerejeira, Lagarto, & Muketova-Ladinska, 2012; Wimo, Jonsson, Bond, Prince, & Winblad, 2013). Overall, this highlights the importance for medical professionals and researchers alike to focus on methods of risk reduction. One method of risk reduction will be to investigate predictors of preclinical dementia syndromes, with the aim of implementing earlier intervention to prevent or delay progression to cognitive disorders.

Past research indicates that depression is predictive for the onset of dementia and cognitive impairment/decline (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Gao et al 2013). However a minimal amount of research has investigated whether specific depressive symptoms and positive or negative affect are predictive of preclinical dementia syndromes. Overall, this gap in the literature suggests that further research is needed within this area.

The current research was conducted in conjunction with the Personality and Total Health (PATH) Through Life Study which is a population based prospective longitudinal study. Study 1 and Study 2 consisted of a total of 2551 participants in the 60+ cohort study. The Brief Patient Health Questionnaire (BPHQ), Goldberg Anxiety Depression Scale (GADS) and Positive and Negative Affect Scale (PANAS) were administered to measure baseline symptoms of depression and positive and negative affect. A two-staged sampling design was implemented to diagnose Mild Cognitive Impairment (MCI) and Any- Mild Cognitive Disorders (Any-MCD).

Study 1 (Chapter 3) examined whether baseline depressive symptoms predicted progression to MCI or Any-MCD from wave 1 to 2 and wave 2 to 3. The results suggest that depressive
symptoms of lacking energy/tired, loss of interest/pleasure, loss of confidence, difficulties concentrating, feeling down, depressed or hopeless and feeling bad about oneself were significant predictors of MCI from wave 1 to 2. Depressive symptoms of lacking energy/tired, loss of interest/pleasure, loss of confidence, difficulties concentrating, feeling down, depressed or hopeless and feeling bad about oneself, psychomotor slowing, felt worse in the morning and poor appetite or overeating were significant predictors of progression to Any-MCD from wave 1 to 2. Specific symptoms including lacking energy/feeling tired, lost interest/pleasure in doing things and difficulties concentrating were stronger predictors of progression to cognitive disorders from wave 1 to 2. These symptoms remained significant when adjusting for demographics of gender and education and covariates (employment, physical activity, anxiety and depression medication, partner status smoking, high blood pressure, diabetes, stroke and heart disease); and were cross validated between two depressive measures. The results suggest that specific symptoms are more predictive of progression to cognitive disorders at distinct time points. The findings for depressive symptoms as predictors of progression to cognitive impairment from wave 2 to 3 were intriguing, indicating that endorsing “yes” to GADS items “lacking energy” and “felt slowed up” significantly decreased the odds of progressing to Any-MCD. While GADS items “lost interest,” “lost confidence,” “felt hopeless” and “lost weight” were excluded from the current analyses due to participants in the healthy/cognitive groups not endorsing “yes” to these symptoms at baseline. The BPHQ items were excluded from analyses from wave 2 to 3 due to participants not endorsing “yes” to these symptoms at baseline. Covariates including gender and partner status were significant predictors of progression to cognitive impairment.

Study 2 (Chapter 4) examined whether baseline measures of positive and negative affect predicted progression to MCI or Any-MCD from wave 1 to 2 and wave 2 to 3. Positive and negative affect were not significant predictors of MCI or Any-MCD from wave 1 to 2 or
wave 2 to 3. Demographics including gender and education were significant predictors of progression to cognitive impairment.

Overall, the results suggest that specific depressive symptoms are predictive of progression to cognitive disorders. Our findings suggest that additional research is needed within the field to increase our understanding of the role of depressive symptomatology and affect in predicting cognitive impairment. The current findings are preliminary however with further research this area could have important clinical implications particularly that depressive symptoms may need to be monitored in individuals aged 60 years and above with the intent of earlier detection, and prevention/delay of the onset of cognitive disorders.
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Chapter 1. General Introduction
Cognitive Disorders in Australia

Dementia is an increasing health problem within Australia, evidenced through our ageing population and associated medical costs (Australian Institute of Health and Welfare, 2012). Past research highlights the future progression of dementia rates within Australia, with an estimate that dementia will be the largest burden of disease for women and the fifth largest for men in Australia by 2016 (Access Economics, 2003). While the rates of dementia are predicted to increase, the focus of individuals and medical professionals alike will undoubtedly be primarily on treatment, though also on risk reduction. It is particularly important to focus on methods to reduce/prevent the onset of cognitive disorders (e.g. dementia) given that the number of people with dementia will exceed 730,000 by the year 2050 if no risk reduction occurs at the population level (Jorm, Dear, & Burgess, 2005). One method of implementing risk reduction will be to investigate predictors of pre-clinical dementia syndromes, with the intention of delivering early intervention to prevent or delay the onset of cognitive disorders. The next section will discuss preclinical dementia syndromes that are important to consider within the context of predicting dementia and risk reduction.

Any-Mild Cognitive Disorder (MCD) and Mild Cognitive Impairment (MCI)

Any-MCD is a broad category of criteria used to diagnose adults with cognitive impairment as being pre-clinical to dementia (Anstey et al., 2008). Any-MCD consists of 6 criteria including Age Associated Memory Impairment (AAMI), Age Associated Cognitive Decline (AACD), Other Cognitive Disorder (OCD), Clinical Dementia Rating (CDR), and Mild Cognitive Impairment (MCI). AAMI represents healthy individuals who report memory impairments across activities of daily living (ADLs) which are validated by performance on psychometric measures (Crook & Sudilovsky, 1987). AACD, indicates specific disturbances in senescent memory which are associated with ageing. The first impairment is a slow progression and represents an inability to recall relatively unimportant details of past
experiences while the second impairment progresses rapidly and represents a loss of recent memories, disorientation and confabulation (Kral, 1962). Other Cognitive Disorder (OCD), is a cognitive dysfunction associated with the direct physiological effect of a medical condition and does not meet criteria for other cognitive disorders (APA, 2000); Mild Neurocognitive Disorder (MND) represents impaired neurocognitive functioning associated with a general medical condition (APA, 2000); and the Clinical Dementia Rating (CDR), is a rating scale used to measure normal cognitive functioning to dementia and associated stages (e.g. mild, moderate and severe) (Peterson et al., 2004). The category also includes Mild Cognitive Impairment (MCI), which is commonly referred to as the transitional stage from which individuals progress to Alzheimer’s Disease (AD), to alternate dementias, or remain stable/recover (Winbald et al., 2004).

MCI is a complex disorder characterised by distinct cognitive presentations and subtypes (Steffens et al., 2006; Winbald et al., 2004). MCI is divided into two subtypes, amnestic and non-amnestic, which are categorised into single or multiple domains based on the present number of cognitive impairments (Peterson, 2004). Amnestic MCI (Single Domain) represents a single memory deficit, while amnestic MCI (Multiple Domain) refers to a memory deficit and other impaired cognitive domains (Petersen, 2004; Steffens et al., 2006). Overall, the amnestic MCI subtype is more likely to progress to AD (Peterson, 2004, Steffens et al., 2006). In contrast, non-amnestic MCI represents an impaired non-memory cognitive deficit (Single Domain) and can also include additional non-memory cognitive deficits (Multiple Domain) (Peterson, 2004). Apart from memory impairments, other cognitive impairments evident in the subtypes of MCI can include language, attention/executive functions and visuospatial abilities (Peterson, 2004).

MCI is also formally recognized as Mild Neurocognitive Disorder (MND) within the new Diagnostic and Statistic Manual of Mental Disorders, 5th edition (DSM-V; American
Psychological Association, 2013) which is implemented in the assessment/diagnosis of cognitive and mental health disorders by clinicians. The addition of MCI within the DSM-V suggests the importance of acknowledging MCI within the context of assessment/diagnosis of cognitive disorders and in conjunction with considering comorbid mental health disorders. Although MCI has received greater attention over the past decade, further research is needed to identify potential predictors for MCI and associated disorders, specifically within the category of Any-MCD. Knowledge of predictors for MCI and other similar disorders may help to prevent or delay the onset of transitional stages, which may progress to dementia. The present study aims to investigate this topic further by including the category of Any MCD in conjunction with MCI alone; on the basis that Any-MCD is considered more stable across time in comparison to the inclusion of MCI status alone (Anstey et al., 2008). Past research indicates poor to fair stability for individuals diagnosed with MCI with 29% re-diagnosed after 4 years (Anstey et al., 2008). In comparison individuals with a diagnosis of Any-MCD had a 89% chance of receiving a cognitive disorder diagnosis at a 4 year follow up (Anstey et al., 2008). Overall the previous research supports the inclusion of the 2 categories Any-MCD (which includes MCI as a subset) and MCI alone.

**Depression as a Predictor of Cognitive Impairment/Decline**

Depression is a complex illness consisting of a range of distinct symptoms (APA, 2013). The DSM-V (APA, 2013) outlines individuals must fulfill five out of nine symptoms to meet a diagnosis for Major Depression Disorder (MDD), which includes at least a depressed mood/loss of interest or pleasure, evident most of the day, nearly every day, and a further four or more symptoms. The additional symptoms may include: significant weight loss when not dieting or weight gain, or an increase/decrease in appetite nearly every day; insomnia/hypersomnia nearly every day; psychomotor agitation or retardation nearly every day; fatigue or loss of energy nearly every day; experiencing worthlessness or excessive guilt
that is inappropriate, nearly every day; a diminished ability to think or concentrate, or indecisiveness, nearly every day; and recurrent thoughts of death, or suicidal ideation without a plan (APA, 2013). A diagnosis of MDD can also be given in accordance with a specifier, for example, “with melancholic features” (APA, 2013). One of the criteria for a DSM-V diagnosis of MDD with melancholic features includes depression regularly being worse in the morning (APA, 2013).

Neurological research investigating biomarkers of AD may offer an explanation for mood changes evident prior to the onset of AD. Jack and colleagues (2010) propose a model of Dynamic Biomarkers of the Alzheimer’s Pathological Cascade. The model outlines a specific cascade of five biomarkers representative of physiological, biochemical and anatomical changes evident prior to AD (Jack et al., 2010). The biomarkers include two categories of Brain Aβ-plaque deposition, for example decreased CSF Aβ and PET amyloid imaging and neurodegeneration including increased CSF tau, decreased flurodeoxyglucose uptake on PET (FDG-PET), and structural MRI measures of cerebral atrophy (Jack et al., 2010). The model proposes that abnormalities in biomarkers are present prior to clinical or cognitive symptoms; for example, Aβ plaque accumulation may be present two decades prior to onset of clinical symptoms (Jack et al., 2010). It is also proposes that biomarkers present in a temporal sequence with Aβ deposition evident earlier than neurodegeneration and neuronal injury, dysfunction (Jack et al., 2010). Jack and colleagues (2010) illustrate the temporal order/changes of biomarkers in relation to the development of the cognitive disease in conjunction with changes in brain structure, memory and clinical function (see Figure 1.1).
Overall, Jack and colleagues (2010) propose a model that suggests a slow progression to clinical AD, which is preceded by a significant degree of neurological changes that occur in a sequential order. It is hypothesised that the range of neurological changes evident prior to clinical manifestation would have a widespread effect on other emotional and behavioural domains, specifically, mood related changes including depression. This could offer an explanation for depression often being evident prior to the onset of AD or other cognitive disorders (i.e. MCI); however, further research is needed and a full review of the literature in this area is beyond the scope of this thesis.

Figure 1.1. Dynamic Biomarkers of the Alzheimer’s Pathological Cascade. Aβ is identified by CSF or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is identified by use of structural MRI.

Aβ = β-amyloid; MCI = Mild Cognitive Impairment
**Past research investigating depression and cognitive disorders/impairment**

Research on depression and cognitive impairment has largely been limited to investigating the development or presentation of depression in individuals. These studies focus on the time course of depression (i.e. late life depression), episodes of depression, number of depressive symptoms and the severity of depression indicated by scores on depressive measures and is discussed in detail in the sections below (Barnes et al., 2012; Gatz et al., 2005; Diniz et al., 2013; Dotson et al., 2012; Ravaglia et al., 2008; Rosenberg et al., 2010; Yaffe et al., 1999). There is minimal research including depressive measures to analyse the role of specific depressive symptoms in relation to cognitive disorders/impairment. Furthermore, past research has focused on investigating depression as a predictor/risk factor for cognitive impairment/decline by including a formal diagnosis of Dementia, AD, Vascular Dementia, Mild Cognitive Impairment or a comparison of cognitive testing (Barnes et al., 2012; Gatz et al., 2005; Diniz et al., 2013, Dotson et al., 2012, Ravaglia et al., 2008, Rosenberg et al., 2010, Yaffe et al., 1999). However, these studies have not included a clinical assessment of other cognitive disorders for which depression symptoms may have a predictive role.

**Time course of depression and cognitive impairment**

A review of the literature supports a relationship between depression and cognitive disorders (Barnes et al., 2012; Diniz et al., 2013; Gao et al., 2013). Previous meta-analyses indicate that depression is a risk factor for dementia and MCI (Diniz et al., 2013; Gao et al., 2013). One study indicated that depression in late life is an independent risk factor for dementia, specifically AD and Vascular Dementia (VaD) (Diniz et al., 2013), while a retrospective cohort study found that depressive symptoms evident in midlife or late life are associated with an increased risk of developing dementia (Barnes et al., 2012). Findings from this study also suggest that chronic depression evident throughout the life course may
increase the risk of developing VaD, in contrast to depression commencing in late life which may be a prodromal feature of AD (Barnes et al., 2012). The suggestion of depression as prodromal to AD reflects the contra argument to the present review of depression being a risk factor for dementia, which has been substantiated in a past meta-analysis (Ownby, Crocco, Acevedo, & Loewenstein, 2006). An analysis of the literature on depression as prodromal is beyond the scope of this review; however it should be considered when reviewing this area of research.

**Episodes of depression and cognitive impairment**

Other longitudinal research supports single and double depressive episodes as predictive of dementia (Dotson, Beydoun, & Zonderman, 2010). In a previous study, participants with a baseline age of 55 were followed for a median of 24.7 years, with subsequent results indicating that a history of one depressive episode was associated with a 87-92% increase in dementia risk and two or more depressive episodes were associated with approximately double the risk (Dotson et al., 2010). Findings from this study suggest that repeated episodes of depression are associated with repeated neural damage to the brain, which contribute to the development of dementia (Dotson, et al., 2010).

**Number of depressive symptoms and cognitive impairment**

Past research suggests that an increased number of baseline depressive symptoms (> 2) is associated with an impaired performance across cognitive tests and cognitive decline. A prospective study including women (age > 65 years) measured participants over four years across measures of cognitive function (Yaffe et al., 1999). The results indicated that participants with 3-5 and > 6 baseline depressive symptoms scored lower across baseline and follow up cognitive tests in comparison to participants with a total of 0-2 baseline depressive symptoms. Similarly, participants with 3-5 baseline depressive symptoms and > 6 depressive symptoms were associated with a 2 fold and 3 fold increase in a diagnosis of dementia,
respectively, in comparison to participants with 0-2 baseline depressive symptoms (Yaffe et al., 1999).

**Scores on depressive measures and cognitive impairment**

Another longitudinal study that followed female participants (age > 70 years) for up to nine years also found depression to be a risk factor for cognitive decline (Rosenberg et al., 2010). The results from this study indicate that a one point increase on the Geriatric Depression Scale (GDS) resulted in a 6-7% increase in the annual risk of cognitive impairment across cognitive domains, and that depression evident at baseline (GDS > 9) doubled this risk for three of the four cognitive domains, specifically on tests of episodic, immediate and delayed memory, psychomotor speed and executive functions (Rosenberg, Mielke, Xue, & Carlson, 2010). Another study found that participants without a prior history of depression, but with higher scores of depression measured from the Centre for Epidemiological Studies Depression Scale (CES-D), were a marginal predictor for the development of AD and dementia across five years (Gatz, Tyas, St. John, & Montgomery, 2005).

**Depression and MCI**

Other cognitive research indicates a relationship between depression and MCI. A previous longitudinal-cohort study was conducted on participants (age > 65 years) over a four year follow up period (Ravaglia et al., 2008). The study concluded that participants with baseline depressive symptoms were more likely to be diagnosed with MCI at four years, particularly the non-amnestic MCI subtype (Ravaglia et al., 2008). Similarly, another prospective longitudinal study of participants (age > 65 years), followed up at six years, found that adults with moderate or higher levels of depressive symptoms at baseline were twice as likely to develop MCI at follow up (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006).
Hypotheses for Depression as a Predictor of Cognitive Impairment/Decline

Several hypotheses have been proposed for depression as a risk factor of cognitive decline or impairment (Jorm, 2001). One hypothesis is that depression affects the threshold for manifesting dementia, suggesting that depression is associated with significant cognitive deficits which may cumulate with those caused by dementing diseases to push forward a clinical diagnosis (Jorm, 2001). Related to this hypothesis is the “reserve threshold theory”, in which depression is associated with various neurological processes (i.e. amyloid deposition and neurofibrillary formation) which collectively result in cognitive dysfunction, thus lowering the brain reserve and resulting in the earlier onset of cognitive impairment (Butters et al., 2008). Findings associated with this hypothesis include a past study in which more recent episodes of depression increased the risk of dementia, suggesting a decrease in the threshold for exhibiting cognitive decline and developing dementia (Fuherer, Dufouil, & Dartigues, 2003).

A second hypothesis is that depression leads to hippocampal damage through a glucorticoid cascade, suggesting that glucocorticoid hypersecretion occurring in depression leads to neuronal death in the hippocampus, disturbing memory and contributing to dementia (Jorm, 2001). Past findings associated with this hypothesis indicate that recurrent depression is associated with an increased risk of dementia, suggesting that recurrent episodes of depression cause repeated glucocorticoid hypersecretion that leads to dementia (Dotson et al., 2010). Further research indicates that recurrent depressive episodes are associated with hippocampal atrophy (Videbech & Ravnkilde, 2004), which may also contribute to recurrent depression being predictive of cognitive impairment/decline. Other neuroimaging findings show that reduced hippocampal volumes are associated with later-life depression (Videbech & Ravnkilde, 2004), which may explain why older adults with depression are more susceptible to progressing to cognitive decline/impairment than non-depressed adults.
Another hypothesis proposed is that depression is prodromal to dementia, suggesting that individuals initially diagnosed with depression will progress to dementia (Jorm, 2001). This hypothesis is consistent with past research indicating that depressive symptoms and late life depression are prodromal to dementia (Chen, Ganguli, Benoit, Mulsant, & DeKosky, 1999; Geerlings et al., 2000; Li et al., 2011).

A final hypothesis includes depression being prodromal of cognitive impairment/decline due to inflammation of the brain (Leonard, 2007). It is suggested that individuals with depression or dementia experience inflammatory changes within the brain along with a reduction in the synthesis of neurotrophic factors (which are a result of increased brain glucocorticoids). It is proposed that the inflammatory changes that occur first as a result of chronic depression predispose the individual to the development of dementia due to the neurological changes that occur.

It is also important to acknowledge that other research on cognitive impairment and depression suggests that depressive symptoms may overlap with cognitive impairment for example concentration difficulties (Barnes et al., 2006). This research suggests that certain depressive symptoms may not only be specific to depression therefore it is important to ensure a sample free of cognitive impairment at baseline to attribute these symptoms to depression alone. A review of the literature on depressive symptoms which overlap between cognitive impairment and depression is beyond the scope of the current thesis however should be considered.

**Limitations of Previous Research on Depression as a Predictor of Cognitive Impairment/Decline**

A large amount of the research reviewed has focused on depression as a syndrome without specifically investigating depressive symptomology in relation to cognitive impairment. However, one study found that specific baseline depressive symptoms were
predictive of AD in a higher educated population (Geerlings et al., 2000). This study included participants 65-84 years old who were free of cognitive impairment at baseline and were followed up at 3.2 years (on average). The Geriatric Mental State Schedule (GMSS) was implemented at baseline to measure depressive symptoms, with findings indicating that a depressed mood and subjective bradyphrenia (e.g. feeling slowed down in thinking) were predictive of AD when adjusting for age, sex and subjective memory complaints (Geerlings et al., 2000). Other symptoms significantly predicted AD, including loss of appetite/weight, psychomotor agitation and suicidal ideation. However, these symptoms were not significant when adjusted for covariates.

A review of the literature also indicates minimal research investigating positive and negative affect as predictors of cognitive impairment despite the two constructs being central to depressive disorders (APA, 2013; Nutt et al., 2007). Positive and negative affect represent a wide range of positive and negative feelings, respectively. To our knowledge no studies have investigated negative affect as a predictor of progression to cognitive impairment despite past research indicating negative affect is associated with cognitive decline and performance across cognitive tasks (Christodoulou et al., 2009; Maclean, Arnell, & Busseri, 2010). There is also minimal research investigating positive affect with two previous studies indicating lack of positive affect was a marginal risk factor for dementia, while another study found symptoms representative of positive affect were elevated 3 years prior to a diagnosis of AD (Berger et al., 1999; Gatz et al., 2005). Although there is limited research, the role of positive and negative affect within depression and the potential relationship of affect and cognitive impairment/performance across cognition suggests further research is necessary (see Study 2; Chapter 4).

Other limitations are evident within the literature reviewed and include the predominantly older population (age > 65) and a minimal follow up period (< 9 years).
(Barnes et al., 2006; Gatz et al., 2005; Geerlings et al., 2000, Ravaglia, et al., 2008; Rosenberg et al., 2010; Yaffe et al., 1999). The inclusion of an older age group is particularly limiting given the younger age at which cognitive decline occurs and the importance of tracking cognitive changes across the life span from mid until late adulthood. It is also important to consider the limits associated with following a population across a minimal number of years, due to the natural fluctuations that can occur across the life span. These fluctuations are particularly true of cognition, for example of MCI that can change from stable to unstable (Winblad et al., 2004), and the severity of depression that can change through the influence of external factors, such as negative life events (Spinhoven et al., 2011). Other limitations include research with samples consisting only of women and no formal diagnosis of cognitive impairment/decline (Yaffe et al., 1999; Rosenberg et al., 2010), while past research conducted on a specific highly educated population is limited in the generalizability of the overall findings to a normal population (Geerlings et al., 2000). Furthermore, past research has been limited to investigating progression to cognitive disorders at one time point (Gatz et al., 2005; Geerling set al., 2000; Yaffe et al., 1999). Failure to assess cognitive changes across more than one time point is particularly important given the trajectories of depression and cognitive decline, as mentioned previously.

Further limitations in past research include the types of depressive measures included in it (Barnes et al., 2012). One study assessed for depression through the question “Do you often feel unhappy or depressed,” after which participants who answered in the affirmative underwent further assessment using the International Classification of Diseases, Ninth Revision (ICD-9) and a search of past hospital records (Barnes et al., 2012). Although this study provided a clinical diagnosis of depression, the exclusion of immediate psychometric measures of depression may have failed to identify individuals who do not meet a clinical cut off but endorse specific depressive symptoms and later progress to cognitive impairment.
Together, these limitations highlight the necessity for future research to include a representative sample consisting of a younger range of ages and to follow participants across a longer number of years. Future research should also aim to conduct more than one follow up assessment and to provide psychometric measures of depression in conjunction with a formal diagnosis of cognitive impairment.

**Limitations of Co-variates Included in Past Research on Depression and Cognitive Impairment/Decline**

A review of the literature highlights the inconsistency across studies to include all three co-variates associated with depression and cognitive impairment/decline, specifically physical activity, employment and medication (anti-depressants and anti-anxiety) (Barnes et al., 2006; Berger Fratiglioni, Forsell, Winblad, & Backman, 1999; Geerlings et al., 2000; Ravaglia et al., 2008; Yaffe et al., 1999). Physical activity is an important co-variate to consider in the context of researching depression and cognition. A past review supports the effect of physical exercise in improving mood and reducing symptoms of depression (Penedo & Dahn, 2005), whilst further research suggests that self-initiated exercise is associated with increasing levels of positive affect in patients diagnosed with Major Depressive Disorder (MDD) (Mata, Thompson, Jaeggi, Buschkuehl, & Gotlib, 2012). Other research suggests that regular physical activity may be a protective factor against cognitive decline and dementia (Laurin, Verreault, Lindsay, MackPherson, & Rockwood, 2001).

Employment is associated with depression and cognitive impairment/decline. Prior research indicates that unemployment affects depression and that being employed is associated with lower levels of depression (Christ et al., 2007; Dooley, Prause & Ham-Rowbottom, 2000). Furthermore, one review suggests a small significant effect of employment on cognitive decline (Valenzuela & Sachdev, 2006), while other research suggests that the nature and complexity of an individual’s employment is associated with risk
of dementia (Dartigues et al., 1992; Kroger et al., 2008) and that working long hours have a negative effect across cognitive performance (Virtanen et al., 2009). However this study was limited to a middle age group (Virtanen et al., 2009). Past research may fail to include employment as a covariate due to the inclusion of an older age group, which results in a minimal number of individuals engaging in employment (Ravaglia et al., 2008; Yaffe et al., 1999). However employment is an important covariate to consider, given that individuals are employed for longer periods of time due to increased living costs and the need to support an ageing population.

Medication for the treatment of depression and anxiety is associated with depression and cognitive impairment. Medication, including antidepressants and benzodiazepines, is commonly used for the treatment of depression/anxiety due to its direct effect upon an individual’s mood (World Health Organisation, 2004). Past research indicates that antidepressants and benzodiazepines directly affect neuronal substrates, for example neuronal plasticity and receptor channels (Castren & Hen, 2013; Levi, Le Roux, Eugene, & Poncer, 2015), which may explain subsequent changes in depression after pharmacological treatment of it, for example, mood and cognitive domains (i.e. concentration). Other research also suggests that medication for depression and anxiety is associated with changes in cognition, but with an increased risk of cognitive decline (Amado-Boccara, Gougoulis, Poirier Littre, Galinowski, & Loo, 1995; Paterniti, Dufouil, & Alperovitch, 2002), while recent studies indicate that the use of benzodiazepines is associated with an increased risk of dementia (Billioti de Gage et al., 2012; Gallacher et al., 2012). The literature indicates a strong relationship between medication and cognition, therefore potential confounding effects of medication should needs to be considered in the context of the current research. Together these findings highlight the importance of considering physical activity, employment and medication as co-variates in the context of researching depression and cognitive impairment.
Past Research on Depression and Cognition and Implications for Future Research

A vast amount of research supports the relationship between depression and cognitive impairment. A review of the literature indicates a focus on the development of and presentation of depression including a history and recurrence of depression (Dotson, et al., 2012), depression evident at specific life stages (Barnes et al., 2012; Diniz et al., 2013), the number of depressive symptoms/severity of depression (Barnes et al., 2006; Gatz et al. 2005; Rosenberg et al., 2010; Yaffe et al., 1999) and baseline depression (Ravaglia et al., 2008) as predictors of cognitive impairment/decline. While most of the research has included formal diagnoses of dementia, MCI and/or cognitive testing to assess cognitive impairment or decline at one time point (Barnes et al., 2012; Gatz et al., 2005; Diniz et al., 2013, Dotson et al., 2012, Ravaglia et al., 2008, Rosenberg et al., 2010, Yaffe et al., 1999). Overall, the previous studies support hypotheses explaining the link between depression and cognitive impairment (Jorm, 2001; Leonard, 2007). Specifically, the evidence of depression, recurrence of depressive episodes and severity of depression support hypotheses that depression affects the threshold for developing cognitive impairment, depression leads to hippocampal death which results in cognitive impairment, and depression as being prodromal to cognitive impairment (Jorm et al. 2001; Leonard, 2007).

To our knowledge there is a limited number of studies investigating which specific depressive symptoms measured at baseline are predictive of cognitive impairment/decline evident across a range of cognitive disorders and assessed on several follow up assessments. This investigation could have implications for hypotheses explaining the link between depression and cognitive impairment which primarily focus on the role of depression as a construct rather than specific symptoms (Jorm, 2001, Leonard, 2007). This could lead to questions of whether specific symptoms play role in lowering the threshold for cognitive impairment, leading to hippocampal damage resulting in impairment or whether depressive
symptoms are prodromal to cognitive impairment. Overall, these questions highlight the necessity for future investigation for clinical and research purposes. On this basis the present study will add to this area of research by following a representative sample of participants from a 60s age cohort, across 8 years, from which three waves of data were collected, from a range of depression assessments and cognitive screenings, measurements, interviews and clinical diagnoses.
Chapter 2. Personality and Total Health (PATH) Through Life Study and General Method for the Current Study
Overview of the Personality and Total Health (PATH) Through Life Study

The Personality and Total Health (PATH) Through Life project is a population based prospective longitudinal study. The study allows for investigation of risk factors and cognitive ability throughout the adult lifespan. The project was approved by the Australian National University Ethics Committee and written informed consent was obtained from the participants.

Method for PATH

Study Participants and Sampling Procedures

Participants were randomly selected from the electoral rolls for Canberra, A.C.T and Queanbeyan, N.S.W in Australia for the purpose of the PATH project (Anstey et al., 2008, 2012). In Australia it is compulsory for all citizens to enrol to vote. The PATH project was designed as a 20 year longitudinal study consisting of approximately 2 500 participants in each of the three age groups of 20-24 (20+ cohort), 40-44 (40+ cohort) and 60-64 (60+ cohort) years (Anstey et al., 2008). The tests were administered by trained interviewers. The participants were asked to complete a questionnaire while under the supervision of a professional interviewer. Participants also completed a range of basic physical tests, including grip strength, blood pressure, visual acuity, lung function and a cheek swab for DNA extraction (Anstey et al., 2008).

Data were collected from the three age groups across three waves, approximately four years apart. See Figure 2.1 for a flow chart of participants in the PATH study. At each wave participants attended a PATH interview (approximately 1.5 hours) in which information was collected about demographics, health, stressor, and social factors, and participants completed a range of cognitive, physical and psychological measures and mental health/general health self-reports. Our study focuses on the 60+ cohort and subsequent participants who were allocated to the Health and Memory sub study across the first (60-64 years), second (68-71
years) and third waves (74-78 years). Data were collected from the 60+ cohort, during 2001-2002 (58.3% participation rate from random sampling), 2005-2006 (87.1% participants from wave 1) and 2009-2010 (88.8% participants from wave 2), respectively. Initially, 4831 people were contacted, of whom 2551 were interviewed at the first wave (Males =1317/51.6% and Females =1234/48.4%), 2222 at the second wave and 1973 at the third wave.

A two stage sampling design was used to diagnose participants with a cognitive disorder. On the basis of their performance across a range of cognitive tests for each of the three waves, participants were allocated to and remained in the Health and Memory sub study where they underwent further assessment in addition to the PATH interview and measures. The sub study included a formal assessment and diagnosis of cognitive disorders (see Method for PATH; Clinical assessment section). The number of participants allocated to the Health and Memory study across the first, second and third waves was 117, 137 and 210, respectively.

Figure 2.1. Flow Chart of Participants across the Three Waves and Allocation to Health and Memory Study
Participants were screened at each of the three waves and assigned to the Health and Memory sub study. Screening across the three waves included the same predetermined cut off score on a cognitive screening battery, after which those meeting the criteria were selected for a clinical assessment. Participants fulfilled the criteria and underwent clinical assessment if they met any of the following: a) a Mini-Mental State Examination (MMSE) score ≤ 25 (Folstein, Folstein, & McHugh, 1975); b) on the immediate or delayed recall of the California Verbal Learning Test (Delis, Kramer, & Kaplan, 1987), on wave 1, a score below the 5th percentile (e.g. a score of < 4 on immediate and < 2 on delayed); c) a score below the 5th percentile for two or more of the subsequent cognitive assessments: Symbol Digit Modalities Tests (SDMT; < 33) (Smith, 1982), Purdue Pegboard with both hands (Purdue; wave 1: <8; wave 2: < 7) (Tiffin, 1968), and simple reaction time (SRT; third set of 20 trials; wave 1: > 310ms; wave 2 > 378ms) (Anstey, Dear, Christensen, & Jorm, 2005).

Clinical Assessment

Participants who screened positive in the screening stage, and provided their consent to participate, were provided with a Structured Clinical Assessment for Dementia by one of two physicians (see Appendix A). Participants were administered a neuropsychological assessment and the Clinical Dementia Rating (CDR) scale (Morris, 1993). Consenting participants also underwent MRI scans, though some participants refused this assessment. Further information was obtained on: medical history in regard to cognitive functioning, duration of symptoms, medical history from medical professionals and family, present treatment and psychiatric history. Informant interviews were conducted when possible. Participants who received a form of clinical diagnosis were referred to their doctor for follow up.

The neuropsychological assessment included: the frontal executive functions (Trails A & B, verbal fluency, and clock drawing) (Reitan, 1958; Borkowski, Benton, & Spreen,
1967; Borod, Goodglass, & Kaplan, 1980), language (short form of the Boston Naming Test) (Kaplan, Goodglass, & Weintraub, 1991), constructional praxis from the Consortium to Establish a Registry for Alzheimer’s Disease (Morris, Heyman, & Mohs, 1989), memory (Rey Auditory Verbal Learning Test with verbal recall and recognition) (Lezak, 1995), and recall of constructional praxis for non-verbal memory and agnosia (Morris, et al., 1989). Clinicians formulated a consensus diagnosis through the use of clinical checklists, results of the neuropsychological assessment, neuropsychiatric history and medical history. A description of the diagnostic criteria for all of the cognitive disorders is included in Appendix B. Criteria were implemented from the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM–4; American Psychiatric Association, 2000) for the assessment of dementia and delirium. Other criteria were applied for the following diagnoses: age-associated memory impairment (AAMI) (Kral, 1962), ageing-associated cognitive decline (AACD) (Crook et al., 1986), Mild Neurocognitive Disorder (MND) (DSM-IV, 2000), impairment on the CDR (Morris, 1993), other cognitive disorders (OCD) (DSM-IV, 2000) and MCI. The Petersen Criteria (Petersen et al., 1999) were implemented at waves 1 and 2 to diagnose MCI and the Winblad Criteria (Winblad et al., 2004) were used at wave 3. Previous research indicates that diagnoses of MCI are somewhat unstable across time (Cherbuin & Anstey, 2012). Therefore researchers investigated a category of Any Mild Cognitive Difficulties (Any-MCD) that included a range of cognitive disorders (e.g. AAMI, AACD, MND, CDR, OCD, CDR and MCI), which showed good stability across a 4 year period (Anstey et al., 2008). The current study will include the categories of MCI and Any-MCD.

**Interviews**

Interviewers received training in administering cognitive and physical measures. The majority of the interviews and assessments were conducted in the participant’s home.
However, interviews were sometimes conducted at the Australian National University, or at the participant’s workplace.

**General Method for the Current Study**

**Study Participants**

This thesis reports longitudinal data collected from the full 60+ cohort at wave 1 (baseline) and waves 2 and 3. When investigating progression to a cognitive disorder from wave 1 to wave 2, participants were excluded from the analysis if they had a wave 1 (baseline) diagnosis of MCI or Any-MCD (see Figure 3.1-3.2). It was necessary to exclude these participants to ensure a baseline sample which was impairment free, and in order to investigate predictors of progression to impairment. A total of 83 cases with a baseline diagnosis of Any-MCD were excluded at Wave 1 which included 28 cases of MCI. A further 10 cases were excluded due to a diagnosis of dementia across the three waves, with one case diagnosed at wave 1, one case diagnosed at wave 1 and 2 and eight cases diagnosed at wave 3.

When investigating progression to Any-MCD and MCI from wave 1 to wave 2, a total of 314 cases were excluded (see Figure 2.2-2.3) due to participants not meeting the criteria for the Health and Memory sub study, and sample attrition at each or both of waves 1 and 2. Within the 314 cases, a total of 294 cases did not complete the PATH interview at waves 1 and 2, and 15 cases did not meet criteria for the Health and Memory sub study at wave 1 and did not complete the PATH interview at wave 2. Overall, a total of 68 and 17 cases progressed to Any-MCD and MCI at wave 2, respectively (see Figure 2.2-2.3). When investigating progression to MCI from wave 1 to wave 2, a total of 51 cases which progressed to Any-MCD from wave 1 to 2 were excluded from the analyses to ensure the binary groups were specifically healthy/healthy versus healthy/MCI.
Cases with a baseline diagnosis (wave 1) of Any-MCD or MCI were also excluded for the analysis of progression to Any-MCD and MCI from wave 2 to wave 3 (see Figure 2.4-2.5), while a further 60 cases were excluded due to a wave 2 diagnosis of Any-MCD and which consisted of 17 cases of MCI. As mentioned previously, it was essential to include a baseline sample free of cognitive impairment to investigate predictors of progression to cognitive disorders; therefore for the purpose of this specific analysis it was necessary that wave 2 was impairment free in order to investigate predictors of progression to cognitive impairment from wave 2 to 3. As mentioned previously, a total of 10 cases were excluded due to a diagnosis of dementia across the three waves.

A total of 571 cases were excluded when investigating Any-MCD and MCI at waves 2 and 3 due to sample attrition represented in the form of absent cognitive assessment, inability to contact participants, participants had moved out of area or did not meet the criteria for the Health and Memory sub study, at each or both waves. Within the 571 cases, a total of nine cases met criteria for the Health and Memory sub study at wave 2 and did not complete the PATH interview at wave 3; 232 cases did not meet the criteria for the Health and Memory sub study at wave 2 and did not complete the PATH interview at wave 3; 15 cases completed the PATH interview but not the cognitive assessment at wave 2 and did not complete the PATH interview at wave 3, one case did not complete the PATH interview at waves 2 and 3; three cases did not complete the PATH interview at wave 2 and completed the health and memory sub study at wave 3; two cases did not complete the PATH interview at wave 2 and were not contactable, so that no cognitive data were collected at wave 3. As previously reported in this general method section, a total of 314 cases were excluded for the analysis of progression to Any-MCD at wave 2. Similarly, these cases were included in the 571 cases excluded for the analysis of progression from wave 2 to wave 3. The 314 cases did not complete the PATH interview at wave 2, while 15 of these cases did not meet criteria for
the Health and Memory sub study at wave 3 and 294 cases did not complete the PATH interview at wave 3. Overall, a total of 21 and 30 cases progressed to MCI and Any-MCD at wave 3, respectively (see Figure 2.4-2.5).
Participants who completed wave 1
\( n = 2551 \)

- Excluded participants due to not meeting Health and Memory substudy criteria and sample attrition at Wave 2.
  - Excluded participants who progressed to Any-MCD (other than MCI) at wave 2
    - Excluded participants with a baseline diagnosis MCI \( n = 28 \)
    - Any-MCD \( n = 83 \) (includes MCI)
    - Excluded participants diagnosed with dementia across the 3 waves \( n = 10 \)

Participants who were allocated to Health and Memory substudy at wave 1
\( n = 117 \)

Participants who completed wave 2
\( n = 2222 \)

Participants who were allocated to Health and Memory substudy at wave 2
\( n = 137 \)

Participants who progressed to a cognitive disorder at wave 2
Any-MCD \( n = 68 \)

Participants who remained healthy at waves 1 and 2
\( n = 2076 \)

**Figure 2.2** Flow of participants (+60 PATH Cohort) from Wave 1 to Wave 2 for Any-MCD

Participants who completed wave 1
\( n = 2551 \)

Excluded participants due to not meeting Health and Memory substudy criteria and sample attrition at Wave 2.
\( n = 314 \)

Participants who completed wave 2
\( n = 2222 \)

 Participants who were allocated to Health and Memory substudy at wave 2
\( n = 137 \)

Participants who progressed to a cognitive disorder at wave 2
MCI \( n = 17 \)

Participants who remained healthy at waves 1 and 2
\( n = 2076 \)

**Figure 2.3** Flow of participants (+60 PATH Cohort) from Wave 1 to Wave 2 for MCI
Excluded participants due to absent data, sample attrition, loss of contact, not meeting study criteria $n = 571$

Participants who completed wave 2 $n = 2222$

Participants who were allocated to Health and Memory substudy at wave 1 $n = 117$

Excluded participants with a baseline diagnosis Any-MCD $n = 83$

Participants who were allocated to Health and Memory substudy at wave 2 $n = 137$

Excluded participants with a cognitive disorder at wave 2
MCI $n = 38$
Any-MCD $n = 60$ (Includes MCI)
Excluded participants diagnosed with dementia across the 3 waves $n = 10$

Participants who completed wave 3 $n = 1973$

Participants who were allocated to Health and Memory substudy at wave 3 $n = 210$

Participants who progressed to a cognitive disorder at wave 3
Any-MCD $n = 30$

Participants who remained healthy at waves 1 and 2 $n = 1797$

Figure 2.4 Flow of participants (+60 PATH Cohort) from Wave 2 to Wave 3 for Any-MCD
Figure 2.5 Flow of participants (+60 PATH Cohort) from Wave 2 to Wave 3 for MCI
In the study, participants who were lost to follow up, in comparison to participants who persisted across all of the waves, differed significantly on baseline scores of positive and negative affect, Mini-Mental Status Examination (MMSE), years of education (see Table 2.1). A total of 16 cases were missing for baseline scores on the MMSE, which were imputed for the analyses (IBM SPSS, 2011; Schafer, & Graham, 2002). There were significant associations between groups (e.g. lost to follow up and not lost to follow up) on covariates including physical activity, heart disease, partner status, and consumption of anxiety and depression medication. Participants lost to follow up were also less likely to engage in physical activity, to report having heart disease, be prescribed medication for anxiety or depression and be in a relationship (see Table 2.1).
<table>
<thead>
<tr>
<th>Table 2.1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics of Sample Persisting to Wave 3 and Those Lost to Follow up</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Persisted to Wave 3 (n = 1887)</th>
<th>Lost to follow-up (n = 571)</th>
<th>Statistic&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (M, SD)</td>
<td>62.54 (1.51)</td>
<td>62.46 (1.51)</td>
<td>t (2456) = -1.07, p = .287</td>
</tr>
<tr>
<td>NA score (M, SD)</td>
<td>13.75 (4.63)</td>
<td>14.38 (5.47)</td>
<td>t (2440) = -2.73, p = .006</td>
</tr>
<tr>
<td>PA score (M, SD)</td>
<td>31.59 (7.16)</td>
<td>30.04 (7.75)</td>
<td>t (2438) = -4.41, p = &lt; .001</td>
</tr>
<tr>
<td>MMSE score (M, SD)</td>
<td>29.02 (1.60)</td>
<td>29.33 (1.11)</td>
<td>t (2456) = 4.40, p = &lt; .001</td>
</tr>
<tr>
<td>Years of Educ (M, SD)</td>
<td>14.02 (2.69)</td>
<td>13.43 (2.90)</td>
<td>t (2456) = -4.46, p = &lt; .001</td>
</tr>
<tr>
<td>Gender (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>972 (51.5%)</td>
<td>306 (53.6%)</td>
<td>χ² (1, n = 2458) = 0.68, p = .41</td>
</tr>
<tr>
<td>Female</td>
<td>915 (48.5%)</td>
<td>265 (46.4%)</td>
<td>χ² (1, n = 2458) = 0.84, p = .36</td>
</tr>
<tr>
<td>Employment (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>783 (41.5%)</td>
<td>224 (39.2%)</td>
<td>χ² (2, n = 2458) = 10.98, p = .004</td>
</tr>
<tr>
<td>Not Employed</td>
<td>1104 (58.5%)</td>
<td>347 (60.8%)</td>
<td></td>
</tr>
<tr>
<td>Physical activity (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/mild</td>
<td>917 (48.6%)</td>
<td>320 (56%)</td>
<td>χ² (1, n = 2458) = 2.71, p = .08</td>
</tr>
<tr>
<td>Moderate</td>
<td>739 (39.2%)</td>
<td>200 (35.1%)</td>
<td></td>
</tr>
<tr>
<td>Vigorous</td>
<td>231 (12.2%)</td>
<td>51 (8.9%)</td>
<td></td>
</tr>
<tr>
<td>Anxiety Medication (N,%),</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>75 (4%)</td>
<td>52 (9.1%)</td>
<td>χ² (1, n = 2458) = 22.53, p = &lt; .001</td>
</tr>
<tr>
<td>Yes</td>
<td>1812 (96%)</td>
<td>519 (90.9%)</td>
<td></td>
</tr>
<tr>
<td>Depression Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>82 (4.3%)</td>
<td>46 (8.1%)</td>
<td>χ² (1, n = 2458) = 11.48, p = .001</td>
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<tr>
<td>No</td>
<td>1805 (95.7%)</td>
<td>525 (81.9%)</td>
<td></td>
</tr>
<tr>
<td>Partner (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1506 (79.8%)</td>
<td>418 (73.2%)</td>
<td>χ² (1, n = 2458) = 10.86, p = .001</td>
</tr>
<tr>
<td>No</td>
<td>381 (20.2%)</td>
<td>153 (26.8%)</td>
<td></td>
</tr>
<tr>
<td>Smoke (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>190 (10.1%)</td>
<td>72 (12.6%)</td>
<td>χ² (1, n = 2458) = 2.71, p = .08</td>
</tr>
<tr>
<td>No</td>
<td>1697 (89.9%)</td>
<td>499 (87.4%)</td>
<td></td>
</tr>
<tr>
<td>High blood pressure (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1114 (59%)</td>
<td>220 (38.5%)</td>
<td>χ² (1, n = 2458) = 0.98, p = .32</td>
</tr>
<tr>
<td>No</td>
<td>773 (41%)</td>
<td>351 (61.5%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>134 (7.1%)</td>
<td>50 (8.8%)</td>
<td>χ² (1, n = 2458) = 1.50, p = .22</td>
</tr>
<tr>
<td>No</td>
<td>1753 (92.9%)</td>
<td>521 (91.2%)</td>
<td></td>
</tr>
<tr>
<td>Stroke (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>78 (4.1%)</td>
<td>32 (5.6%)</td>
<td>χ² (1, n = 2458) = 1.89, p = .17</td>
</tr>
<tr>
<td>No</td>
<td>1809 (95.9%)</td>
<td>539 (94.4%)</td>
<td></td>
</tr>
<tr>
<td>Heart disease (N, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>264 (14%)</td>
<td>105 (18.4%)</td>
<td>χ² (1, n = 2458) = 6.31, p = .01</td>
</tr>
<tr>
<td>No</td>
<td>1623 (86%)</td>
<td>466 (81.6%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Means and SD shown for continuous variables. P values are 2 sided t-tests for continuous variables and χ² for categorical variables. A chi square test for independence using Yates Continuity Criteria was used for all categorical variables apart from physical activity which used Pearson Chi Square.
Chapter 3. Study One: Depressive Symptoms and Prediction of Progression to Cognitive Disorders in a Population Based Sample Aged 60+
Depressive Symptoms and Predictors of Progression to Cognitive Disorders in a Population Based Sample +60

Chapter 1 outlined the role of depression as a predictor of cognitive disorders, with research supporting evidence that depression, recurrent depression, the number of depressive symptoms and onset of depression (e.g. life stage) were associated with the development of cognitive impairment. Although there is a large amount of research supporting the role of depression in the context of cognitive disorders, to our knowledge few studies have investigated specific depressive symptoms as predictors of cognitive disorders, across various follow up assessments (Geerlings et al., 2000). As mentioned in Chapter 1, one study concluded that specific baseline depressive symptoms were predictive of AD at one follow up period, on average 3.2 years later, in a higher educated (> 8 years) and older population (age > 65 years) (Geerlings et al., 2000). In this study depressive symptoms that predicted AD included a loss of appetite/weight, psychomotor agitation, suicidal ideation, depressed mood and subjective bradyphrenia (experiencing slowness in thinking) (Geerlings et al., 2000). Further analyses indicated that depressed mood and bradyphrenia remained significant when adjusting for age, sex and subjective memory complaints (Geerlings et al., 2000). This study provides preliminary evidence for depressive symptoms as predictors of cognitive disorders, specifically AD. However further research is needed to ascertain whether collective depressive symptoms are predictive of cognitive disorders other than AD across more than one follow up assessment and in a general population.

Although there is limited research on depressive symptoms predicting the onset of cognitive disorders, other research suggests a relationship between certain depressive symptoms and cognition. These depressive symptoms are representative of part of the criteria for Major Depressive Disorder (MDD; APA, 2013). The next section will discuss the relationship between depressive symptoms and cognition, and potential implications for
research of depressive symptomology and cognitive impairment/decline.

**Depressive Symptoms, Cognition, and Cognitive Impairment/Decline**

The DSM-V (APA, 2013) outlines a range of depressive symptoms that are representative of the criteria for a diagnosis of MDD (see Chapter 1, Depression as a predictor of cognitive impairment/decline). The current thesis focuses specifically on the following symptoms which were available in the datasets on which the current research was based: sleep difficulties, depressed mood, psychomotor agitation/retardation, reduced pleasure or interest in activities, fatigue or loss of energy, weight loss, decreased/increased appetite, concentration difficulties, recurrent thoughts of death/suicide, and feeling worse in the morning. Depressive symptoms that were not available in the datasets were excluded, including feeling excessive worthlessness/guilt, reduced ability to think, and indecisiveness.

**Sleep difficulties**

Sleep disturbance is a common symptom of depression, evidenced by nearly 50-90% of individuals diagnosed with depression as having sleep difficulties (Tsuno, Besset, & Ritchie, 2010). This high rate highlights the importance of sleep as a depressive symptom, which is further supported by the inclusion of the assessment of sleep difficulties within psychometric measures of depression and as part of the DSM-V criteria for MDD represented through “insomnia and hypersomnia evident nearly every day” (APA, 2013; Koloski, Smith, & Pachana, 2008; Spitzer, Kroenke, & Williams, 1999). Sleep is integral to achieving a normal level of functioning, and is associated with cognitive performance. Previous literature indicates a positive correlation between quality of sleep and the recall of non-related words in a population of elderly adults aged 61-75 years (Mazzoni et al. 1999). Although the study is limited through the inclusion of an older age-group, the results suggest that an individual’s quality of sleep impacts upon verbal memory. Another study shows that chronic insomnia is associated with cognitive impairment, as indicated across tasks of memory span, attention
and executive function (Haimov, Hanuka, & Horowitz, 2008). Further findings suggest that when the amount of sleep per night is restricted, specifically by four and six hours, over a two week period, performance on cognitive tasks declines over a two week period (Van Dongen, Maislin, Mullington, & Dinges, 2003). Specifically, the researchers found that performance worsened on cognitive tasks of attention, working memory and cognitive throughput (Van Dongen et al. 2003). Overall, sleep difficulties are a fundamental symptom of depression and are associated with cognitive impairment and decline, evidenced by performance measured over time intervals and on a range of cognitive tasks. However future research is needed to investigate whether sleep difficulties predict the progression to cognitive disorders.

Other research suggests that ageing is associated with an increased likelihood of sleep difficulties, which may confound the effects of depression. Past research indicates that ageing is associated with changes in sleep patterns (Crowley, 2011; Prinz, 2004). Specifically, ageing directly affects daily sleep wake cycle, quantity and pattern of sleep stages, and wakefulness (Crowley, 2011; Prinz, 2004). This evidence suggests that ageing may confound the effects of depression, particularly when investigating sleep as a depressive symptom and progression to cognitive disorders within a relatively older population. Past research investigated this potential confounding effect, with one study researching ageing and changes in sleep in depressed and non-depressed individuals (Gillin et al., 1981). The findings from this study indicate that, relative to normal individuals and after adjusting for age, the depressed individuals exhibited an increased range of sleeping difficulties, for example, a reduction in sleep efficiency, increased early morning wake time and intermittent awake time (Gillin et al., 1981). Other research suggests that depression in comparison to age was the most significant predictor for excessive daytime sleepiness (Bixler et al., 2005), which is representative of hypersomnia (Ohayon, 2008). Further research found that ageing is not associated with self-reported sleep disturbances; instead other factors including; general
health, and mild/moderate/severe depressed mood are associated with reported sleep disturbances (Grandner et al., 2012). Overall, past research suggests that sleep changes related to depression may be distinct from the ageing process, supporting further investigation of sleep difficulties as a depressive symptom in the context of cognitive disorders.

**Depressed mood and feeling worse in the morning**

In the DSM-V criterion for MDD, depressed mood is indicated through subjective reports of feeling sad, empty or hopeless (APA, 2013). Previous research supports a relationship between a sad mood and cognitive impairment. One study showed that induced sad mood affects memory for emotional words and facial emotional recognition (Chepnick, Farah, & Cornew, 2007), while other research found that a sad mood induced by music resulted in participants showing an increased recall of sad words on a delayed task and in autobiographical memory (Knight, Maines, & Robinson, 2002). Additional neuroimaging research supports an association between mood and cognition, with past findings showing an interaction between mood and cognition to be mediated by the Prefrontal Cortex (PFC) (Aoki et al., 2011; Mayberg et al., 1999).

Various limitations are evident within the research on depressed/sad mood and cognition. Numerous studies induced a sad mood on a relatively healthy sample of participants (Chepnick et al., 2007; Knight et al., 2002; Mitchell & Phillips, 2007), which makes it difficult to generalize the results to individuals experiencing depression and who indicate the experience of a sad mood. Particularly, the severity or intensity of the ‘sad mood’ in a depressed individual versus a healthy individual would differ significantly. Furthermore, the studies include an ‘induced sad mood’ which may not be representative of a continuous sad mood experienced by individuals with the depressive symptom. The past studies also included salient processing of emotional cognitive information (Chepnick et al., 2007; Knight
et al., 2002); however results may differ from processing non-emotional information. Despite these limitations the past research suggests a relationship between depressed/sad mood and cognition.

The DSM-V diagnosis for MDD with melancholic features includes the criterion of depression regularly being worse in the mornings (APA, 2013). When this symptom, in conjunction with other symptoms, is evident in the most severe stage of depression, a diagnosis of MDD with melancholic features is considered (APA, 2013). Therefore the symptom of “feeling worse in the morning” is often included within depressive measures (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988). While there is a limited amount of research directly investigating the diurnal pattern of mood as a predictor of cognitive impairment, other related research suggests a possible relationship. As mentioned in Chapter 1, a depressed mood in general is associated with cognitive impairment (Aoki et al., 2011; Chepnick et al., 2007; Knight et al., 2002; Mayberg et al., 1999; Mitchell & Phillips, 2007), and specifically repeated episodes of depression are predictive of dementia (Dotson et al., 2010). As feeling worse in the morning is indicative of melancholia, it is hypothesised that the symptom of “feeling worse in the morning” may also be associated with cognitive impairment, for it includes a depressed mood and occurs on a regular basis, similarly to recurrent episodes of depression. However further research is needed to investigate this symptom in relation to progression to cognitive disorders.

**Psychomotor retardation or agitation**

Past research demonstrates the importance of psychomotor symptoms within depression, with evidence supporting psychomotor symptoms of retardation and agitation as independent constructs that may contribute significantly to diagnosis, prognosis and potential pathophysiology of depression (Sobin & Sackeim, 1997). Psychomotor retardation is observed through slowed speech and thinking, facial expression, speech lowered in volume,
inflection, amount, variety of content or muteness, eye movement, self-touching, posture, and speed and degree of movements (APA, 2013; Buyukdura, McClintock, & Croarkin, 2011). Past research shows that somatic and vegetative symptoms are related to a 10% risk in the chance of developing dementia (Gatz et al., 2005). However a limited number of studies exist supporting this finding or generalizing the results to other specific cognitive disorders.

Further research highlights that individuals with depression display specific manifestations of psychomotor slowing, which may be associated with cognition. Some of these psychomotor manifestations include poor eye movement and slowed motor reaction (Buyukdura et al., 2011; Sobin & Sackeim, 1997). Particularly, eye movement is fundamental to cognitive processes including visual search and reading of information (Liversedge & Findlay, 2000), while motor reaction is a combination of motor and cognitive processes (Sobin & Sackeim, 1997).

Another psychomotor symptom of depression includes agitation (APA, 2013). Agitation is represented through the inability to stay still, pacing, hand wringing, or pulling and rubbing the skin, clothing or alternate objects (APA, 2013). Similar to psychomotor slowing and cognition, there is a limited amount of research investigating agitation and cognitive impairment/decline. To our knowledge, only one study, previously mentioned, found the depressive symptom of agitation to predict AD (Geerlings et al., 2000). However, based on the presentation of agitation as mentioned above, it is possible that agitated behaviours would result in distraction and impair cognitive ability, for example one’s ability to encode information successfully into memory. However, further investigation is needed to ascertain the relationship.
Reduced pleasure or interest in activities, fatigue or loss of energy and loss of confidence

Positive affect consists of a wide range of positive feelings including attentive, interested, alert, excited, enthusiastic, inspired, proud, determined, strong and active (Watson, Clarke, & Tellegen, 1988). These states are often impaired in individuals presenting with depression and are evident through a decreased pleasure/interest in activities or the experience of fatigue and loss of energy (APA, 2013; Nutt et al., 2007). Past research on depression and cognitive impairment found an elevation in depressive symptoms and dominance of motivational symptoms, for example loss of energy and lack of interest, three years prior to incidence of AD (Berger et al., 1999), while other research found that reduced positive affect was a marginal risk factor for dementia with positive affect being represented through one item representative of loss of confidence including “I felt I was just as good as other people” (Gatz et al., 2005). Overall, the previous research suggests that symptoms of reduced interest in activities, fatigue or loss of energy and loss of confidence may be associated with the development of a cognitive disorder. However further research is needed to confirm this hypothesised relationship, particularly the symptom of fatigue associated with loss of energy. Further research is also required into a general population free of cognitive impairment, given that past research focused on participants in the preclinical stage of AD (Berger et al., 1999).

The inability to experience pleasure, a common symptom of depression, is also referred to as anhedonia (Lemke, Puhl, Koethe, & Winkler, 2007). A past study included individuals diagnosed with co-morbid Major Depressive Disorder and Parkinson’s Disease (dPD) and further categorized them into three groups pending their presentation of depressive symptoms (e.g. depressed mood, apathy/anhedonia and both depressed mood and apathy/anhedonia) (Santangelo et al., 2009). The study found that individuals who met the
criteria for the apathy/anhedonia group scored significantly lower on cognitive tasks (Copying Task, Frontal Assessment Battery and Phonological Tasks) in comparison to individuals who fulfilled the criteria for the depressed mood (Santangelo et al., 2009). This finding suggests that anhedonia may be associated with cognition; however it is difficult to specify the relationship due to the combination of apathy and anhedonia.

Further research suggests that emotional processing is impaired in individuals with cognitive disorders, which may indirectly effect their ability to experience pleasure. Past findings indicate that impaired emotional recognition of faces is associated with cognitive disorders specifically in MCI and AD (Drapeu, Gosselin, Gagnon, Peretz, & Lorrain, 2009; Spoletini et al., 2008). A lot of the evidence supporting impaired emotional recognition is conducted on individuals who have received a diagnosis of a cognitive disorder or once the cognitive disorder has progressed. Therefore it is difficult to ascertain whether impaired emotional recognition is prodromal to cognitive impairment. However the finding that impaired emotional recognition is evident in pre-dementia syndromes such as MCI (Spoletini et al., 2007) could suggest a prodromal basis. If this is true, the presence of impaired emotional recognition could affect an individual’s ability to experience pleasure, thus indirectly leading to a symptom of depression, a syndrome that is a risk factor for cognitive impairment. However, as mentioned previously, there is a limited amount of research investigating this hypothesis or the specific symptoms of reduced pleasure, interest in activities, fatigue or loss of energy; therefore further research is needed.

**Poor concentration, suicidal ideation, weight loss and appetite**

Additional symptoms of depression include poor concentration, suicidal ideation and weight loss/poor appetite/overeating (APA, 2013). Past research on depression and cognitive impairment indicates that the depressive symptom of difficulties with concentration was dominant three years prior to a diagnosis of AD (Berger et al., 1999). This finding suggests
that difficulties with concentration may have a role in predicting AD itself, or are part of the prodromal phase, given that the study was performed on participants in the preclinical phase of AD. Furthermore, the participants were aged $\geq 75$ years and in the preclinical phase of AD; therefore it is difficult to generalise these findings to a general population. A limited amount of research exists investigating difficulties with concentration, as a depressive symptom, for predicting cognitive impairment, which may be explicable by the view of this symptom as being prodromal to cognitive disorders. However concentration is a necessary component for cognitive performance, specifically of working memory (Lichtenberger, & Kaufman, 2012), suggesting that poor concentration, as a depressive symptom, may affect performance on cognition. Overall, this depressive symptom may predict cognitive impairment/decline; however this is a preliminary suggestion and additional research is required.

Recurrent thoughts of death and suicidal ideation are also symptomatic of depression (APA, 2013). To our knowledge there is limited research investigating the relationship between this specific depressive symptom and cognitive impairment, with one study, as previously discussed, finding suicidal ideation to be predictive of AD (Geerlings et al., 2000). Other research on suicidal ideation suggests that the depressive symptom is associated with cognitive inflexibility and the inability to problem solve (Dixon, Heppner & Anderson, 1991; Miranda, Gallagher, Bauchner, Vaysman, & Morroquin, 2011; Priester & Clum, 1993). Therefore the presence of cognitive inflexibility and inability to problem solve could impact upon the ability to function at a normal cognitive level, overall contributing to the rate at which an individual presents with cognitive difficulties. However more research is needed to support this hypothesis and establish whether this symptom is predictive of cognitive impairment/decline.
Weight loss and increase/loss of appetite are symptoms representative of depression (APA, 2013). To our knowledge, there is a limited amount of research investigating these symptoms within the context of depression and cognitive disorders, with a study finding loss of appetite and weight were predictive of AD (Geerlings et al., 2000). Other research has focused on weight loss/gain as a separate construct from depression and as prodromal to cognitive disorders, and with limited research on the direct effects of appetite not related to dieting. Past research also found a relationship between weight and the incidence of dementia (Fitzpatrick et al., 2009; Power et al., 2011; Stewart et al., 2005). Specifically, overweight men and men with a waist-to-hip ratio $\geq 9$ (indicative of obesity) had a lower hazard of dementia in comparison to men with a normal weight and waist-to-hip ratio $\leq 9$ (Power et al., 2011). However this study was limited to the investigation of a male population and adiposity within later life. In contrast, another study found that higher adiposity evident in mid-life increased the risk of developing dementia in later life (Fitzpatrick et al., 2009). Higher adiposity may be the result of an increased appetite, which could potentially impact upon weight gain and increase the risk of dementia. However further research is needed to ascertain this relationship between increased appetite and risk of cognitive disorders.

Further research found that weight loss evident two to four years prior to a diagnosis of dementia was associated with the incidence of dementia (Stewart et al., 2005). Poor appetite and hence limited caloric intake may directly impact on weight loss, and contribute to an increased incidence of dementia. However future research is needed to investigate this potential relationship between poor appetite and cognitive disorders.

Overall, there is evidence to support a relationship between weight gain/loss and dementia, which is hypothesised to be affected by appetite. On the basis of past research it is difficult to ascertain the role of weight or appetite as a depressive symptom, in the context of predicting progression to cognitive disorders. This gap in the literature suggests that future
research is needed to investigate the potential association between these depressive symptoms and cognitive disorders.

**Summary of depressive symptoms**

Research supports that specific depressive symptoms are predictive of AD and dementia (Gatz et al., 2005; Geerlings et al., 2000; Fitzpatrick et al., 2009; Power et al., 2011; Stewart et al., 2005; Buyukdura et al., 2011; Chepnick et al., 2007; Haimov et al., 2008; Knight et al., 2002; Liversedge, & Findlay, 2000; Mayber et al., 1999; Mazzoni et al. 1999; Santangelo et al., 2009; Van Dogen et al. 2003; Berger et al., 1999; Gatz et al., 2005). Specific depressive symptoms, including a loss of appetite/weight, psychomotor agitation, suicidal ideation, depressed mood, and bradyphrenia, are predictive of AD (Geerlings et al., 2000). Furthermore only depressed mood and bradyphrenia remained significant predictors while adjusting for sex, age and subjective memory complaints (Geerlings et al., 2000). These findings are limited to a highly educated population and prediction of AD and no other cognitive disorders. The findings are also limited to one follow up assessment, on average 3.2 years later, and the exclusion of other covariates apart from age, sex and subjective memory complaints. Further research supports that somatic and vegetative symptoms representative of psychomotor retardation are associated with an increased risk of dementia (Gatz et al., 2005). However this finding has not been replicated, nor has it been investigated in the context of alternate cognitive disorders. Other research suggests that weight is associated with dementia risk (Fitzpatrick et al., 2009; Power et al., 2011; Stewart et al., 2005); and it is hypothesised that weight is directly impacted by increase/decrease of appetite, both of which are symptomatic of depression. However further research is needed to understand the role of increased/decreased appetite as symptoms of depression in the context of cognitive disorders. This is also true of the symptom of weight loss, which is well less understood as a symptom of depression in predicting specific cognitive disorders other than dementia.
Further literature supports the relationship between specific depressive symptoms and cognition. Individual symptoms, including sleep, depressed mood, psychomotor retardation, reduced pleasure/interest in activities and fatigue/loss of energy, are associated with cognition (Buyukdura et al., 2011; Chepnick et al., 2007; Haimov et al., 2008; Knight et al., 2002; Liversedge, & Findlay, 2000; Mayber et al., 1999; Mazzoni et al. 1999; Santangelo et al., 2009; Van Dogen et al. 2003;). Limitations within these past studies include the use of outcome measures primarily based on performances across cognitive tasks (Chepnick et al., 2007; Haimov et al., 2008; Knight et al., 2002; Mazzoni et al. 1999; Santangelo et al., 2009; Van Dogen et al. 2003). The use of these outcome measures makes it difficult to generalize these findings to whether symptoms are predictive of cognitive disorders.

Other studies suggest that the level of positive affect experienced is associated with the presentation of depressive symptoms, including reduced pleasure/interest in activities and fatigue/loss of energy (APA, 2013; Nutt et al., 2007), while past research found that elevated mood states associated with positive affect are associated with incidence of AD, and that positive affect is a marginal risk for dementia at one follow up assessment period (Berger et al., 1999; Gatz et al., 2005). The limitations of these studies include the inability to generalise the findings to a normal population who develop other cognitive disorders (e.g. MCI), and that they use only a single follow up assessment, while the role of other depressive symptoms and cognition is less well understood, with a limited amount of research on symptoms that include poor concentration and suicidal ideation (Dixon, et al., 1991; Lichtenberger & Kaufman, 2012; Miranda et al., 2011; Priester & Clum, 1993).

Overall, the research suggests preliminary evidence for certain depressive symptoms as predictors of AD. Other research supports that specific depressive symptoms are associated with cognition, evidenced by performance across cognitive tasks. Together the limitations of the past research indicate that further research is required to understand the role
of individual depressive symptoms as predictors of progression from normal ageing to cognitive disorders across various follow up assessments, while adjusting for additional covariates and demographic factors.

The aim of the current study is to investigate whether specific depressive symptoms are predictive of progression to cognitive disorders (MCI and Any-MCD) from normal ageing across two follow assessments at wave 2 and wave 3. On the basis of previous findings (Berger et al., 1999; Gatz et al., 2005; Geerlings et al., 2000; Santangelo et al., 2009) it is hypothesised that depressive symptoms, including depressed mood and feeling worse in the morning, psychomotor agitation/retardation, loss of appetite/weight, suicidal ideation, reduced pleasure or interest in activities, fatigue and loss of energy, and loss of confidence, will predict progression to cognitive disorders. It is difficult to predict whether other symptoms of depression (e.g. reduced ability to concentration, sleep difficulties or increased appetite) will predict progression to cognitive disorders, due to the limited amount of research conducted in this area. However, on the basis of Jack and colleagues (2010) model the “Dynamic Biomarkers of the Alzheimer’s Pathological Cascade” (see Chapter 1; page 19) it is suggested that significant neurological changes evident to the onset of cognitive impairment may result in a range of cognitive, emotional and behavioural depressive symptoms (e.g. reduced ability to concentration, sleep difficulties or increased appetite).
Method

Data presented in this study are from the PATH project which has previously been described in detail (see Chapter 2, Method for PATH). This study focuses on cross sectional analyses and data collected from the 60+ cohort assessed at baseline, and followed up at waves 2 and 3. The sample used in the current study has previously been described in detail (see Chapter 2, Method for PATH & Chapter 3, General Method for the Current Study).

Materials

Assessment of Depressive Symptoms

Brief Patient Health Questionnaire (BPHQ)

The Brief Patient Health Questionnaire (BPHQ) is a self-report measure for mood and anxiety disorders and includes diagnostic validity (Spitzer et al., 1999; see Appendix C). The BPHQ was originally developed from The Primary Care Evaluation of Mental Disorders (Prime-MD), which is a screening instrument for mental health disorders (Spitzer et al., 1999). In addition to items measuring anxiety, the BPHQ consists of nine items measuring depression that will be used for purpose of the current analyses.

The nine items represent a range of depressive symptoms, including depressed mood, anhedonia, appetite change, sleep disturbance, psychomotor agitation or retardation, loss of energy, diminished concentration and suicidal thoughts/attempts (Cannon et al., 2007). Participants must self-report how often they have been bothered by the symptom over the past two weeks. Individuals are scored 0-3 points according to their answer on a 4 point scale ranging from; “not at all,” “several days,” “more than half the days,” and “nearly every day” (Spitzer, et al., 1999). Overall scores range from 0-27 points with higher scores indicative of a potential DSM-IV diagnosis for depression (Spitzer, Williams, Kroenke, Hornyak, & McMurray, 2000).
Past research supports BPHQ as a valid and reliable measure of depression, with much of this evidence gathered from research conducted on the Patient Health Question 9 item questionnaire (PHQ-9) which is representative of the depression measurement in the BPHQ. A past systematic review indicates the PHQ-9 is a well validated measure with superior sensitivity and specificity for the detection and monitoring of depression (Kroenke, Spitzer, Williams, & Lowe, 2010). Specific literature analysed within the review indicates that the PHQ-9 performs in the same manner across sex and age groups, while the PHQ-9 showed increased internal consistency across a range of cognitive levels (Kroenke et al., 2010). Further research supports the summed score for the PHQ-9 as a valid and reliable measure for screening depression in elderly individuals, specifically aged > 59 (Lamers et al., 2008). However this study was limited to elderly patients who were currently chronically ill.

**Goldberg Anxiety and Depression Scale (GADS)**

The Goldberg Anxiety and Depression Scale (GADS) is a self-report measure of anxiety and depression, which is widely used within community studies and for clinical samples (Goldberg et al., 1988; Koloski et al., 2008; see Appendix D). The GADS consists of a total of 18 items with nine items measuring anxiety and nine items measuring depression. The nine items measuring depression were used for the present analyses. The nine items represent symptoms of depression, including anhedonia, loss of energy, loss of confidence, hopelessness, weight loss/poor appetite, disrupted sleep, psychomotor slowing, and feeling worse in the morning (Goldberg et al., 1988). Participants must report if they have recently felt these symptoms and record their answer as yes/no. Scores range from 0 to 9 with higher scores indicating the presence of depressive symptoms.

Other research supports the implementation of the GADS as a measure of depression. One study investigating the effect of age on depression included the GADS as a measure of psychological distress (Jorm et al., 2005). The findings from this study suggest that the
GADS had a weak factorial invariance between the age groups of 20-24, 40-44 and 60-64, supporting the implementation of this measurement across a wide age range (Jorm et al., 2005). This finding is consistent with previous research which implemented the GADS to predict change in depressive symptomology across a population sample 18-79 years old (Christensen et al., 1999; Henderson et al., 1998), further supporting the implementation of this measure across a wide age range. Overall, these findings support the implementation of the GADS in the current study, which assessed participants at baseline who were 60-64 years old.

**Assessment of Demographics and Covariates**

Participants were questioned by an interviewer at the PATH interview on their total years of education, employment status and marital status. Employment status was recorded and categorized as: employed full-time/employed part-time, looking for full-time work/employed part time/unemployed and looking for work/not in the labour force, while marital status was categorized as married/de facto/separated/divorced/widowed/never married. For the purpose of the present analyses employment was collapsed into a binary variable: employed whether full-time or part-time (employed full time/employed part-time, looking for full-time work/employed part-time) and not employed (unemployed and looking for work/not in the labor force). Marital status was collapsed into a binary variable called partner status and comprised the categories partnered (married/de facto) and not partnered (separated/divorced/widowed/never married).

Lifestyle factors were assessed at the interview. Throughout the interview high blood pressure was measured twice by implementing the Omron M4 blood pressure monitor, from which diastolic and systolic pressures were averaged (Jorm, Anstey, Christensen, & Rodgers, 2004). A value of ≥ 85mm Hg represented diastolic hypertension, while ≥ 140 mm Hg was indicative of systolic hypertension (Barrett-Connor, & Palinkas, 1994). Based on these values
a binary variable titled high blood pressure was created (yes/no). Stroke, diabetes, heart disease, antidepressants and anxiety medication consumption, and current smoking status, were self-reported and recorded as a binary variable (yes/no). Participants were assessed for physical activity based on the UK Whitehall II Study assessment and were coded into none/mild (< .05 hours per week), moderate (0.5 -1.49 hours per week) and vigorous (> 1.49 hours per week) categories (Stafford, Hemingway, Stansfield, Brunner, & Marmot, 1998).

**Sample Size**

Sample size was predetermined by the original aims of the larger cohort study (Anstey et al., 2012). The sample size was sufficient to allow for investigation of risk and protective factors and interactions among risk factors. The sample size was based on participation rate in the PATH study recruited in the first wave (N =2551). Participants were allocated to one of two categories for analyses based on their progression to a diagnosis of cognitive impairment at specific time points at wave 2 and wave 3 (i.e. healthy/healthy or healthy/cognitive impairment). Participants were allocated to the healthy/healthy group if they remained stable across waves and free of cognitive impairment from wave 1 to 2 or wave 2 to 3.

When investigating progression to MCI from wave 1 to 2, the healthy/healthy group consisted of 2076 participants and the healthy/MCI group consisted of 17 participants. When analysing Any-MCD from wave 1 to 2, the healthy/healthy group consisted of 2076 participants and the healthy/Any-MCD group included 68 participants (see Figures 2.2-2.3). When investigating MCI from wave 2 to 3 the healthy/healthy consisted of 1797 and the healthy/MCI group included 21 participants; and when analysing Any-MCD from wave 2 to 3, 1797 participants were allocated to the healthy/healthy group and 30 participants to the healthy/Any-MCD group (see Figures 2.4.-2.5).
Statistical Analysis

SPSS version 22 was used to perform the analysis. A Generalized Linear Model (GZLM) using binary logistic regression was implemented to investigate items of the BPHQ and GADS as predictors of progression to a binary group diagnostic membership (e.g. healthy/healthy, and healthy/Any-MCD or healthy/MCI), while controlling for demographics and covariates. A GLZM, binary logistic regression model is an applicable method of analyses for data that include a dependent variable with a binary outcome that is not normally distributed (Garson, 2013). Therefore, based on the nature of the current research question, investigating prediction to a binary outcome (healthy/MCI or healthy/Any-MCD) with a non-normal distribution, this model was considered applicable for the present analyses.

Predictor variables included individual BPHQ and GADS items, which were entered individually into the GLZM model. For the purpose of the current analyses the BPHQ items were collapsed into a binary variable (no/yes) to indicate the presence of a depressive symptom. Endorsement of “not at all” was coded as having no depressive symptom, while the presence of a depressive symptom was indicative of endorsement of “several days,” “more than half of the day,” or “nearly every day”. Other demographics/covariates were adjusted for, and included education, physical activity, employment status, depression and anxiety medication, partner status, current smoking status, high blood pressure, diabetes, stroke and heart disease. A series of hierarchical models was tested. In Model 1, the 10 GADS items and 9 BPHQ items were entered separately to analyse prediction to Any-MCD/MCI from wave 1 to 2 and wave 2 to 3. Items that significantly predicted progression to Any-MCD/MCI in Model 1 were analysed in Model 2 and entered separately while adjusting for gender and education. Items that were significant in Model 2 were entered into Model 3 individually while adjusting for all other covariates (physical activity, employment, depression and anxiety medication, partner status, current smoking status, high blood pressure, diabetes,
stroke and heart disease). Age was excluded from all the models due to the narrow aged cohort included in the current analyses. Results in model 1 are displayed in tables while results from model 2 and 3 are discussed in text within the results section. A Pearson product-moment correlation coefficient indicated a small negative correlation between gender and education \( (r = -0.16, n = 2551, p < .001) \). The association between covariates in model 3 was analysed using the Phi Coefficient, with results indicating small to large effects between specific variables (see Appendix E).

There is no assumption for the distribution of the predictor or dependent variables in binary logistic regression (Pallant, 2011); therefore it was not necessary to investigate normality (e.g. skewness/kurtosis). The maximum number of predictors entered within a model across the waves was 11, which was relatively small compared to the overall sample size \( (N = 1827 \text{ to } 2514) \), and therefore did not violate an assumption of binary logistic regression (Pallant, 2011). Similarly, the assumption of Multicollinearity was not violated, with analysis indicating that the tolerance values for the predictors in the model were not \(< .10 \) (Pallant, 2011).

**Data Screening**

The data were screened for accuracy of input and plausibility of frequencies, which indicated that both were satisfactory. A missing values analysis indicated a range of three to eight cases missing for each of the following covariates: employment, depression and anxiety medication, partner status, current smoking status, diabetes, stroke and heart disease. Past research recommends imputing missing values rather than deleting cases to retain the full sample size and avoid loss of power (Schafer & Green, 2002). Imputation is also recommended for cases that are missing at random (IBM, SPSS, 2011; Schafer & Green, 2002). Therefore imputation in the form of substituting the most common answer (yes/no) was implemented to deal with the current missing cases. The most common answer, i.e. “no”
was imputed for missing cases for depression and anxiety medication, smoking status, diabetes, stroke and heart disease, while the most common answer including “unemployed” was imputed for employment and “married/de facto” for partner status.

Further missing values analysis indicated 302, 128 and 64 missing cases for the covariates/demographics of physical activity, years of education and high blood pressure, respectively. Imputation using an Expectation Maximization (EM) method was implemented to deal with the missing data for physical activity, years of education and high blood pressure.

A Missing Values Analysis indicated that 9 to 12 cases were missing across each item of the BPHQ and GADS. The cases appeared missing at random, therefore imputation using EM methods was considered the appropriate method for dealing with these cases (IBM SPSS, 2011; Schafer, & Graham, 2002). Distribution of the variables was examined, which indicated a total of 4-17 cases as outliers for each BPHQ items and 7-15 cases as outliers for 6 items on the GADS (items 11-15 & 18). However, based on the robustness of the study’s large sample size, the cases were included in the present analyses.

As mentioned previously (see Chapter 3, General Method), a total of 314 cases were excluded for the analysis of progression to Any-MCD from wave 1 to 2, while 571 cases were excluded from the analysis of progression to Any-MCD from wave 2 to 3. Due to the necessity of including the outcome variable of Any-MCD and MCI for the specific research question under investigation, cases of missing outcome data were excluded from the analysis by implementing the case pairwise option.
Results

Description of Participants

A total of 1818 to 2144 participants were included in the current analyses (see Figures 2.2-2.5). Table 3.1 presents demographic and covariate information for participants belonging to a diagnostic category within each analysis (e.g. Wave 1 to 2 MCI model) across the three waves (e.g. healthy/healthy versus healthy/cognitive disorder). Figures 3.1-3.6 show the differences in the prevalence of depressive symptoms (GADS & BPHQ) between the diagnostic groups (e.g. healthy/healthy and healthy/cognitive disorder) across the waves (e.g. wave 1 to 2 and wave 2 to 3). Participants in the diagnostic groups healthy/MCI and healthy/Any-MCD from waves 2 to 3 did not endorse any of the nine BPHQ items at baseline, therefore a comparison between diagnostic groups (e.g. healthy/healthy and healthy/cognitive disorder) was not included for BPHQ items from wave 2 to 3 for the MCI and Any-MCD model.
Table 3.1

Demographics and Partner Status for Diagnostic Categories across the Waves

<table>
<thead>
<tr>
<th>Wave 1 to 2</th>
<th>Gender</th>
<th>Age</th>
<th>Years of education</th>
<th>Partner Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F/M</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>Yes/No</td>
</tr>
<tr>
<td><strong>MCI model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>1020/1056</td>
<td>62.53(.03)</td>
<td>14.10(.60)</td>
<td>1636/440</td>
</tr>
<tr>
<td>Healthy/MCI</td>
<td>7/10</td>
<td>61.76(.37)</td>
<td>12.76(.62)</td>
<td>14/3</td>
</tr>
<tr>
<td><strong>Any-MCD model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>1020/1056</td>
<td>62.53(.03)</td>
<td>14.10(.06)</td>
<td>1636/440</td>
</tr>
<tr>
<td>Healthy/Any-MCD</td>
<td>30/38</td>
<td>62.44(.19)</td>
<td>12.99(.27)</td>
<td>62/6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wave 2 to 3</th>
<th>Gender</th>
<th>Age</th>
<th>Years of education</th>
<th>Partner Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F/M</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>Yes/No</td>
</tr>
<tr>
<td><strong>MCI model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>881/916</td>
<td>62.51(.04)</td>
<td>14.22(.06)</td>
<td>1421/376</td>
</tr>
<tr>
<td>Healthy/MCI</td>
<td>8/13</td>
<td>62.57(.36)</td>
<td>12.81(.71)</td>
<td>21/0</td>
</tr>
<tr>
<td><strong>Any-MCD model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>881/916</td>
<td>62.51(.04)</td>
<td>14.22(.06)</td>
<td>1421/376</td>
</tr>
<tr>
<td>Healthy/Any-MCD</td>
<td>13/18</td>
<td>62.53(.31)</td>
<td>13.03(.57)</td>
<td>30/0</td>
</tr>
</tbody>
</table>

Note. MCI = Mild Cognitive Impairment; Any-MCD = Any Mild Cognitive Disorder; Partner status Yes = married, partnered or defacto and No = separated, divorced, widowed or never married.
**Figure 3.1.** Percentage of Sample Endorsing Depressive Items on the GADS for Wave 1 to 2 in the MCI Model; Healthy/healthy $n = 2076$, Healthy/MCI $n = 17$

**Figure 3.2.** Percentage of Sample Endorsing Depressive Items on the GADS for Wave 1 to 2 in the Any-MCD Model; Healthy/healthy $n = 2076$, Healthy/Any-MCD $n = 68$
Figure 3.3. Percentage of Sample Endorsing Depressive Items on the GADS for Wave 2 to 3 in the MCI Model; Healthy/healthy $n = 1797$, Healthy/MCI $n = 21$

Figure 3.4. Percentage of Sample Endorsing Depressive Items on the GADS for Wave 2 to 3 in the Any-MCD Model; Healthy/healthy $n = 1797$, Healthy/Any-MCD $n = 30$
Figure 3.5. Percentage of Sample Endorsing Depressive Items on the BPHQ for Wave 1 to 2 in the MCI Model; Healthy/healthy $n = 2480$, Healthy/MCI $n = 34$

Figure 3.6. Percentage of Sample Endorsing Depressive Items on the BPHQ for Wave 1 to 2 in the Any-MCD Model; Healthy/healthy $n = 2079$, Healthy/Any-MCD $n = 68$
Overall depression scores were calculated from depressive items on the GADS & BPHQ recorded at baseline. See Table 3.2 for the overall scores for participants belonging to a diagnostic category (e.g. healthy/healthy and healthy/cognitive disorder) within each analysis across the three waves (e.g. MCI model, Wave 1 to 2). A series of independent t-tests were performed, as part of descriptive statistics, to analyse the differences in overall depressive scores from BPHQ and GADS items between groups (e.g. healthy/healthy and healthy/cognitive disorder) within each analysis across waves 1 to 2 and 2 to 3 (see Table 4.2). The overall BPHQ depression score was not analysed between groups at wave 2 to 3 due to no participants in the healthy/MCI or healthy/Any-MCD groups endorsing “yes” on BPHQ items at baseline. There were significant differences between overall depressive GADS scores for the diagnostic groups in the MCI and Any-MCD model from wave 1 to 2, and from wave 2 to 3 \((p < .05)\). There were significant differences between overall BPHQ depression scores for the diagnostic groups in the MCI and Any-MCD models from wave 1 to 2 \((p < .001)\).
Table 3.2

Baseline Overall Depression Scores for GADS and BPHQ and T-tests Results Comparing Scores between Diagnostic Groups within the Models across Waves 1, 2 and 3

<table>
<thead>
<tr>
<th></th>
<th>Overall depression score on GADS(^a)</th>
<th>Overall Depression Score on BPHQ(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(M) ((SD))(^c)</td>
<td>(t)</td>
</tr>
<tr>
<td><strong>Wave 1 to 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI model(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>1.27 (1.53)</td>
<td>-2.59(^{\text{**}})</td>
</tr>
<tr>
<td>Healthy/MCI(^e)</td>
<td>2.24 (1.72)</td>
<td></td>
</tr>
<tr>
<td>Any-MCD(^b) model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>1.27 (1.53)</td>
<td>-5.65(^{\text{**}})</td>
</tr>
<tr>
<td>Healthy/Any-MCD(^f)</td>
<td>2.34 (1.71)</td>
<td></td>
</tr>
<tr>
<td><strong>Wave 2 to 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI model(^g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>1.37 (1.58)</td>
<td>2.43(^{\text{**}})</td>
</tr>
<tr>
<td>Healthy/MCI(^h)</td>
<td>0.52 (0.75)</td>
<td></td>
</tr>
<tr>
<td>Any-MCD(^i) model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>1.37 (1.58)</td>
<td>3.12(^{\text{**}})</td>
</tr>
<tr>
<td>Healthy/Any-MCD(^j)</td>
<td>0.47 (0.68)</td>
<td></td>
</tr>
</tbody>
</table>

*Note. \(p\) = two tailed

\(^a\)Overall GADS scores range 0-9
\(^b\)Overall BPHQ scores range 9-36
\(^c\)Results for \(t\), \(df\) and \(p\) values are the same as the healthy/healthy diagnostic category within each model comparing overall GADS depression scores
\(^d\)Sample size across both GADS and BPHQ scores was the same. Healthy/healthy = 2076 and healthy/MCI = 17
\(^e\)Sample size across both GADS and BPHQ scores was the same. Healthy/healthy = 2076 and healthy/Any-MCD = 68
\(^f\)Sample size for the GADS; Healthy/healthy = 1797 and healthy/MCI = 21
\(^g\)Sample size for the GADS; Healthy/healthy = 1797 and healthy/Any-MCD = 30
Goldberg Items and Progression to MCI from Wave 1 to 2

Table 3.3 presents the results for items of the GADS entered separately into the model as a predictor of progression to MCI at wave 2. Items 13 and 15 were excluded from the analysis due to participants in the healthy/MCI category not endorsing “yes” for these items (see Figure 4.1). Item 10 “lacking energy” and item 12 “lost confidence” were significant ($p < .05$). Items 11 “lost interest,” and 14 “difficulties concentrating” were significant ($p < .01$). Items 16 “waking early,” 17 “felt slowed up” and 18 “felt worse in the morning” were not significant ($p > .05$).

Table 3.3

<table>
<thead>
<tr>
<th>GADS Items</th>
<th>Model 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$B$</td>
<td>$SE$</td>
<td>$OR$</td>
<td>$95% CI$</td>
<td>$p$</td>
</tr>
<tr>
<td>10. Lacking energy</td>
<td>1.20</td>
<td>0.49</td>
<td>3.33</td>
<td>[1.28, 8.69]</td>
<td>.014</td>
</tr>
<tr>
<td>11. Lost interest</td>
<td>1.58**</td>
<td>0.58</td>
<td>4.84</td>
<td>[0.56, 1.07]</td>
<td>.006</td>
</tr>
<tr>
<td>12. Lost confidence</td>
<td>1.43*</td>
<td>0.64</td>
<td>4.19</td>
<td>[1.19, 14.82]</td>
<td>.026</td>
</tr>
<tr>
<td>13. Felt hopeless</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14. Difficulties concentrating</td>
<td>1.70**</td>
<td>0.50</td>
<td>5.48</td>
<td>[2.07, 14.54]</td>
<td>.001</td>
</tr>
<tr>
<td>15. Lost weight</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16. Waking early</td>
<td>-0.44</td>
<td>0.51</td>
<td>0.64</td>
<td>[0.24, 1.74]</td>
<td>.386</td>
</tr>
<tr>
<td>17. Felt slowed up</td>
<td>0.68</td>
<td>0.30</td>
<td>0.01</td>
<td>[0.73, 5.39]</td>
<td>.180</td>
</tr>
<tr>
<td>18. Felt worse in the morning</td>
<td>0.86</td>
<td>0.58</td>
<td>2.37</td>
<td>[0.77, 7.31]</td>
<td>.135</td>
</tr>
</tbody>
</table>

*Note.* $^* p < .05$, $^{**} p < .01$. 
Lacking energy

Item 10, which is representative of “have you been lacking energy” (OR = 3.33; 95% CI 1.28-8.69; \( p = .014 \)) was a significant predictor of progression to MCI. This finding suggests that when participants answered “yes” for lacking energy, the odds of progressing to MCI increase by a factor of 3.33. In the second model, Item 10 was non-significant when controlling for gender and age \((p > .05)\). Gender and education were also non-significant \((p > .05)\).

Lost interest

Item 11, which is representative of “have you lost interest in things” (OR = 4.84; 95% CI 0.56-1.07; \( p = .006 \)), was a significant predictor of progression to MCI. This result indicates that when participants endorsed “yes” for losing interest the odds of progressing to MCI at wave 2 increase by a factor of 4.84. When adjusting for education and gender in the second model, item 11 was non-significant \((p > .05)\). Gender and education were also non-significant \((p > .05)\).

Lost confidence

Item 12, which is representative of “have you lost confidence in yourself” (OR = 4.19; 95% CI 1.19-14.82; \( p = .026 \)), was a significant predictor of progression to MCI. This result indicates that when a participant endorsed “yes” for losing energy the odds of progressing to MCI at wave 2 increased by a factor of 4.19. When adjusting for gender and education in Model 2, item 12 did not remain significant \((p > .05)\). Gender and education were also non-significant \((p > .05)\).

Difficulties concentrating

Item 14, which is representative of “have you had difficulty concentrating” (OR = 5.48; 95% CI 2.07-14.54; \( p = .001 \)), was a significant predictor of progression to MCI. This finding suggests that when participants answered “yes” for having difficulties concentrating,
the odds of progressing to MCI increase by a factor of 5.48. In the second model, item 14 was non-significant \((p > .05)\) when controlling for gender and education, which were also non-significant \((p > .05)\).

**Goldberg Items and Progression to Any-MCD from Wave 1 to 2**

Table 3.4 presents the results for items of the GADS entered separately into the model as predictors of progression to Any-MCD from wave 1 to 2. Item 15 was excluded from the analyses due to participants in the healthy/Any-MCD group not endorsing “yes” to this item at baseline. Items 13 “felt hopeless” and 16 “waking early” were non-significant \((p > .05)\). Item 10 “lacking energy,” item 11 “lost interest,” item 14 “difficulties concentrating” and item 17 “felt slowed up” were significant predictors of progression to MCI \((p < .001)\). Item 12 “lost confidence” and item 18 “felt worse in the morning” were also significant predictors of progression to MCI \((p < .01)\).
**Table 3.4**

*GADS Items as Predictors of Progression to Any-MCD from Wave 1 to 2*

<table>
<thead>
<tr>
<th>GADS Items</th>
<th>Model 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>10. Lacking energy</td>
<td>1.50*</td>
</tr>
<tr>
<td>11. Lost interest</td>
<td>1.41**</td>
</tr>
<tr>
<td>12. Lost confidence</td>
<td>1.22*</td>
</tr>
<tr>
<td>13. Felt hopeless</td>
<td>0.28</td>
</tr>
<tr>
<td>14. Difficulties concentrating</td>
<td>1.18**</td>
</tr>
<tr>
<td>15. Lost weight</td>
<td>-</td>
</tr>
<tr>
<td>16. Waking early</td>
<td>-0.13</td>
</tr>
<tr>
<td>17. Felt slowed up</td>
<td>1.05**</td>
</tr>
<tr>
<td>18. Felt worse in the morning</td>
<td>0.86*</td>
</tr>
</tbody>
</table>

*Note.* **p < .001. *p < .01.

**Lacking energy**

Item 10, which is representative of “have you been lacking in energy” (OR = 4.48; 95% CI 2.75-7.30; p = .000), was a significant predictor of progression to Any-MCD. This finding indicates that when participants endorsed lacking energy, the odds of progressing to Any-MCD at wave 2 increase by a factor of 1.50. In the second model, item 10 (OR = 4.68; 95% CI 2.86-7.65; p < .001) remained a significant predictor of for progression to Any-MCD, while controlling for education and gender. Within this model, gender was significant (OR = 1.91; CI 1.13-3.19; p = .014), suggesting the odds of males progressing to Any-MCD increase by a factor of 1.91. Education was non-significant (p > .05) and there were no significant interaction effects for gender and item 10 (p > .05).
In model 3, item 10 was significant (OR = 4.58; 95% CI 2.73-7.65; p = <.001) when adjusting for all other covariates including: employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease. The finding suggests that when participants reported “yes” for lacking energy the odds of progressing to Any-MCD increase by a factor of 4.58, when adjusting for other variables in the model. In the model, partner status (OR = 3.01; 95% CI 1.28-7.07; p = .012) was a significant predictor of Any-MCD at wave 2. This finding suggests that when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by a factor of 3.01. Item 10 (OR = 4.70; 95% CI 2.88-7.68; p = <.001) and partner status (OR = 3.13; 95% CI 1.34-7.33; p = .008) remained significant predictors of Any-MCD when all non-significant covariates were removed from the model including: employment, physical activity, anxiety and depression medication, smoking, high blood pressure, diabetes, stroke and heart disease.

Lost interest

Item 11, which is representative of “have you lost interest in things” (OR = 4.08; 95% CI 2.21-7.55; p < .001), was a significant predictor of progression to Any-MCD. This finding indicates that when participants endorsed losing interest, the odds of progressing to Any-MCD at wave 2 increase by a factor of 4.08. In the second model, item 11 (OR = 3.91; 95% CI 2.11-7.26; p < .001) remained significant when adjusting for gender and age. In the model, gender and education (p > .05) were non-significant.

In model 3, item 11 was significant (OR = 4.71; 95% CI 2.45-9.06; p <.001) when adjusting for all other covariates including: employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease. The finding suggests that when participants reported “yes” for losing interest in things the odds of progressing to Any-MCD increase by a factor of 4.71, when adjusting for
other variables in the model. In the model, partner status (OR = 3.17; 95% CI 1.34-7.51; \( p = .009 \)) was a significant predictor of Any-MCD at wave 2. This finding suggests that when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by a factor of 3.17. Item 11 (OR = 4.72; 95% CI 2.53-8.82; \( p < .001 \)) and partner status (OR = 3.28; 95% CI 1.39-7.70; \( p = .007 \)) remained significant predictors of Any-MCD when all non-significant covariates were removed from the model including: employment, physical activity, anxiety and depression medication, smoking, high blood pressure, diabetes, stroke and heart disease.

**Lost confidence**

Item 12, which is representative of “have you lost confidence in yourself” (OR = 3.37, 95% CI 1.67-6.79; \( p = .001 \)), was a significant predictor of progression to Any-MCD. This finding indicates that when participants endorsed losing confidence the odds of progressing to Any-MCD at wave 2 increase by a factor of 3.37. In the second model, item 12 remained significant (OR = 3.45; 95% CI 1.71-6.99; \( p = .001 \)) when adjusting for gender and education. Within the model, gender was significant (OR = 1.75; 95% CI 1.05-2.03; \( p = .031 \)) suggesting that for males the odds of progressing to Any-MCD increase by a factor of 1.75. Education was non-significant (\( p > .05 \)) and there were no significant interaction effects for gender and item 12 (\( p > .05 \)).

In model 3, item 12 was significant (OR = 3.33; 95% CI 1.59-6.98; \( p = .001 \)) when adjusting for all other covariates including: employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease. The finding suggests that when participants reported “yes” for losing confidence the odds of progressing to Any-MCD increase by a factor of 3.33, when adjusting for other variables in the model. In the model, partner status (OR = 2.91; 95% CI 1.24-6.84; \( p = .014 \)) was a significant predictor of Any-MCD at wave 2. This finding suggests that when
participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by a factor of 2.91.

**Difficulties concentrating**

Item 14, which is representative of “have you had difficulty concentrating” (OR = 3.26; 95% CI 1.90-5.60; p < .001), was a significant predictor of progression to Any-MCD. This finding indicates that when participants endorsed difficulties with concentration the odds of progressing to Any-MCD at wave 2 increase by a factor of 3.26. In the second model, item 14 remained significant (OR = 3.23; 95% CI 1.03-2.86; p < .001) when adjusting for gender and education. Within the model, gender was significant (OR = 1.72; 95% CI 1.03-2.86; p = .038) suggesting the odds of males progressing to Any-MCD increase by a factor of 1.72. Education was non-significant (p > .05) and there were no significant interaction effects for gender and item 14 (p > .05).

In model 3, item 14 was significant (OR = 3.20; 95% CI 1.82-5.63; p < .001) when adjusting for all other covariates including: employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease. The finding suggests that when participants reported “yes” for difficulties concentrating the odds of progressing to Any-MCD increase by a factor of 3.20, when adjusting for other variables in the model. In the model, partner status (OR = 2.82; 95% CI 1.20-6.61; p = .017) was a significant predictor of Any-MCD at wave 2. This finding suggests that when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by a factor of 1.20.

**Felt slowed up**

Item 17, which is representative of “have you felt slowed up” (OR = 2.87; 95% CI 1.76-4.68; p < .001), was a significant predictor of progression to Any-MCD. This finding indicates that when participants endorsed feeling slower the odds of progressing to Any-
MCD at wave 2 increase by a factor of 2.87. In the second model, item 17 (OR = 2.85; 95% CI 1.74-4.66; \( p < .001 \)) remained a significant predictor of progression to Any-MCD, while controlling for gender and education. Within the model, gender (OR = .171; 95% CI 1.03-2.84; \( p = .039 \)) was significant, suggesting the odds of males progressing to Any-MCD increase by a factor of 1.71. Education was non-significant (\( p > .05 \)) and there were no significant interaction effects for gender and item 17 (\( p > .05 \)).

In model 3, item 17 was significant (OR = 2.78; 95% CI 1.67-4.62; \( p = .000 \)) when adjusting for all other covariates including: employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease. The finding suggests that when participants reported “yes” for feeling slower the odds of progressing to Any-MCD increase by a factor of 2.78, when adjusting for other variables in the model. In the model, partner status (OR = 2.86; 95% CI 1.22-6.73; \( p = .016 \)) was a significant predictor of Any-MCD at wave 2. This finding suggests that when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by a factor of 2.86.

**Felt worse in the morning**

Item 18, which is representative of “have you tended to feel worse in the mornings” (OR = 2.37; 95% CI 1.33-4.21; \( p = .003 \)), was a significant predictor of progression to Any-MCD. The results indicate that when participants endorsed feeling worse in the morning the odds of progressing to Any-MCD at wave 2 increase by a factor of 2.37. In the second model, item 18 (OR = 2.43; 95% CI 1.36-4.35; \( p = .003 \)) remained a significant predictor of progression to Any-MCD, while adjusting for gender and education. In the model, gender (OR = 1.77; 95% CI 1.06-2.94; \( p = .029 \)) was significant, suggesting the odds of males progressing to Any-MCD increase by 1.77. Education was non-significant (\( p > .05 \)) and there were no significant interaction effects for gender and item 18 (\( p > .05 \)).
In model 3, item 18 was significant (OR = 2.47; 95% CI 1.36-4.48; p = .003) when adjusting for all other covariates including: employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease. The finding suggests that when participants reported “yes” for feeling worse in the morning the odds of progressing to Any-MCD increase by a factor of 2.47, when adjusting for other variables in the model. In the model, partner status (OR = 2.86; 95% CI 1.22-6.71; p = .016) was a significant predictor of Any-MCD at wave 2. This finding suggests that when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by a factor of 2.86.
Goldberg Items and Progression to MCI from Wave 2 to 3

Table 3.5 presents the results for items of the GADS entered separately into the model as predictors of progression to MCI at wave 3. All items were non-significant ($p > .05$). Items 11-13 and 15 were excluded from the analyses due to participants in the healthy/MCI group not endorsing “yes” on the specific items at baseline.

Table 3.5

<table>
<thead>
<tr>
<th>GAD Items</th>
<th>Model 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$B$</td>
</tr>
<tr>
<td>10. Lacking energy</td>
<td>-1.85</td>
</tr>
<tr>
<td>11. Lost interest</td>
<td>-</td>
</tr>
<tr>
<td>12. Lost confidence</td>
<td>-</td>
</tr>
<tr>
<td>13. Felt hopeless</td>
<td>-</td>
</tr>
<tr>
<td>14. Difficulties</td>
<td>1.05</td>
</tr>
<tr>
<td>concentrating</td>
<td></td>
</tr>
<tr>
<td>15. Lost weight</td>
<td>-</td>
</tr>
<tr>
<td>16. Waking early</td>
<td>0.21</td>
</tr>
<tr>
<td>17. Felt slowed up</td>
<td>-1.83</td>
</tr>
<tr>
<td>18. Felt worse in the</td>
<td>-1.06</td>
</tr>
<tr>
<td>morning</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* $^{**}p < .01.$
Goldberg Items and Progression to Any-MCD from wave 2 to 3

Table 3.6 presents the results for each item of the GADS entered separately into the model as a predictor of progression to Any-MCD at wave 3. Items 11-13 and 15 were excluded from the analyses due to participants in the healthy/Any-MCD not endorsing “yes” on the specific items at baseline. Items 14, 16 and 18 were non-significant (p > .05). Item 10 “lacking energy” and item 17 “felt slowed up” were significant (see Table 3.6). However the findings suggest when participants endorsed “yes” to lacking energy, the odds of progressing to Any-MCD decrease by a factor of 0.02 (OR = 0.02; CI 95% 0.02-0.03; p = < .001). While other results suggest that when participants endorsed “yes” to felt slowed up the odds of progressing to Any-MCD decrease by a factor of 0.23 (OR = 4.35; CI 95% 0.05-0.97; p = .045).

Table 3.6

GADS Items as Predictors of Progression to Any-MCD from Wave 2 to 3

<table>
<thead>
<tr>
<th>GAD Items</th>
<th>Model 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Lacking energy **</td>
<td>-2.19</td>
</tr>
<tr>
<td>Lost interest</td>
<td>-</td>
</tr>
<tr>
<td>Lost confidence</td>
<td>-</td>
</tr>
<tr>
<td>Felt hopeless</td>
<td>-</td>
</tr>
<tr>
<td>Difficulties concentrating</td>
<td>-1.42</td>
</tr>
<tr>
<td>Lost weight</td>
<td>-</td>
</tr>
<tr>
<td>Waking early</td>
<td>-0.73</td>
</tr>
<tr>
<td>Felt slowed up</td>
<td>-1.47</td>
</tr>
<tr>
<td>Felt worse in the morning</td>
<td>-1.43</td>
</tr>
</tbody>
</table>

Note. *p < .05. **p < .001.
Overall Depression Score on the GADS as a Predictor of Progression to MCI and Any-MCD

Overall depression score from the GADS was entered as a predictor of progression to MCI and MCD across the waves in separate models. Overall depression score (OR 1.33; 95% CI 1.06-0.12; p = .012) was a significant predictor of progression to MCI at wave 2. This finding suggests that, for every one point increase on overall depressive score, the odds of progressing to MCI increase by a factor of 1.33. Overall depression score (OR = 1.37; 95% CI 1.22-1.53; p = <.001) was a significant predictor of progression to Any-MCD at wave 2. This result indicates that, for every one point increase on overall depressive score, the odds of progressing to Any-MCD increase by a factor of 1.19. Overall depressive score was significant for Any-MCD (OR = .48; 95% CI 0.29-0.77; p = .003) at wave 3, however the results suggest that for every one point decrease on overall depressive score, the odds of progressing to Any-MCD increase by a factor of .48. Overall depression score was not significant for predicting MCI at wave 3 (p > .05).
BPHQ Items as Predictors of Progression to MCI across Waves 1 to 2 and Waves 2 to 3

As mentioned previously, the participants in the healthy/MCI group at wave 2 to 3 did not endorse “yes” for 9 of the BPHQ items at baseline therefore an analyses for this specific time point was unable to be completed. Table 3.7 presents the results for items of the BPHQ entered separately into the model as predictors of progression to MCI at wave 2. Items A. “little interest or pleasure,” B. “feeling down depressed or hopeless,” D. “feeling tired or having little energy,” F. “feeling bad about yourself” and G. “Trouble concentrating” were all significant predictors of progression to MCI at wave 2 (p < .001). All other items were non-significant (p > .05).

Table 3.7

| BPHQ Items as Predictors of Progression to MCI from Wave 1 to 2 |
|-----------------|-------|-------|-------|-------|
| BPHQ Items      | Model 1 |       |       |       |
|                 |       |       |       |       |
| a. Little interest/pleasure | 1.49 | 0.51 | 4.44 | [1.63, 12.13] | .004 |
| b. Felt down, depressed or hopeless | 1.98** | 0.35 | 7.23 | [2.76, 18.86] | < .001 |
| c. Trouble falling/staying asleep or sleeping too much | 0.31 | 0.50 | 1.37 | [0.52, 3.61] | .528 |
| d. Felt tired/little energy | 2.39* | 0.75 | 10.95 | [2.50, 48.00] | .002 |
| e. Poor appetite or overeating | 0.79 | 0.64 | 2.20 | [0.63, 7.74] | .218 |
| f. Feeling bad about self | 1.77* | 0.51 | 5.85 | [2.14, 16.01] | .001 |
| g. Trouble concentrating | 2.05** | 0.49 | 7.78 | [2.97, 20.36] | < .001 |
| h. Moving/speaking slowly or being fidgety/restless | 1.42 | 0.76 | 4.13 | [0.92, 18.41] | .063 |
| i. Thoughts you would be better off dead or hurting self | 1.52 | 1.05 | 4.57 | [0.59, 35.67] | .147 |

Note. *p < .01, **p < .001.
**Little interest or pleasure**

Item A, which is representative of “little interest or pleasure in doing things” (OR = 4.44, 95% CI 1.63-12.13, p = .004), was a significant predictor of progression to MCI at wave 2. This finding indicates that when participants endorsed “yes” to experiencing little interest or pleasure in doing things the odds of progressing to MCI at wave 2 increase by a factor of 4.44.

In the second model, item A (OR = 4.42, 95% CI 1.62-12.08, p < .001) remained a significant predictor for progression to MCI, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to MCI at wave 2 increase by a factor of 4.42, while controlling for other factors in the model. Within the model gender and education were non-significant (p > .05).

In model 3, item A remained significant (OR = 4.36, 95% CI 1.54-12.36, p = .006) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for little interest or pleasure in doing things, the odds of progressing to MCI increase by a factor of 4.36, while adjusting for other variables in the model. All covariates were non-significant (p > .05).

**Feeling down, depressed or hopeless**

Item B, which is representative of “feeling down, depressed or hopeless” (OR = 7.23, 95% CI 2.76-18.86, p < .001), was a significant predictor of progression to MCI at wave 2. This finding indicates that when participants endorsed “yes” to feeling down, depressed or hopeless, the odds of progressing to MCI at wave 2 increase by a factor of 7.23.

In the second model, item A (OR = 7.23, 95% CI 2.77-18.92, p < .001) remained a significant predictor for progression to MCI, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing
to MCI at wave 2 increase by a factor of 7.23, while controlling for other factors in the model. Within the model gender and education were non-significant ($p > .05$).

In model 3, item A. remained significant (OR = 7.32, 95% CI 2.71-19.84, $p < .001$) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for feeling down, depressed or hopeless, the odds of progressing to MCI increase by a factor of 7.32, while adjusting for other variables in the model. All covariates were non-significant ($p > .05$).

**Feeling tired or having little energy**

Item D, which is representative of “feeling tired or having little energy” (OR = 10.95, 95% CI 2.50-48.00, $p = .002$), was a significant predictor of progression to MCI at wave 2. This finding indicates that when participants endorsed “yes” to feeling tired or having little energy the odds of progressing to MCI at wave 2 increase by a factor of 10.95.

In the second model, item D (OR = 11.08, 95% CI 2.52-48.63, $p = .001$) remained a significant predictor for progression to MCI, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to MCI at wave 2 increase by a factor of 11.08, while controlling for other factors in the model. Within the model gender and education were non-significant ($p > .05$).

In model 3, item D. remained significant (OR = 10.78, 95% CI 2.43-47.86, $p = .002$) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for feeling tired or having little energy, the odds of progressing to MCI increase by a factor of 10.78, while adjusting for other variables in the model. All covariates were non-significant ($p > .05$).
**Feeling bad about yourself**

Item F, which is representative of “feeling bad about yourself – or that you are a failure or have let yourself or family down” (OR = 5.85, 95% CI 2.14-16.01, p = .001), was a significant predictor of progression to MCI at wave 2. This finding indicates that when participants endorsed “yes” to feeling bad about yourself – or that you are a failure or have let yourself or family down the odds of progressing to MCI at wave 2 increase by a factor of 5.85.

In the second model, item F (OR = 5.83, 95% CI 2.13-15.97, p = .001) remained a significant predictor for progression to MCI, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to MCI at wave 2 increase by a factor of 5.83, while controlling for other factors in the model. Within the model gender and education were non-significant (p > .05).

In model 3, item F, remained significant (OR = 5.69, 95% CI 1.97-16.42, p = .001) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for “feeling bad about yourself or that you are a failure or have let yourself or family down,” the odds of progressing to MCI increase by a factor of 5.69, while adjusting for other variables in the model. All covariates were non-significant (p > .05).

**Trouble concentrating**

Item G, which is representative of “Trouble concentrating on things, such as reading the newspaper or watching television” (OR = 7.78, 95% CI 2.97-20.36, p < .001), was a significant predictor of progression to MCI at wave 2. This finding indicates that when participants endorsed “yes” to trouble concentrating on things, such as reading the newspaper or watching television the odds of progressing to MCI at wave 2 increase by a factor of 7.78.
In the second model, item G (OR = 7.73, 95% CI 2.94-20.33, p < .001) remained a significant predictor for progression to MCI, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to MCI at wave 2 increase by a factor of 7.73, while controlling for other factors in the model. Within the model gender and education were non-significant (p > .05).

In model 3, item G remained significant (OR = 7.21, 95% CI 2.64-19.66, p = < .001) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for trouble concentrating on things, such as reading the newspaper or watching television, the odds of progressing to MCI increase by a factor of 7.21, while adjusting for other variables in the model. All covariates were non-significant (p > .05).

**BPHQ Items as Predictors of Progression to Any-MCD across Waves 1 to 2 and Waves 2 to 3**

Similarly, participants in the healthy/Any-MCD group from wave 2 to 3 did not endorse “yes” for the 9 BPHQ items therefore analyses was unable to be performed for the specific time point. Table 3.8 presents the results for items of the BPHQ entered separately into the model as predictors of progression to Any-MCD at wave 2. Items A. “little interest or pleasure,” B. “feeling down depressed or hopeless,” D. “feeling tired or having little energy,” E. “poor appetite or overeating,” F. “feeling bad about yourself” and G. “Trouble concentrating” were all significant predictors of progression to Any-MCD at wave 2 (p < .01). All other items were non-significant (p > .05).
**Table 3.8**

*BPHQ Items as Predictors of Progression to Any-MCD from Wave 1 to 2*

<table>
<thead>
<tr>
<th>BPHQ Items</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Little interest/pleasure</td>
<td>3.28**</td>
<td>0.29</td>
<td>26.47</td>
<td>[14.87, 47.14]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>b. Felt down, depressed or hopeless</td>
<td>2.28**</td>
<td>0.26</td>
<td>9.74</td>
<td>[5.90, 16.08]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>c. Trouble falling/staying asleep or sleeping too much</td>
<td>0.13</td>
<td>0.26</td>
<td>1.14</td>
<td>[0.69, 1.87]</td>
<td>.619</td>
</tr>
<tr>
<td>d. Felt tired/little energy</td>
<td>2.39**</td>
<td>0.38</td>
<td>10.95</td>
<td>[5.21, 23.01]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>e. Poor appetite or overeating</td>
<td>0.98*</td>
<td>0.31</td>
<td>2.67</td>
<td>[1.45, 4.89]</td>
<td>.002</td>
</tr>
<tr>
<td>f. Feeling bad about self</td>
<td>1.27**</td>
<td>0.29</td>
<td>3.58</td>
<td>[2.02, 6.32]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>g. Trouble concentrating</td>
<td>1.36**</td>
<td>0.27</td>
<td>3.91</td>
<td>[2.29, 6.66]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>h. Moving/speaking slowly or being fidgety/restless</td>
<td>0.36</td>
<td>0.60</td>
<td>1.43</td>
<td>[0.44, 4.66]</td>
<td>.555</td>
</tr>
<tr>
<td>i. Thoughts you would be better off dead or hurting self</td>
<td>0.80</td>
<td>0.74</td>
<td>2.22</td>
<td>[0.52, 9.50]</td>
<td>.284</td>
</tr>
</tbody>
</table>

*Note.* *p* < .01, **p** < .001.

**Little interest or pleasure**

Item A, which is representative of “little interest or pleasure in doing things” (OR = 26.47, 95% CI 14.87-47.14, *p* < .001), was a significant predictor of progression to Any-MCD at wave 2. This finding indicates that when participants endorsed “yes” to experiencing little interest or pleasure in doing things, the odds of progressing to Any-MCD at wave 2 increase by a factor of 26.47.
In the second model, item A (OR = 26.66, 95% CI 14.94-47.58, \( p < .001 \)) remained a significant predictor for progression to Any-MCD, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to Any-MCD at wave 2 increase by a factor of 26.66, while controlling for other factors in the model. In the model gender was significant (OR =1.77; 95% CI 1.04-3.04; \( p = .036 \)) which suggests the odds of males progressing to Any-MCD increase by 1.77. There were no significant interaction effects for gender and item A \( (p > .05) \). Within the model education was non-significant \( (p > .05) \).

In model 3, item A remained significant (OR = 30.56, 95% CI 16.94-55.11, \( p < .001 \)) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for little interest or pleasure in doing things, the odds of progressing to Any-MCD increase by a factor of 30.56, while adjusting for other variables in the model. All covariates were non-significant \( (p > .05) \) except for partner status which was significant (OR = 3.45; 95% CI 1.41-8.44, \( p = .007 \)). This finding suggests when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by 3.45. There were no significant interaction effects for item A and partner status \( (p > .05) \).

**Feeling down, depressed or hopeless**

Item B, which is representative of “feeling down, depressed or hopeless” (OR = 9.74, 95% CI 5.90-16.08, \( p < .001 \)), was a significant predictor of progression to Any-MCD at wave 2. This finding indicates that when participants endorsed “yes” to feeling down, depressed or hopeless the odds of progressing to Any-MCD at wave 2 increase by a factor of 9.74.
In the second model, item B (OR = 9.88, 95% CI 5.97-16.35, \( p < .001 \)) remained a significant predictor for progression to Any-MCD, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to Any-MCD at wave 2 increase by a factor of 9.88, while controlling for other factors in the model. Within the model gender and education were non-significant (\( p > .05 \)).

In model 3, item B remained significant (OR = 10.59, 95% CI 6.32-17.75, \( p < .001 \)) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for feeling down, depressed or hopeless, the odds of progressing to Any-MCD increase by a factor of 10.59, while adjusting for other variables in the model. All covariates were non-significant (\( p > .05 \)) except for partner status which was significant (OR = 3.20; 95% CI 1.34-7.61, \( p = .009 \)). This finding suggests when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by 3.20. There were no significant interaction effects for item B and partner status (\( p > .05 \)).

**Feeling tired or having little energy**

Item D, which is representative of “feeling tired or having little energy” (OR = 10.95, 95% CI 5.21-23.01, \( p < .001 \)), was a significant predictor of progression to Any-MCD at wave 2. This finding indicates that when participants endorsed “yes” to feeling tired or having little energy the odds of progressing to MCI at wave 2 increase by a factor of 10.95.

In the second model, item D (OR = 11.37, 95% CI 5.41-23.95, \( p < .001 \)) remained a significant predictor for progression to Any-MCD, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to Any-MCD at wave 2 increase by a factor of 11.37, while controlling for
other factors in the model. Within the model gender and education were non-significant \((p > .05)\).

In model 3, item D remained significant \((OR = 11.15, 95\% \ CI 5.27-23.60, p < .001)\) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for feeling tired or having little energy, the odds of progressing to MCI increase by a factor of 11.15, while adjusting for other variables in the model. All covariates were non-significant \((p > .05)\) except for partner status which was significant \((OR = 3.02; 95\% \ CI 1.28-7.13, p = .012)\). This finding suggests when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by 3.02. There were no significant interaction effects for item D and partner status \((p > .05)\).

**Poor appetite or overeating**

Item E, which is representative of “poor appetite or overeating” \((OR = 2.67, 95\% \ CI 1.45-4.89, p = .002)\), was a significant predictor of progression to Any-MCD at wave 2. This finding indicates that when participants endorsed “yes” to poor appetite or overeating the odds of progressing to Any-MCD at wave 2 increase by a factor of 2.67.

In the second model, item E \((OR = 2.84, 95\% \ CI 1.54-5.24, p = .001)\) remained a significant predictor for progression to Any-MCD, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to Any-MCD at wave 2 increase by a factor of 2.84, while controlling for other factors in the model. In the model gender was significant \((OR =1.80; 95\% \ CI 1.08-3.01; p = .024)\) which suggests the odds of males progressing to Any-MCD increase by 1.80. There were no significant interaction effects for gender and item E \((p > .05)\). Within the model education was non-significant \((p > .05)\).
In model 3, item E, remained significant (OR = 2.71, 95% CI 1.44-5.08, p = .002) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for poor appetite or overeating, the odds of progressing to Any-MCD increase by a factor of 2.71, while adjusting for other variables in the model. All covariates were non-significant (p > .05) except for partner status which was significant (OR = 2.86; 95% CI 1.22-6.70, p = .016). This finding suggests when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by 2.86. There were no significant interaction effects for item E and partner status (p > .05).

**Feeling bad about yourself**

Item F, which is representative of “feeling bad about yourself –or that you are a failure or have let yourself or family down” (OR = 3.58, 95% CI 2.02-6.32, p < .001), was a significant predictor of progression to Any-MCD at wave 2. This finding indicates that when participants endorsed “yes” to feeling bad about yourself –or that you are a failure or have let yourself or family down the odds of progressing to Any-MCD at wave 2 increase by a factor of 3.58.

In the second model, item F (OR = 3.56, 95% CI 1.99-6.23, p < .001) remained a significant predictor for progression to Any-MCD, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to Any-MCD at wave 2 increase by a factor of 3.56, while controlling for other factors in the model. Within the model gender and education were non-significant (p > .05).

In model 3, item F, remained significant (OR = 3.81, 95% CI 2.11-6.87, p < .001), was a significant predictor of progression to Any-MCD at wave 2. This finding indicates that
when participants endorsed “yes” to “feeling bad about yourself –or that you are a failure or have let yourself or family down” the odds of progressing to Any-MCD at wave 2 increase by a factor of 3.81. All covariates were non-significant (p > .05) except for partner status which was significant (OR = 2.92; 95% CI 1.24-6.86, p = .014). This finding suggests when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by 2.92. There were no significant interaction effects for item F and partner status (p > .05)

Trouble Concentrating

Item G, which is representative of “trouble concentrating on thing, such as reading the newspaper or watching television” (OR = 3.91, 95% CI 2.29-6.66, p < .001), was a significant predictor of progression to Any-MCD at wave 2. This finding suggests that when participants endorsed “yes” to trouble concentrating on things, such as reading the newspaper or watching the television the odds of progressing to Any-MCD at wave 2 increase by a factor of 3.91.

In the second model, item G (OR = 3.86, 95% CI 2.26-6.60, p < .001) remained a significant predictor for progression to Any-MCD, while controlling for gender and education. This finding suggests that when participants answered “yes” on this item the odds of progressing to Any-MCD at wave 2 increase by a factor of 3.86, while controlling for other factors in the model. Within the model gender and education were non-significant (p > .05).

In model 3, item G, remained significant (OR = 3.91, 95% CI 2.25-6.81, p <.001) when adjusting for all other covariates (employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease). This finding suggests that when participants reported “yes” for trouble concentrating on things, such as reading the newspaper or watching television, the odds of
progressing to Any-MCD increase by a factor of 3.91, while adjusting for other variables in the model. All covariates were non-significant (p > .05) except for partner status which was significant (OR = 2.73; 95% CI 1.16-6.41, p = .021). This finding suggests when participants endorsed having a partner (married/defacto) the odds of progressing to Any-MCD increase by 2.73. There were no significant interaction effects for item G and partner status (p > .05).

**Overall BPHQ Depression Score as a Predictor of Progression to MCI and Any-MCD**

Overall depression score from the BPHQ was entered as a predictor of progression to MCI and MCD across the waves in separate models. Overall depression score were a significant predictor of progression to Any-MCD (OR =1.30, 95% CI 1.21-1.38, p < .001) and MCI (OR = 1.26, 95% CI 1.13-1.41, p < .001) across waves 1 to 2.

**Summary of Depressive Symptoms Predictive of Progression to MCI and Any-MCD**

Overall, the results indicate that specific depressive symptoms are predictive of progression to MCI or Any-MCD specifically from waves 1 to 2. Depressive symptoms from the GADS that were predictive of progression to a cognitive disorder included: lacking energy, lost interest, lost confidence, difficulties concentrating, felt slowed up, felt worse in the morning, while depressive symptoms from the BPHQ included: feeling little interest/pleasure, feeling down, depressed or hopeless, tired and little energy, poor appetite or overeating, feeling bad about self, and trouble concentrating. See Table 3.9 for a summary of the depressive symptoms and progression time points to MCI or Any-MCD.
Table 3.9

**Summary of Depressive Symptoms from the GADS and BPHQ which were Predictive of Progression to Any-MCD and MCI**

<table>
<thead>
<tr>
<th>GADS items</th>
<th>Wave progression</th>
<th>Progression to Any-MCD or MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lacking energy</strong>¹</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Lost interest</strong>¹</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Lost confidence</strong>¹</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Difficulties concentrating</strong>¹</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Felt slowed up</strong>¹</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Felt worse in the morning</strong>¹</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BPHQ items</th>
<th>Wave progression</th>
<th>Progression to Any-MCD or MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Little interest or pleasure in doing things</strong>¹²</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Feeling down, depressed or hopeless</strong>¹²</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Feeling tired or having little energy</strong>¹²</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Poor appetite or overeating</strong>¹</td>
<td>Waves 1-2</td>
<td>MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any-MCD</td>
</tr>
<tr>
<td><strong>Feeling bad about yourself</strong>¹²</td>
<td>Waves 1-2</td>
<td>MCI</td>
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<td>Any-MCD</td>
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<td><strong>Trouble concentrating</strong>¹²</td>
<td>Waves 1-2</td>
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<td>Any-MCD</td>
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¹ In the Any-MCD model the depressive symptoms remained significant when adjusting in Model 2 for gender and education and in Model 3 for all other covariates including employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease.

² In the MCI model the depressive symptoms remained significant when adjusting in Model 2 for gender and education and in Model 3 for all other covariates including employment, physical activity, anxiety and depression medication, partner status, smoking, high blood pressure, diabetes, stroke and heart disease.
Discussion

This study found that specific depressive symptoms were significant predictors of progression to MCI or Any-MCD across specific time points, with particular symptoms reaching significance across two depressive measures and when adjusting for demographics and covariates. The significant depressive symptoms included: lacking energy, lost interest, lost confidence, difficulties concentrating, felt slowed up, felt worse in the morning, little interest or pleasure in doing things, feeling down, depressed or hopeless, feeling tired or having little energy, poor appetite or overeating, and feeling bad about yourself. Depressive symptoms from the GADS (e.g. lacking energy, lost interest, lost confidence, difficulties concentrating, felt slowed up and felt worse in the morning) remained significant when analysing progression to Any-MCD from wave 1 to 2 and adjusting for demographics and other lifestyle, heart disease and medication covariates. However specific depressive symptoms from the GADS (e.g. lacking energy, lost interest, lost confidence and difficulties concentrating) did not remain significant when analysing progression to MCI from wave 1 to 2 and adjusting for covariates and lifestyle, heart disease and medication demographics. This finding suggests demographics and covariates may have an important role for mediating the relationship between depressive symptoms and progression to MCI which should be considered for future research. Demographics and covariates were also significant, specifically participants who were male or endorsed having a partner (e.g. defacto/married) had an increased odds of progressing to cognitive impairment. These findings are contrary to previous research which suggests there is no strong consensus on gender as a predictor of cognitive impairment (Peterson et al., 2014). However supports recent research indicating higher incidence rates of MCI in men (Roberts et al., 2012). Our findings also show that a higher number of men progressed to cognitive impairment. This outcome may be a result of women’s longevity and attrition within the sample, with the resulting number of male
participants affecting the current findings. Our research also suggested that participants who endorsed having a partner/defacto were more likely to progress to cognitive impairment which is dissimilar from past findings which suggest marriage is a protective factor against progression to cognitive impairment (Fratiglioni, & Wang, 2007). Similarly, there were higher numbers of participants who endorsed having a partner which may have impacted the current findings. Overall, further research is needed to understand the role of partner status and gender in predicting cognitive impairment.

Depressive symptoms from the BPHQ (e.g. little interest/pleasure in doing things, feeling down, depressed or hopeless, feeling tired or having little energy, poor appetite or overeating, feeling bad about yourself and trouble concentrating) remained significant when analysing progression to MCI and Any-MCD from wave 1 to 2 and adjusting for demographics and lifestyle, heart disease and medication covariates. Specific depressive symptoms were significant and cross validated between 2 depressive measures when analysing progression to MCI and Any-MCD from wave 1 to 2. Cross validation was evident for the GADS item “loss of interest” and the BPHQ item of “little interest/pleasure,” which were significant predictors of progression to Any-MCD and MCI at wave 2. The symptom of “trouble concentrating” on the BPHQ and “difficulties concentrating” on the GADS were significant predictors of Any-MCD and MCI at wave 2. While the GADS item “lacking energy” and BPHQ item “feeling tired or having little energy” were both significant predictors of cognitive impairment at wave 2.

Our finding of specific depressive symptoms as predictive of cognitive impairment (e.g. MCI or Any-MCD) is partially consistent with past hypotheses explaining the relationship between depression and dementia (Jorm, 2001). In particular, our finding of difficulties concentrating as predictive of progression to cognitive disorders may support the hypothesis that cognitive deficits associated with depression cumulate with those of dementia
to increase the threshold for developing a diagnosis (Jorm, 2001). Overall, this hypothesis may explain why participants who endorsed difficulties with concentration, when assessed for depression, were more likely to progress to a diagnosed cognitive disorder across waves. However our other results suggest that mood related depressive symptoms also predicted progression to cognitive disorders (e.g. lacking energy, lost interest, lost confidence, felt slowed up, felt worse in the morning, little interest or pleasure in doing things, feeling down, depressed or hopeless, feeling tired or having little energy, poor appetite or overeating, and feeling bad about yourself). This finding may support another hypothesis which suggests depression is associated with glucocorticoid hypersecretion, leading to neuronal death in the hippocampus that can result in memory deficits and dementia (Jorm, 2001) therefore the presence of specific depressive symptoms or a cluster of symptoms may result in neurological changes and cognitive impairment. Furthermore, our finding that a range of cognitive, emotional and behavioural depressive symptoms are endorsed at baseline and predictors of cognitive impairment may support Jack and colleagues (2010) model which states various neurological changes occur prior to cognitive impairment.

Overall, our findings partially confirm our hypothesis of specific depressive symptoms as predictors of progression to cognitive disorders. However, other hypothesised symptoms including psychomotor agitation, loss of weight and suicidal ideation did not significantly predict progression to a cognitive disorder. Other symptoms which we could not predict whether there would be a relationship with cognitive impairment based on limited past research, were significant (e.g. difficulties concentrating and increased appetite). However sleep difficulties was non-significant for predicting progression to Any-MCD or MCI at wave 2. Our findings that specific symptoms remained significant when adjusting for demographics and lifestyle, heart disease and medication covariates and/or were cross validated between 2 depressive measures suggests certain depressive symptoms were stronger
predictors than other symptoms which were non-significant or failed to remain significant across models when adjusting for demographics or covariates and between depressive measures. The following section will discuss these findings in relation to past research, the limitations and strengths of the current study and implications for the future research.

**Lacking energy and feeling tired and progression to MCI and Any-MCD from Wave 1 to 2**

The GADS item “have you been lacking energy” and the BPHQ item “feeling tired or little energy” significantly predicted progression to MCI and Any-MCD. When analysing progression to MCI, the GADS item, “have you been lacking energy” did not remain significant when adjusting for gender and education which suggests a strong effect of these two demographic factors. However when analysing progression to Any-MCD, the GADS item “have you been lacking energy” remained significant when adjusting for demographics and lifestyle, heart disease and medication covariates, suggesting this symptom was a strong predictor of cognitive impairment. Similarly, the BPHQ item “feeling tired or little energy” was significant when analysing progression to MCI and Any-MCD and remained significant when adjusting for demographics and lifestyle, heart disease and medication covariates, which suggests this symptom is a strong predictor of progression to cognitive impairment.

This symptom is represented in the DSM-V criterion for MDD as fatigue or loss of energy nearly every day (APA, 2013), while low positive affect is characterised by the presence of lethargy in conjunction with other feelings (Watson et al., 1988). Our findings of “lacking in energy” and “feeling tired or little energy” as significant predictors is consistent with past research indicating the depressive symptom of “loss of energy” was elevated 3 years prior to the incidence of AD (Berger et al., 1999). Our result extends on this past study by indicating that loss of energy/feeling tired is predictive of progression to Any-MCD in a baseline sample with no cognitive impairment. While our finding that this specific depressive
symptom was significant across 2 measures from wave 1 to 2 suggests a strong relationship between reduced energy and feeling tired and progression to cognitive impairment.

**Lost interest or pleasure in doing things and progression to MCI and Any-MCD from Wave 1 to 2**

The GADS item representative of “lost interest in things” and the BPHQ item “little interest or pleasure in doing things” were significant predictors of progression to MCI and Any-MCD. When analysing progression to MCI, the GADS item, “lost interest in things” did not remain significant when adjusting for gender and education which suggests a strong effect of these two demographic factors. However when analysing progression to Any-MCD the GADS item “lost interest in things” remained significant when adjusting for demographics and lifestyle, heart and disease and medication covariates, suggesting this symptom was a strong predictor of cognitive impairment. Similarly, the BPHQ item “little interest of pleasure in doing things” was a significant predictor of progression to MCI and Any-MCD and remained significant when adjusting for demographics and covariates, which suggests this symptom is a strong predictor of progression to cognitive impairment.

The GADS item “lost interest in things” and BPHQ item “little interest or pleasure in doing things” are representative of the depressive symptom “reduced pleasure or interest in activities” (APA, 2013). Past research suggests that positive affect encompasses a wide range of positive mood states (e.g. interest) which are directly related to the presentation of this symptom of depression (APA, 2013; Nutt et al., 2007). Furthermore, past research found that mood states associated with positive affect, for example “a loss of interest”, was an elevated symptom evident 3 years prior to a diagnosis of AD (Berger et al., 1999). Our result supports this past finding and demonstrates this symptom is a strong predictor of cognitive impairment as it remained significant when adjusting for demographics and covariates and was cross validated between two depressive measures at a specific time point.
Difficulties concentrating and progression to MCI and Any-MCD from Wave 1 to 2

The GADS item “have you had difficulty concentrating” and the BPHQ item “trouble concentrating on things, such as reading the newspaper or watching TV” were significant predictors of progression to MCI and Any-MCD. The GADS item did not remain significant when analysing progression to MCI while adjusting for demographics, suggesting a strong effect of these variables. The GADS item remained significant when analysing progression to Any-MCD and adjusting for demographics and lifestyle, heart disease and medication variables. The BPHQ item “trouble concentrating on things, such as reading the newspaper or watching TV” was a significant predictor of progression to MCI and Any-MCD and when adjusting for demographics, lifestyle and medication covariates.

The two items are part of the DSM-V MDD criterion of diminished ability to think or concentrate, or indecisiveness nearly every day (APA, 2013). The current finding that difficulties concentrating remained significant when adjusting for demographics and all other covariates and that the symptom was cross-validated and significant across two measures, suggests the strength of this symptom as a predictor of progression to cognitive impairment. However the GADS item did not remain a significant predictor of progression to MCI when adjusting for demographics which suggests gender and education have a strong effect.

The current finding extends on limited research investigating this depressive symptom as a predictor of cognitive impairment, with only one study showing that concentration was not a significant predictor of AD (Geelings et al., 2000). However it remains difficult to ascertain whether this symptom is specific to depression or merely prodromal to cognitive impairment. Our study addressed this inherent limitation by excluding baseline participants with cognitive impairment to investigate this symptom as an independent predictor of a cognitive disorder. Overall, our results highlight the necessity to consider this symptom as a
potential risk factor for cognitive disorders and the need for future studies to further investigate this potential relationship.

Lost Confidence, Depressed Mood, Psychomotor Slowing, Felt Worse in the Morning, and Poor Appetite or Overeating and Progression to MCI and Any-MCD from Wave 1 to 2

Lost confidence

The GADS item “have you lost confidence in yourself” was a significant predictor of progression to MCI and Any-MCD. The item did not remain a significant predictor of MCI when adjusting for demographics which suggests a strong effect of gender and education in mediating the relationship between loss of confidence and cognitive impairment. The item remained a significant predictor for Any-MCD when adjusting for demographics and lifestyle, heart disease and medication covariates which suggests this depressive symptom is a strong predictor of cognitive impairment.

The symptom of “lost confidence” is not specifically outlined in the criteria for MDD (APA, 2013). However past research shows that self-confidence is a positive mood state included within the construct of positive affect, a construct which is often impaired in individuals with depression (Nutt et al., 2007). This finding is consistent with past research suggesting that reduced positive affect is a marginal risk factor for dementia, which was endorsed through one of four depressive items on the CES-D including “I felt that I was just as good as other people” (Gatz et al., 2005). However our research identifies “loss confidence in yourself” as a separate symptom which predicted cognitive impairment. Furthermore it is important to consider that the symptom of loss of confidence reached significance concurrently with difficulties concentrating within the same time period (e.g. from wave 1 to 2 for MCI and Any-MCD). Endorsement of loss of confidence may be a consequence of experiencing difficulties concentrating and individuals becoming increasingly aware of this
symptom. However this consideration is beyond the scope of this discussion and should be considered for future research. Overall, the results suggest that loss of confidence is a strong predictor of progression to cognitive impairment, suggesting that it should be considered in future research.

**Depressed mood**

The BPHQ item “feeling down, depressed or hopeless,” was a significant predictor of progression to MCI and Any-MCD. This item did not remain a significant predictor of MCI when adjusting for demographics, supporting the strong effect of theses variables in moderating this relationship. However this item remained a significant predictor of Any-MCD when adjusting for lifestyle, heart disease and medication covariates, suggesting this symptom is a strong predictor of Any-MCD. This item is representative of the DSM-V criterion for MDD that a depressed mood is indicated through subjective reports of feeling sad, empty or hopeless (APA, 2013). Past findings have been limited to inducing a sad mood within participants to demonstrate the effect on performance across cognitive tasks (Chepnick et al., 2007; Knight et al., 2002). However our result extends previous findings by indicating subjective self-reports of depressive symptoms, specifically “feeling down, depressed or hopeless,” is associated with progression to cognitive impairment and subsequent diagnosis. Overall, additional research is required to replicate the current findings and investigate the association between depressed mood as a predictor of cognitive impairment.

**Psychomotor slowing**

The GADS item “have you felt slowed up” was a significant predictor of progression to Any-MCD and remained significant when adjusting for demographics and covariates, suggesting a strong relationship between this symptom and cognitive impairment. This item is representative of the depressive symptom psychomotor retardation (APA, 2013).
Overall, the evidence that psychomotor slowing is predictive of progression to cognitive disorders is consistent with one study which found that psychomotor slowing, representative though somatic and vegetative symptoms, increased the risk of dementia (Gatz et al., 2005). Our finding also supports past cognitive studies which suggest that cognitive functions impaired through psychomotor slowing including eye movement and motor reaction are necessary for normal cognitive function (Buyukdura et al., 2011; Liversedge & Findlay, 2000; Sobin & Sackeim, 1997). It is suggested that people who endorsed psychomotor slowing may have shown gradual impairment across cognitive functions (e.g. eye movement and motor reaction), leading to increased progression to a diagnosis of cognitive disorder.

Although the GADS item for psychomotor slowing reached significance, the BPHQ item which concurrently assesses psychomotor slowing and agitation (e.g. “moving or speaking so slowly that other people have noticed? Or the opposite –being so fidgety or restless that you have been moving around a lot more than usual”) was not a significant predictor for cognitive impairment. This finding suggests psychomotor slowing and agitation may need to be assessed as separate constructs for future research. The Hamilton Depression Rating Scale (HDRS) is one of the most widely implemented scales to assess depression severity (Williams, 2001). The 17 item scale is used to quantify information obtained from an interview (Hamilton, 1960). The scale consists of two items that assess psychomotor agitation and retardation as separate constructs (Hamilton, 1960). Future research would benefit from the inclusion of depressive measures, for example the HDRS to assess psychomotor agitation and slowing.

**Felt worse in the morning**

The GADS item “have you tended to feel worse in the morning” was a significant predictor of progression to Any-MCD and remained significant when adjusting for
demographics and covariates, supporting a strong relationship between this symptom and cognitive impairment. This item is representative of the criterion for MDD with melancholic features including that depression is regularly worse in the morning (APA, 2013). Previous research has been limited to investigating depressed mood, recurrent episodes of depressed mood (Aoki et al., 2011; Chepnick et al., 2007; Dotson et al., 2010; Knight et al., 2002; Mayberg et al., 1999; Mitchell & Phillips, 2007) and progression to cognitive impairment. To our knowledge there is minimal research that has found the diurnal pattern of mood as a predictor of cognitive impairment therefore our findings suggest this symptom may have an important role in predicting progression to cognitive impairment and needs to be investigated further in future research.

**Poor appetite or overeating**

The BPHQ item “poor appetite or overeating” was a significant predictor of Any-MCD and remained significant when adjusting for demographics and covariates, suggesting a strong relationship between the two variables. Increased or decreased appetite is a symptom representative of depression (APA, 2013). Our findings support past research suggesting a loss of appetite or weight predicts cognitive impairment and that higher adiposity predicts cognitive impairment (Fitzpatrick et al., 2009; Geerlings et al., 2000). Specifically, a loss of weight or higher adiposity may be associated with reduced or increased appetite, respectively. Our finding supports that appetite changes within the context of depression predicts progression to cognitive impairment. However, the GADS item “have you lost weight (due to poor appetite)” did not reach significance which leads to the question of whether participants who endorsed the BPHQ item were indicating overeating instead of poor appetite. It is suggested that alternate measures assessing increased and reduced appetite as separate constructs may further the limitations of the current findings. Other depressive measures may be useful to implement for future research, for example the Beck Depression Inventory II.
(BDI-II), which is a 21 item self-report measure including the separate assessment of decreased and increased appetite (Beck, Steer, & Brown, 1996).

**Non-significant Symptoms of Sleep Difficulties, Psychomotor Agitation, Suicidal Ideation and Loss of Weight and progression to MCI and Any-MCD from Wave 1 to 2**

Symptoms of sleep difficulties, psychomotor agitation, suicidal ideation, and loss of weight were not significant predictors of progression to MCI or Any-MCD. The finding that sleep difficulties did not reach significance is surprising, given that this symptom is a primary presenting concern for depression and is associated with cognitive performance (APA, 2013; Haimov et al., 2008; Mazzoni et al., 1999; Van Dogen et al., 2003). However our study found that, across two measures of depression, sleep difficulties did not predict progression to cognitive disorders.

Psychomotor agitation was not a significant predictor of progression to cognitive impairment which is inconsistent with past findings of this symptom significantly predicting AD (Geerlings et al., 2000). However out finding supports past research suggesting that psychomotor agitation and slowing are separate constructs (Sobin & Sackeim, 1997), particularly because psychomotor slowing was a significant predictor of cognitive impairment within the current study. Suicidal ideation was not a significant predictor of progression to cognitive impairment. This finding is consistent with the limited amount of previous findings supporting a relationship between the two variables with only one past study finding a relationship between suicidal ideation and cognitive impairment (Geerling et al., 2000). The symptom of weight loss due to poor appetite was not a significant predictor of cognitive impairment. This finding was inconsistent with previous research supporting a relationship between weight loss and dementia (Geerlings et al., 2000; Stewart et al., 2005) and our current finding that reduced/increased appetite was a significant predictor of progression to cognitive impairment which it is hypothesized would impact upon weight.
However, out data suggested that no participants in the healthy/MCI and healthy/Any-MCD groups endorsed “yes” for this symptom at baseline, which suggests this symptom may not be a predominant depressive symptom evident at baseline and/or that this symptom alone is not predictive of cognitive impairment. Overall, further research is needed to address whether weight loss is a predictor of progression to cognitive impairment.

**GADS Depressive Symptoms and Progression to MCI and Any-MCD from Wave 2 to 3**

GADS items including lacking energy, difficulties concentrating, waking early, felt slowed up and felt worse in the morning were not significant predictors of progression to MCI. The finding that “difficulties concentrating” was non-significant is inconsistent with our results that concentration issues predicted progression to MCI and Any-MCD from wave 1 to 2. However this result is consistent with one past study indicating concentration difficulties was a not a significant predictor of AD (Geerlings et al., 2000). Other symptoms of “lacking energy,” “waking early,” “felt slowed up” and “felt worse in the morning” were not significant. This finding was inconsistent with our previous results, specifically lacking energy, psychomotor slowing and felt worse in the morning, which were significant predictors of cognitive impairment from wave 1 to 2. Other items including “lost interest,” “lost confidence,” “felt hopeless,” and “lost weight” were excluded from the analyses due to participants in the healthy/MCI group not endorsing “yes” on these items at baseline. This outcome leads to questions including: are depressive symptoms evident 8 years prior to progression to cognitive impairment and do depressive symptoms change overtime therefore is it necessary to assess the trajectory of depressive symptoms in conjunction with progression to cognitive impairment across time and between closer time intervals? Overall, these questions suggest further research is needed to assess whether depressive symptoms at
baseline can predict progression to cognitive impairment at later time intervals, for example 8 years later.

The GADS items “lacking energy” and “felt slowed up” were significant from wave 2 to 3. However the results were intriguing suggesting that endorsing “yes” to these items decreased the likelihood of progressing to Any-MCD from wave 2 to 3. Overall these findings suggest further research is needed.

**Study Limitations and Strengths**

Type 1 error rates were not investigated within the current study. The decision to exclude type 1 error rates was on the basis that previous authors suggest controlling for this error effects the interpretation of result (Johnson et al., 2000; Ottenbacher, 1998; Rothman, 1990). A further limitation within the study was the inclusion of the BPHQ, which assessed symptoms concurrently within one item, for example psychomotor agitation and retardation. This resulted in difficulties ascertaining whether slowing or agitation, as distinct constructs, are predictive of progression to cognitive disorders. This issue may have been avoided with the implementation of an alternate depressive measure in conjunction with an interview, for example the HDRS (Hamilton, 1960). However it is important to note that the HDRS does not include part of the DSM-V MDD criterion for increase/decrease in appetite. Similarly, the BPHQ assessed increased and decreased appetite concurrently, making it difficult to disentangle the two symptoms. The BDI-II may have been useful to overcome this limitation, through the measurement’s separate assessment of increased and decreased appetite (Beck et al., 1996). However the BDI-II does not include the DSM-V MDD symptom of psychomotor slowing. Overall, a review of other depressive measures (e.g. HDRS and BDI-II) highlights the lack of consistency between DSM-V criteria for MDD and items on depressive assessments. This limitation suggests a need for the development of self-report measures of depression that represent the criteria for MDD, with each symptom assessed separately.
Another limitation included the implementation of the GADS, which assessed symptoms as “occurring recently” and does not reflect the DSM criteria for MDD, which outline symptoms that have been present in the past 2 weeks (APA, 2013). The GADS also excluded the symptom of weight gain; therefore it is not representative of all depressive symptoms. Furthermore, the BPHQ and GADS are measurements inherently associated with self-report bias. However, given the size of our sample, the implementation of the GADS and BPHQ was convenient and time effective. Another limitation is the exclusion from these depressive measures of DSM-V MDD symptoms, particularly of feeling excessive worthlessness and guilt, and reduced ability to think/indecisiveness, while other general study limitations include sample attrition and the exclusion of participants across the waves which may have resulted in sample bias.

An additional limitation was that participants in the healthy/cognitive impairment groups from wave 2 to 3 did not endorse “yes” on BPHQ items or specific GADS items at baseline therefore we were unable to complete an analysis of depressive symptoms as predictors of progression to cognitive impairment for this specific time point or compare results across two time intervals (e.g. from wave 1 to 2 and wave 2 to 3). This issue raises questions as to whether depressive symptoms assessed at baseline are able to predict progression at later time intervals and whether it would be beneficial to assess depressive symptoms as predictors of cognitive impairment within a closer time interval, for example assess depressive symptoms at wave 2 for progression of cognitive impairment from wave 2 to 3. Furthermore, depressive symptoms may change over time therefore it may be beneficial to reassess depressive symptoms not only at baseline but also wave 2. Overall, these issues should be considered for future research.

The strengths of this study included the implementation of two measurements of depression. This allowed for cross validation between results on one item/depressive
symptom across the BPHQ and GADS. Depressive symptoms/items (e.g. difficulties concentrating, lacking energy or feeling tired and lost interest or pleasure in doing things) that reached significance across the two measures suggest a stronger relationship of progression to cognitive disorders. This study also investigated progression to a range of cognitive disorders including MCI and Any-MCD, which extends previous research limited to investigating risk of AD (Geerlings et al., 2000). Other strengths of this general study include the large 60+ population-based community sample, high retention of the sample, a narrow age range that enables avoidance of cohort effects, a detailed assessment and clinical diagnosis of cognitive impairment, and the collection of data across three time points with eight years of follow-up.

These data suggest that specific depressive symptoms significantly predict progression to cognitive disorders from wave 1 to 2. Symptoms include: lacking energy/feeling tired, lost interest or pleasure in doing things, lost confidence, difficulties concentrating, psychomotor slowing, feeling worse in the morning, feeling down, depressed or hopeless, poor appetite/overeating and feeling bad about oneself. All of the BPHQ symptoms remained significant when adjusting for demographics and covariates when analysing progression to Any-MCD and MCI. While all of the BPHQ items remained significant when adjusting for demographics and covariates when analysing progression to Any-MCD, however did not remain significant when analysing progression to MCI. A total of 3 symptoms were cross validated between two measures at a specific time point (e.g. wave 1 to 2) and include: difficulties concentrating, lacking energy/feeling tired and loss of interest/pleasure in doing things. The finding of depressive symptoms that remained significant when adjusting for demographics and covariates and were cross validated between the GADS and BPHQ suggests a strong association for the following symptoms and
cognitive impairment: difficulties concentrating, lacking energy/feeling tired and loss of interest/pleasure in doing things.

**Future Research and Clinical Implications**

The present findings provide important considerations for future research within the field and to develop our understanding of the role of depression in cognitive impairment. The current research suggests specific baseline depressive symptoms are predictive of progression to cognitive disorders from wave 1 to 2. However further research is needed to investigate whether the effect of depressive symptoms on progression to cognitive differs between time points (i.e. 4 versus 8 years) and for distinct cognitive disorders. It will also be important to investigate why specific symptoms on the GADS “felt slowed up” and “felt worse in the morning” were only significant for progression to Any-MCD and not MCI from wave 1 to 2 and why specific GADS items (i.e. lacking energy, lost interest, lost confidence and difficulties concentrating) do not remain significant predictors of progression to cognitive impairment when adjusting for gender and education.

Other directions for future research include the implementation of alternate forms of depressive assessments at more than one time point. This would allow researchers to investigate the trajectory of identified depressive symptoms (e.g. stability) and resulting changes in diagnoses of cognitive disorders. Alternate self-report depression measures should be considered to ensure that all DSM-V MDD symptoms are assessed and as separate constructs. On the basis of past psychometrics discussed (BDI-II and HDRS), future research should look towards developing one depressive measure which assesses all depression symptoms and as separate constructs. Furthermore, other research should aim to include a two stage screening process which includes an initial depressive checklist/psychometric measure after which individuals who endorse symptoms are subject to a more thorough interview to assess specific depressive symptoms.
Additional research is needed prior to conclusions being drawn about the clinical implications of the current study. However further research could provide important clinical implications in the future including potentially monitoring of specific depressive symptoms for individuals and health professionals in individuals aged 60 years and over, and who are potentially at risk of developing a cognitive disorder. This could also lead to appropriate assessment and screening of depressive symptoms in the at risk population which may result in appropriate detection and referral for earlier prevention or delay of the onset of cognitive disorders. However, these clinical implications are preliminary and as previously mentioned more research is needed prior to establishing the clinical benefits.

In summary, the current research supports the role of specific depressive symptoms in cognitive impairment. Future research needs to investigate this relationship further, including alternate depressive measures at more than one time, analyzing the role of depressive symptoms as predictors across more than one time period and using a two stage-sampling design to assess depression. Additional research will increase our understanding of depressive symptoms as predictors of cognitive impairment and will contribute to knowledge within the field.
Chapter 4. Study Two: Affect and Prediction of Progression to Cognitive Disorders in a Population Based Sample Aged 60+
Chapter 1 outlined that a vast amount of research supports depression as a risk factor for the development of cognitive disorders. Positive and negative affect are important to consider in this research context, particularly because they are central to depressive disorders (APA, 2013; Nutt et al., 2007). Positive affect encompasses a wide range of positive feelings including attentive, interested, alert, excited, enthusiastic, inspired, proud, determined, strong and active (Watson et al., 1988). In contrast, negative affect represents various negative feelings including distressed, upset, hostile, irritable, scared, afraid, ashamed, guilty, nervous and jittery (Watson et al., 1988).

To our knowledge, a limited number of studies have investigated negative affect as a predictor of cognitive disorders, while few studies have specifically investigated positive affect as predictive of cognitive disorders. Generally, the objective of past studies has been to investigate the relationship between depression and the incidence/onset of AD or Dementia (Berger et al., 1999; Gatz et al., 2005). Therefore these studies have included a broad measure of depression with a minimal number of items assessing mood states representative of positive affect. A past study found that depression was a significant predictor for dementia and AD, using total cut off scores from the Centre for Epidemiological Studies Depression Scale (CES-D; Gatz et al., 2005). The CES-D is a self-report measure consisting of 20 items measuring depression and includes four items which are representative of positive affect (Radloff, 1977). Items representative of positive affect comprise: “I felt that I was just as good as other people”, “I felt hopeful about the future”, “I was happy”, and “I enjoyed life” (Radloff, 1977). Further results from this study suggest that a lack of positive affect was a marginal risk factor for dementia (Gatz et al., 2005). Another study found an elevation in depressive symptoms three years prior to a diagnosis of AD, with symptoms predominantly
being motivation related, for example, loss of energy and lack of interest (Berger et al., 1999). These symptoms are also representative of feelings encompassed within positive affect (Watson et al., 1988). Findings from this study were drawn from the implementation of the Comprehensive Psychopathological Rating Scale (CPRS) to question and observe depressive symptoms, only few of which were specifically related to positive affect, in addition to measuring other psychotic and sleep disturbance symptoms (Berger et al., 1999). However this study was limited to investigating participants in the preclinical phase of AD and aged 75 years and older, making it difficult to generalise these findings to the general population.

Further evidence supports an association of negative and positive affect with performance across cognitive domains. Past research indicates that affect is associated with cognitive domains that are often impaired in cognitive disorders, including: working memory, episodic memory, visuo-spatial awareness and attention (Gagnon & Belleville, 2011; Saunders & Summers, 2011; Taler & Phillips, 2008). One study supports the relationship of positive affect and working memory (Carpenter, Peters, Vastfjall, & Isen, 2013). In this study a total of 46 participants aged 63-85 years were recruited from a community sample, with findings indicating participants who were assigned to a positive feeling condition, in comparison to a neutral feeling condition, performed better across tasks of working memory, for example recalling letters (Carpenter et al., 2013). These findings are supported by neuropsychological theory which proposes that positive affect is associated with increased dopamine release into the prefrontal cortex, which facilitates working memory (Ashby, Isen, & Turken, 1999). In other research, participants’ positive mood elicited by music resulted in broadened visual spatial processing, further supporting the role of positive affect in cognition (Rowe, Hirsh, & Anderson, 2007). However, this study consisted of a sample of 24 university students (Rowe et al., 2007). In contrast, other studies support the role of negative affect and cognition, particularly high rates of negative affect at baseline, in predicting cognitive decline.
(Christodoulou et al., 2009). However, this finding was specific to a study investigating 38 participants who were diagnosed with relapsing remitting or secondary progressive Multiple Sclerosis (MS), making it difficult to generalise these findings to other populations. Other research indicates that increased negative affect is associated with narrower focus on an attentional blink program, though this study included a sample of 68 university students (Maclean, Arnell, & Busseri, 2010).

Other longitudinal research suggests that positive affect has an important role in cognitive function. Dolcos and colleagues (2012) investigated functional markers (i.e. positive affect) associated with changes in cognitive status. The study consisted of 294 participants assessed across two waves and assigned to one of two cognitive status groups including NIC (not impaired controls) and MCI (mild cognitive impairment). The results show that higher scores on positive affect predict a decreased risk of cognitive decline in the stable NIC-NIC and MCI-MCI groups (Dolcos et al., 2012). Furthermore, higher scores of positive affect predict cognitive improvement in the unstable MCI-NCI group.

Psychological theories also suggest mechanisms for the influence of affect on cognition. Particular theories of affect congruence state that affect has a role in cognition through two mechanisms including inferential and memory processes (Schwarz, 1990). The Inferential Model posits that when individuals are performing a task they may ask “how do I feel about this?”, and through questioning they may mistake previous feelings to the target as a result, suggesting that overall the individual incorrectly processes information (Schwarz, 1990). The Affect Priming Model specifies that affect is central to individual’s cognitive representations of the world (Bower, 1981). This model suggests that affect immediately primes associated memories and ideas when an individual is doing a cognitive task that utilities memory based information (Bower, 1981).
An additional theory is that affect influences how people think, particularly that positive affect influences assimilative, schema based processing style (Bless & Fieldler, 2006). Assimilation is referred to as a process in which processing is guided by knowledge structures, therefore producing top-down deductive thinking (Bless & Fieldler, 2006). In contrast, negative affect is associated with accommodative, externally focused thinking, which refers to focusing on the external world/information and using inductive bottom up thinking (Bless & Fieldler, 2006).

Positive affect may also impact on cognition through indirectly increasing behaviours or lifestyle factors that enhance mental and physical wellbeing and are protective for cognitive decline. Protective factors, including engagement in social activities, daily and high levels of physical activity, are all associated with lower risks of developing dementia (Buchman et al., 2012; Laurin et al., 2001; Wang et al., 2002). Social engagement and physical activities require mental activity and provide a sense of meaning/social role (Hillman, Erickson, & Kramer, 2008; Wang et al., 2002), which may contribute to these factors being protective against cognitive decline. Furthermore, engagement in social interaction and/or physical activity may result in feelings of accomplishment and an improved mood, which is particularly important given that depression (e.g. depressed mood) increases the risk of cognitive decline/impairment (Diniz et al., 2013; Gao et al., 2013). It is hypothesised that an individual’s initial engagement in social activities and physical activity would require some degree of interest, enthusiasm and energy, which are all associated with positive affect (Watson et al., 1988). This notion is supported by findings which suggest that positive affect is positively related to evaluation of interaction quality, the number of social interactions and the amount of time spent in social interactions (Berry & Hansen, 1996), while other research indicates that higher scores of positive affect (i.e. interest, excitement,
enthusiasm and alertness) are associated with increased levels of habitual physical activity (Pasco, et al., 2011).

Overall, the past research and theories support an association between positive and negative affect and areas of cognition, which are evident in cognitive decline/impairment. Furthermore, there is some evidence to support the role of positive affect in predicting specific cognitive disorders and to suggest that it provides a protective factor against cognitive decline, while the role of negative affect is less understood. However it is evident that more research is required to understand the specific role of positive and negative affect in predicting cognitive disorders.

The aim of the current research is to further investigate positive and negative affect as predictors of progression to Any-MCD/MCI from normal ageing. This aim will be investigated in conjunction with implementing a specific affect measure, the Positive and Negative Affect Scale (PANAS), and with measuring progression to cognitive impairment at follow up assessments at waves 2 and 3. It is hypothesised that low positive affect will predict progression to Any-MCD/MCI. Due to the lack of past research on negative affect and prediction of progression to cognitive impairment/decline, we cannot predict whether negative affect will predict progression to Any-MCD/MCI. However, based on the past findings of the relationship between negative affect and cognition and research on depression and dementia (Barnes et al., 2012; Diniz et al., 2013; Dotson et al., 2010; Gao et al., 2013), it is predicted that there may be an association between the two constructs.
Method

Data presented in this study are from the PATH project, which has previously been described in detail (see Chapter 2, Method for PATH). This study focuses on analyses of longitudinal data collected from the 60+ cohort assessed at baseline, and followed up at waves 2 and 3. The sample used in the current study has previously been described in detail (see Chapter 2, Method for PATH and Chapter 3, General Method for the Current Study).

Materials

Assessment of affect

The PANAS is a reliable measure of mood, which includes scales that are highly internally consistent, and largely uncorrelated (Watson, et al., 1988; see Appendix E). The PANAS is a self-report measure consisting of 20 items. Half of the items assess negative affect and the other half assess positive affect. The 20 items consist of words that describe different emotions. Participants are required to rate the extent to which the word represents how they feel at the present moment/over the past week. Participants rate their answer on a 5 point scale ranging from very slightly/not at all to extremely.

Previous research supports the implementation of the PANAS within non-clinical samples (Crawford & Henry, 2004). One study found the PANAS to have adequate validity in measuring positive and negative affect (Crawford & Henry, 2004), while the PANAS was found to be a reliable measure with Cronbach’s α 0.89 for the positive affect scale and 0.85 for the negative affect scale (Crawford & Henry, 2004). Overall, past research supports the PANAS as an appropriate measure of affect for the current study (Crawford & Henry, 2004; Watson et al., 1988). However, past research on the psychometric properties of the PANAS is limited to non-clinical samples (Crawford & Henry, 2004), and additional research on the psychometric properties of the PANAS is needed within clinical populations. This limitation
is particularly relevant to the current study, which includes a clinical sample of individuals diagnosed with cognitive disorders, and suggests that further research is needed in this area.

Assessment of demographics and covariates

The following demographics and covariates were included: gender, years of education, employment and marital status, high blood pressure, stroke, diabetes, heart disease, antidepressant medication, anxiety medication, smoking status, and number of hours of physical activity. A detailed description of each covariate is included in Study 1 (see Chapter 4; Method).

Sample size

Sample size was predetermined by the original aims of the larger cohort study (Anstey et al., 2012). The sample size was sufficient to allow for investigation of risk and protective factors and interactions among risk factors.
Statistical Analyses

SPSS version 22 was used to perform the analyses. A Generalized Linear Model (GZLM), using binary logistic regression, was implemented to investigate whether affect was a significant predictor of progression to a binary group membership (e.g. healthy/healthy, and healthy/Any-MCD or healthy/MCI), while adjusting for demographics and covariates. As previously reported in Study 1, the GLZM model was selected based on its suitability for analysing a dependent variable with a binary outcome and non-normal distribution (Garson, 2013).

Within the analyses the predictor covariates included baseline measurements of overall positive and negative affect scores (PANAS), while the controlled demographics included baseline assessment of gender and education. The analyses included 8 Generalised Linear Models that predicted progression to Any-MCD and MCI. Further models adjusting for other covariates (i.e. employment, physical activity, depression and anxiety medication, partner status, current smoking status, high blood pressure, diabetes, stroke and heart disease) were not included due to non-significant findings in the previous models when affect was entered separately and/or when adjusting for education and gender. In the Model 1 positive or negative affect predictors were entered separately and in Model 2, positive or negative affect predictors were entered separately while adjusting for gender and education. The covariate age was excluded from all the models due to the narrow age of the cohort. An additional measure of verbal intelligence, Spot The Word (STW), was included to adjust for premorbid IQ.

As previously mentioned, the binary logistic regression does not assume that the dependent variable is normally distributed. Furthermore, it does not assume the distribution of the predictor variables (Pallant, 2011). Therefore it was not necessary to analyse the variables for normality (e.g. skewness/kurtosis). The maximum number of predictors entered
within a model was 3, which was relatively small in comparison to the sample size \(N = 2500\); therefore an assumption of logistic regression was not violated (Pallant, 2011). Similarly, another assumption was not violated, with analysis revealing no high intercorrelations between the predictor variables (positive and negative affect scores and demographics/covariates) indicated by tolerance values not being < .10 (Pallant, 2011).

**Data Screening**

The data were screened for accuracy of input and plausibility of frequencies, which indicated that both were satisfactory. The number of missing cases for the demographics/covariates (education, physical activity, employment, depression and anxiety medication, partner status, current smoking status, high blood pressure, diabetes, stroke and heart disease) and outcome variables (Any-MCD and MCI) was reported previously (see Chapter 3, General Method for the Current Study and Chapter 4, Statistical Analysis). As previously reported, the missing cases were dealt with by substitution of the most common answer, imputation using the EM method and the case pairwise option. A total of 66 cases were missing for STW, which as mentioned previously is a measure of verbal intelligence and was included in the exploratory analysis. Imputation using the EM method was implemented to deal with missing data for STW.

Additional analysis indicated that 18 cases and 16 cases were missing for positive and negative affect, respectively. However the cases with missing values for positive and negative affect did not have sufficient outcome data for inclusion in the current analyses; therefore the ‘exclude case pairwise’ option was selected to deal with missing data. The case pairwise option allows for the exclusion of cases on the basis of missing data required for a specific analysis (Pallant, 2011).

The distribution of the continuous variables was examined and indicated 15 outliers for positive affect and 30 outliers for negative affect. However, the number of outliers was
small in comparison to the large sample size included in the current research, which is robust; therefore the outliers were included in the current analyses.
Results

Description of Participants

Participants were allocated to the healthy/healthy group if they remained stable across waves and were free of cognitive impairment from wave 1 to 2 and wave 2 to 3. When investigating progression to MCI from wave 1 to 2, the healthy/healthy group consisted of 2076 participants and the healthy/MCI group consisted of 17 participants. When analysing Any-MCD from wave 1 to 2, the healthy/healthy group consisted of 2076 participants and the healthy/Any-MCD group included 68 participants. When investigating progression to MCI from wave 2 to 3 the healthy/healthy consisted of 1797 and the healthy/MCI group included 21 participants; and when analysing Any-MCD from wave 2 to 3, a total of 1797 participants were allocated to the healthy/healthy group and 30 participants to the healthy/Any-MCD group.

See Table 2.1 in Chapter 2 for demographic and characteristics (gender, age and years of education and partner status). Table 4.1 presents baseline affect scores for participants belonging to a diagnostic category (e.g. healthy/healthy versus healthy/cognitive disorder) within each analysis (e.g. Wave 1 to 2 MCI model) across the three waves. A series of independent-samples t-tests were conducted to compare negative and positive affect scores between groups (e.g. healthy/healthy and healthy/cognitive disorder) within the four models across wave 1 to 2 and wave 2 to 3 (see Table 4.2). There were no significant differences in negative or positive affect scores for the diagnostic groups across the MCI and Any-MCD models across all the waves.
Table 4.1

*Baseline Affect Scores for Diagnostic Categories across the Waves*

<table>
<thead>
<tr>
<th></th>
<th>Overall NA score</th>
<th>Overall PA score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>M (SD)</em></td>
<td><em>M (SD)</em></td>
</tr>
<tr>
<td><strong>Wave 1 to 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MCI model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>13.88(4.82)</td>
<td>31.42(7.26)</td>
</tr>
<tr>
<td>Healthy/MCI</td>
<td>15.06(4.75)</td>
<td>31.06(6.60)</td>
</tr>
<tr>
<td><strong>Any-MCD model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>13.88(4.82)</td>
<td>31.42(7.26)</td>
</tr>
<tr>
<td>Healthy/Any-MCD</td>
<td>13.68(4.30)</td>
<td>30.85(7.51)</td>
</tr>
<tr>
<td><strong>Wave 2 to 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MCI model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>13.73(4.63)</td>
<td>31.62(7.13)</td>
</tr>
<tr>
<td>Healthy/MCI</td>
<td>14.38(4.83)</td>
<td>32.29(9.83)</td>
</tr>
<tr>
<td><strong>Any-MCD model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>13.73(4.63)</td>
<td>31.62(7.13)</td>
</tr>
<tr>
<td>Healthy/Any-MCD</td>
<td>15.13(4.96)</td>
<td>30.87(9.16)</td>
</tr>
</tbody>
</table>

*Note.* MCI = Mild Cognitive Impairment; Any-MCD = Any Mild Cognitive Disorder
Table 4.2

*T-test Results Comparing Affect Scores between Diagnostic Categories within Models across Waves*

<table>
<thead>
<tr>
<th>Wave 1 to 2</th>
<th>PA score</th>
<th>NA score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>t</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>31.42 (7.26)</td>
<td>0.20</td>
</tr>
<tr>
<td>Healthy/MCI</td>
<td>31.06 (6.60)</td>
<td></td>
</tr>
<tr>
<td>Any-MCD model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>31.42 (7.26)</td>
<td>0.63</td>
</tr>
<tr>
<td>Healthy/Any-MCD</td>
<td>30.85 (7.51)</td>
<td></td>
</tr>
<tr>
<td>Wave 2 to 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>31.62 (7.13)</td>
<td>-0.42</td>
</tr>
<tr>
<td>Healthy/MCI</td>
<td>32.29 (9.83)</td>
<td></td>
</tr>
<tr>
<td>Any-MCD model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy/healthy</td>
<td>31.62 (7.13)</td>
<td>0.57</td>
</tr>
<tr>
<td>Healthy/Any-MCD</td>
<td>30.87 (9.16)</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* NA = negative affect; PA = positive affect; p = P-values are 2 tailed.

Results for t, df and p value are the same as healthy/healthy diagnostic category within each model comparing positive or negative affect scores.
Positive Affect and Progression to Any-MCD/MCI from Wave 1 to 2 Any-MCD

PA was not a significant predictor of progression to Any-MCD at wave 2 ($p > .05$). PA remained non-significant when adjusting for gender and education ($p > .05$). However gender was significant (OR = 1.70; 95% CI 1.02-2.82; $p = .04$), suggesting that for males the odds of progressing to Any-MCD increase by a factor of 1.70. There was no significant interaction effect for gender and PA ($p > .05$).

MCI

PA was not a significant predictor of progression to MCI from wave 1 to 2 ($p > .05$). PA was not significant for predicting progression to MCI, when adjusting for gender and education which were also non-significant ($p > .05$).

Positive Affect and Progression to Any-MCD/MCI from Wave 2 to Wave 3

Any-MCD

PA was not a significant predictor of progression to Any-MCD from wave 2 to 3 ($p > .05$). PA was not significant when adjusting for gender and education ($p > .05$). Gender and education were also non-significant ($p > .05$).

MCI

PA was not a significant predictor of progression to MCI from wave 2 to 3 ($p > .05$). PA remained non-significant when adjusting for gender and education ($p > .05$). Education was non-significant ($p > .05$) however gender was significant (OR = 3.56, 95% CI 1.28-9.87, $p = .02$) suggesting that for males the odds of progressing to MCI increases by a factor of 3.56. There was no significant interaction effect for gender and PA ($p > .05$).
Negative Affect and Progression to Any-MCD/MCI from Wave 1 to Wave 2

Any-MCD

Negative affect (NA) did not significantly predict progression to Any-MCD from wave 1 to 2 ($p > .05$). NA remained non-significant when adjusting for gender and education ($p > .05$). Education was non-significant ($p > .05$) however gender was significant (OR = 1.71, 95% CI 1.03-0.38, $p = .03$). This result suggests that for males the odds of progressing to MCI increase by a factor of 1.71. There was no significant interaction effect for gender and NA ($p > .05$).

MCI

NA was not a significant predictor of progression to MCI and remained non-significant when adjusting for gender and education ($p > .05$). Gender and education were not significant ($p > .05$).

Negative Affect and Progression to Any-MCD/MCI from Wave 2 to Wave 3

Any-MCD

NA was not a significant predictor for progression to Any-MCD and remained non-significant when adjusting for education and gender ($p > .05$). Education and gender were not significant ($p > .05$).

MCI

NA was not a significant predictor of progression to MCI and remained non-significant when adjusting for education and gender. Education was significant (OR = 0.86, 95% CI 0.74-0.99, $p = .04$) suggesting that for every additional year of education the odds of progressing to MCI decreased by 14%. There was no significant interaction effect between education and NA ($p > .05$). Gender was significant (OR = 3.53, 95% CI 1.28-9.77, $p = .02$), suggesting that for males the odds of progressing to MCI increase by a factor of 3.53. There was no significant interaction effect between gender and NA ($p > .05$).
Exploratory analysis was implemented using a GLZM binary regression. The analysis investigated affect as a predictor of progression to MCI/Any-MCD from wave 1 to 2 and wave 2 to 3, while adjusting for verbal intelligence. Overall scores from STW were used as a measure of verbal intelligence (Baddeley, Emslie, & Nimmo-Smith, 1993). Results showed that positive and negative affect remained non-significant for progression to MCI or Any-MCD at all time points, across the other waves when adjusting for STW scores ($p > .05$).
Discussion

Positive affect was not significant for predicting progression to MCI or Any-MCD across waves 1 to 2 and waves 2 to 3. Positive affect also remained non-significant when adjusting for demographics of education and gender. Negative affect was not significant for predicting progression to MCI or Any-MCD across waves 1 to 2 and waves 2 to 3 and remained non-significant when adjusting for demographics. A further analysis adjusting for other lifestyle, heart disease, and medication covariates was not completed due to non-significant results in models 1 and 2. Our results do not support our hypothesis that low positive affect would predict progression to cognitive impairment and is discussed further in relation to past research in the section below.

Our findings that positive and negative affect were non-significant predictors of progression to cognitive impairment is inconsistent with past research supporting the relationship between affect and cognitive impairment (Berger et al., 1999; Carpenters et al., 2013; Gatz et al., 2005; Rowe et al., 2007). However past research has primarily focused on depression and cognitive impairment therefore has not included a specific measure of affect or has induced affect within experimental groups to test performance on cognitive tasks (Berger et al., 1999; Carpenters et al., 2013; Gatz et al., 2005; Rowe et al., 2007). Therefore it is difficult to generalise the past findings to our current study based on the differences in methodology, specifically that our study included a specific assessment of affect, a population based sample and diagnoses of cognitive disorders.

Another study which found a significant relationship between negative affect and cognitive decline using the PANAS as a measurement of affect was limited to participants with a diagnosis of MS (Christodoulou et al., 2009). This finding by Christodoulou and colleagues (2009) in conjunction with our non-significant results for negative affect as a predictor of progression to cognitive impairment highlights whether the PANAS reliably
assesses affect across different clinical populations or if another measurement of affect needs to be considered. Indeed, one of the few past studies which found higher scores on positive affect predicted a decrease in the risk of cognitive decline included an alternate assessment of affect called the Bradburn Affect Balance Scale (Bradburn, 1969; Dolcos et al., 2012). However it is important to note these findings were limited to positive affect and did not include negative affect. A comparison of the two measurements of affect, indicates the PANAS (Watson, et al., 1988) includes instructions which specifically ask the individual to indicate the extent to which you feel this way right now or over the past week, which may impact the reliability of the answers across participants who may answer according to current feelings or how they felt during the past week. In comparison the Bradburn Affect Balance Scale (Bradburn, 1969) instructs the participant to answer based on how they felt over the past few weeks. Overall, this issue suggests that further research should investigate negative and positive affect as predictors of cognitive impairment and include alternate measures of affect.

Our findings also indicate demographics including education and gender were significant for predicting progression to Any-MCD or MCI at specific time points. This finding indicates that males were more likely to progress to Any-MCD and MCI and reflects past research supporting higher incidences of MCI in male populations (Roberts et al., 2012). Our finding that increased years of education decrease progression to MCI, supports previous research that higher levels of education reduces the risk for MCI (Sattler et al., 2012). Overall, these findings suggest gender and education have an important role in predicting cognitive impairment and need to be considered for future research.

As previously mentioned one limitation within our study was the inclusion of the PANAS for the current population and that it is a self-report measure therefore may result in participants underreporting their symptoms. Other issues include the occurrence of sample
attrition across the three waves which resulted in the exclusion of participants from the current analyses. An inherent problem arising from the exclusion of participants is sample bias, which may have impacted upon our overall findings. The current study may have been strengthened by seeking cross-validation of self-report scores, and the collection of affect scores from more than one time point (e.g. baseline and wave 2) to assess whether affect remained constant or changed across time and continued to be non-significant or became a significant predictor of progression to cognitive disorders. However current study strengths included the inclusion of a large 60+ population based community sample, a detailed assessment and clinical diagnosis of cognitive impairment, and the collection of data across three time points and an 8 year period.

Overall, the results from the current study indicate that positive and negative affect are not significant predictors of progression to Any-MCD or MCI. Demographics of education and gender were significant of Any-MCD or MCI at specific time points. Further research is needed including alternate measures of affect with cross validation of these scores using assessments or interview, the assessment of affect at more than one time point and the inclusion of adjusting for lifestyle, heart disease and medication covariates. Overall, additional research will develop our understanding of the role of affect in cognitive impairment and contribute to the research field.
5. General Discussion
This chapter discusses the main findings of Study 1 and 2 and their theoretical implications. The results are discussed collectively, limitations of the current research and directions for future research and clinical implications are considered.

**Study 1: Depressive Symptoms as Predictors of Progression to Cognitive Disorders**

The findings from Study 1 partially fulfill the hypothesis that depressive symptoms predict progression to cognitive disorders. As predicted, symptoms of lacking energy/feeling tired, lost interest/little pleasure in doing things, loss of confidence, psychomotor slowing, feeling worse in the morning, feeling down, depressed or hopeless, loss/increase of appetite, and feeling bad about oneself were predictive of progression to MCI and/or Any-MCD from wave 1 to 2. In contrast to our hypothesis, difficulties concentrating and increased appetite were significant predictors of progression to Any-MCD and/or MCI from wave 1 to 2. Psychomotor agitation and suicidal ideation were not significant predictors which is inconsistent with our hypothesis.

The BPHQ items (e.g. little interest/pleasure, feeling down, depressed or hopeless, feeling tired/little energy, feeling bad about oneself and difficulties concentrating) remained significant when adjusting for demographics and covariates and analysing progression to Any-MCD and MCI. However the BPHQ item “poor appetite or overeating” was a significant predictor for Any-MCD only, and remained significant when adjusting for demographics and covariates. This finding suggests this symptom was a predictor for a range of cognitive disorders and not MCI alone. This result may be associated with the stability of Any-MCD diagnoses across time in comparison to MCI and highlights the importance of analysing the two diagnostic categories simultaneously.

The GADS items (lacking energy, lost interest, lost confidence, difficulties concentrating, felt slowed up and felt worse in the morning) remained significant when adjusting for demographics and covariates and analysing progression to Any-MCD. However
the GADS items (e.g. lacking energy, lost interest, lost confidence and difficulties concentrating) did not remain significant when analysing progression to MCI and adjusting for gender and education. This finding suggests that gender and education moderated this relationship between depressive symptoms and MCI. Other GADS items which were significant predictors of Any-MCD from wave 1 to 2 including “felt slowed up in the morning” and “felt worse in the morning” did not reach significance for MCI from wave 1 to 2. As mentioned previously this finding may be a result of the stability of Any-MCD diagnoses across time in comparison to MCI alone and reinforces analysing the two diagnostic categories concurrently.

Symptoms of lacking energy/feeling tired, little interest or pleasure in doing things, and difficulties concentrating were more significant predictors of progression to cognitive impairment than other depressive symptoms. The three symptoms remained significant when adjusting for demographics and covariates and analysing progression to Any-MCD and were cross validated by two depressive measures (e.g. the symptoms on the GADS and the BPHQ reached significance when analysing progression to Any-MCD and MCI in Model 1).

Overall, our findings extend previous research by indicating that specific depressive symptoms are predictive of progression to MCI and Any-MCD at one time point and that specific symptoms which remained significant and were cross validated between two measures were stronger predictors than other symptoms (Barnes et al., 2012; Gatz et al., 2005; Geerlings et al., 2000; Diniz et al., 2013, Dotson et al., 2012, Ravaglia et al., 2008, Rosenberg et al., 2010, Yaffe et al., 1999). Our findings support previous literature, specifically, the hypothesis that depression is associated with significant cognitive deficits that may cumulate with those caused by the dementing disease to bring forward a diagnosis of dementia and the “reserve threshold theory” (Butters et al., 2008; Jorm, 2001). Our finding that concentration difficulties were a stronger predictor of progression to cognitive disorders
in comparison to other depressive symptoms may have reflected the accumulation of this symptom with other symptoms (e.g. associated with cognitive impairment) and resulted in an earlier diagnosis/progression to MCI and Any-MCD. While our finding that other mood-related and behavioural depressive symptoms were predictive of progression to cognitive impairment may reflect the hypothesis that depression is associated with neural damage resulting in memory deficit and dementia (Jorm, 2001). This raises the question of whether individual depressive symptoms or a cluster of specific symptoms are the result of neural damage, however this is beyond the scope of review in this thesis and should be considered in future.

Our finding that specific depressive symptoms are predictive of progression to cognitive disorders may have implications for past literature, specifically, the hypothesis that depression is prodromal to cognitive impairment (Jorm, 2001). Our finding that specific symptoms are predictive of progression could suggest that individuals presenting with specific symptoms of depression progress to a clear diagnosis of a cognitive disorder. However, our study focused on depressive symptoms as independent risk factors rather than prodromal features; therefore it is difficult to ascertain this distinction. Future research should consider whether distinct depressive symptoms are prodromal to cognitive disorders.

The present results also indicate that a range of depressive symptoms (i.e. behavioural, mood and cognitive) were significant predictors of progression to cognitive disorders. This finding may reflect previous literature which outlines a specific cascade of biomarkers (physiological, biochemical and anatomical) that precede the onset of AD (Jack et al., 2010). Specifically, the range of significant depressive symptoms in the current research may reflect the substantial neurological changes occurring prior to the onset of cognitive impairment.
Study 2: Positive and Negative Affect and Progression to Cognitive Disorders

Our findings from Study 2 indicate positive and negative affect did not significantly predict progression to cognitive impairment. Our findings are inconsistent with our hypothesis that low scores on positive affect would predict progression to cognitive impairment. Our results are also inconsistent with psychological theories and past research supporting a relationship between affect and cognition/cognitive impairment (Berger et al., 1999; Bower, 1981; Bless & Tieldler, 2000; Carpenters et al., 2013; Gatz et al., 2005; Rowe et al., 2007; Schwarz, 1990). However past research has been limited to studies investigating depression and cognitive impairment therefore no specific affect measure was implemented or affect was induced within experimental groups and performance assessed on cognitive tasks (Berger et al., 1999; Carpenters et al., 2013; Gatz et al., 2005; Rowe et al., 2007). Our results are also inconsistent with other studies which included the PANAS and Bradburn Affect Balance Scale as measures of affect and support a relationship between affect and cognitive impairment (Christodoulou et al., 2009; Dolcos et al., 2012). It is hypothesized in the current study the PANAS did not tap into positive or negative affect well enough to identify these constructs therefore alternate measures of affect should be considered in future research.

Positive Affect, Depressive Symptoms and Progression to Cognitive Disorders

The findings in Study 1 support the relationship between depression and cognitive disorders however our results in Study 2 were not significant therefore do not support past research (Diniz et al., 2013; Gao et al., 2013). The overall findings from the two studies are intriguing given that many of the significant symptoms in Study 1 were reflective of positive and negative affect. Specifically, symptoms of lacking energy, lost interest/pleasure, and loss of confidence are associated with positive affect (Watson et al., 1988). While symptoms of feeling down, depressed or hopeless and feeling bad about oneself represent emotional states
of negative affect (Watson et al., 2004). The discrepancy in our findings between the two studies, reinforces whether the PANAS tapped into positive and negative affect well enough to identify these constructs within a clinical population. To our knowledge there is a limited amount of research on the psychometric properties of the PANAS within a clinical sample, with studies restricted to non-clinical samples (Crawford & Henry, 2004), which may have impacted upon the current research.

Limitations and Future Directions

Limitations

Limitations of the two studies have been discussed in depth previously in Study 1 and 2 (see Chapters 4 and 5, Discussion). As previously stated, limitations in Study 1 included depressive measures which did not measure depressive symptoms separately, assessed depressive symptoms that occurred “recently,” excluded specific depressive symptoms, and included inherent self-report bias. Additional issues included the exclusion of analysis of BPHQ items as predictors of progression to cognitive disorders from wave 2 to 3 due to participants not endorsing items at baseline. Other limitations of Study 2 include the implementation of the PANAS as a measure of affect and questions about the extent to which it taps into constructs of positive and negative affect. Other limitations associated with PANAS include its apparent limited implementation within clinical populations (Crawford & Henry, 2004), the short time period it measures and choice to report feelings based on 2 options (i.e. present moment/past week) and associated self-report bias.

General limitations of the two studies include the decision to include only one baseline assessment of affect and depression. Changes may have occurred in depression and affect across time; therefore it is important to consider this trajectory and the effect upon cognitive impairment. As well, the small number of participants in the diagnostic categories,
(Any-MCD or MCI) in comparison to the large number of participants in the healthy categories, may have impacted upon the power within the analyses for the studies.

**Future directions**

Directions for future research include the inclusion of different measures of depression and affect across more than one time point to measure the trajectory of these constructs in relation to cognitive changes/diagnosis of cognitive disorders. It is also suggested that research include a two stage screening process during which individuals complete a depressive checklist/psychometric measure, after which individuals who endorse symptoms are assessed thoroughly through interview about these symptoms.

To our knowledge this is the first study to investigate affect and depressive symptoms as predictors of progression to cognitive disorders across two time points. Other research is needed within this area to replicate and extend our current findings. Future research needs to investigate whether the symptoms that were stronger predictors than other symptoms (i.e. lost interest/pleasure, difficulties concentrating and lacking energy/feeling tired) collectively predict progression to cognitive disorders, while other clusters of significant depressive symptoms should also be investigated as predictors of progression to cognitive disorders. Another important point to consider from the present findings is that symptoms of positive and negative affect were significant on depressive measures but not specific affect measures (i.e. lacking energy, loss of confidence/interest, feeling bad about oneself and feeling down, depressed or hopeless). Future research should include a different measure of affect in conjunction with depressive measures to analyse whether affect and depressive symptoms reach concurrent significance for predicting cognitive impairment.

**Clinical Implications**

The results of the current research highlight the importance of further research in this field if we are to develop methods of monitoring specific depressive symptoms in individuals
aged 60 years and over and who are potentially at risk of developing a cognitive disorder. Continued research into the specific role of depressive symptoms may have clinical implications for health professionals to monitor clusters of depressive symptoms that may make it more likely for an individual to develop a cognitive disorder. It may also highlight the importance of not waiting for a clinical diagnosis of depression in order to screen for potential risk factors of cognitive impairment. Overall the current findings in conjunction with future research may result in the implementation of appropriate depressive measures in conjunction with interviewing of individuals aged 60 and over to screen for the presence of depressive symptoms. Earlier identification of these predictors may result in facilitating prompt intervention (medication or psychological treatment) which may target the depression and prevent or delay the course of progression to a cognitive disorder. However, the current clinical implications are preliminary and further research is required to increase our knowledge prior to the application of these findings within clinical settings.

Conclusion

Dementia is a significant health problem within Australia, with the rates of diagnosis predicted to increase in conjunction with associated medical costs within our ageing population (Access Economics, 2003; Australian Institute of Health and Welfare, 2012). Due to the widespread burden of this disease, much of the focus has turned to methods of risk reduction of dementia. The results of the current research suggest the importance of considering specific depressive symptoms in predicting progression to pre-clinical dementia syndromes including Any-MCD and MCI. While additional research is needed to establish the role of affect in predicting progression to cognitive impairment. It is hoped that further research into the field will lead to a greater understanding of specific depressive symptoms and affect as predictors of progression to cognitive disorders, and in turn may have long-term clinical implications for the intervention and prevention/delay of cognitive disorders in
individuals aged 60 years and over. Overall, further research into this topic will help to manage the increasing problem of dementia within Australia by identifying possible risk factors, and lead to appropriate identification and reduction of onset of cognitive disorders to help the ageing population and associated burden of costs within Australia.


doi: http://dx.doi.org/10.1016/0028-3932(67)90015-2


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Appendices
Appendix A. Structured Clinical Assessment for Dementia
XII. Diagnostic Formulation

This is a summary section, to be completed after evaluating all information. The neuropsychological and neuroimaging data should be available for this.

<table>
<thead>
<tr>
<th>DSM-V Major Neurocognitive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>Both of the following:</td>
</tr>
<tr>
<td>No Yes u/k</td>
</tr>
<tr>
<td>A1.</td>
</tr>
<tr>
<td>Concern of self or informant of significant cognitive decline</td>
</tr>
<tr>
<td>0 1 8</td>
</tr>
<tr>
<td>A2.</td>
</tr>
<tr>
<td>Substantial impairment on at least one domain:</td>
</tr>
<tr>
<td>0 1 8</td>
</tr>
<tr>
<td>a) Complex Attention</td>
</tr>
<tr>
<td>b) Executive Function</td>
</tr>
<tr>
<td>c) Learning and Memory</td>
</tr>
<tr>
<td>d) Language</td>
</tr>
<tr>
<td>e) Perceptual Motor</td>
</tr>
<tr>
<td>f) Social cognition</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>A1 &amp; A2 each interfere with independence at a minimum requiring assistance with complex IADLs</td>
</tr>
<tr>
<td>0 1 8</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>Not exclusively during delirium</td>
</tr>
<tr>
<td>0 1 8</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>Not due to an Axis I disorder (depression, Schizophrenia)</td>
</tr>
<tr>
<td>0 1 8</td>
</tr>
</tbody>
</table>

Does participant meet DSM-V Major Neurocognitive Disorder? 0 1 8

If dementia absent, go to Minor Cognitive Disorder.

<table>
<thead>
<tr>
<th>DSM-V Minor Neurocognitive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>Both of the following:</td>
</tr>
<tr>
<td>No Yes u/k</td>
</tr>
<tr>
<td>A1.</td>
</tr>
<tr>
<td>Concern of self or informant of significant cognitive decline</td>
</tr>
<tr>
<td>0 1 8</td>
</tr>
<tr>
<td>A2.</td>
</tr>
<tr>
<td>Substantial impairment on at least one domain:</td>
</tr>
<tr>
<td>0 1 8</td>
</tr>
<tr>
<td>a) Complex Attention</td>
</tr>
<tr>
<td>b) Executive Function</td>
</tr>
<tr>
<td>c) Learning and Memory</td>
</tr>
<tr>
<td>d) Language</td>
</tr>
</tbody>
</table>
e) Perceptual Motor
f) Social cognition

B A1 & A2 each DO NOT interfere with independence complex IADLs preserved but need greater effort or compensation 0 1 8

C Not exclusively during delirium 0 1 8

D Not due to an Axis I disorder (depression, Schizophrenia) 0 1 8

Does participant meet criteria for a Minor N-C Disorder? 0 1 8

1. DSM-IV Dementia

Q901A Both of the following: No Yes u/k
A1. Memory Impairment 0 1 8
A2. One (or more) of following:
   a) Aphasia
   b) Apraxia
   c) Agnosia
   d) Disturbance executive functioning

Q901B A1 & A2 each cause significant social/occup. dysfunction & represent a decline 0 1 8
Q901E Not exclusively during delirium 0 1 8
Q901F Not due to an Axis I disorder (depression, Schizophrenia) 0 1 8

Q91 Does participant meet DSM-IV criteria for Dementia? 0 1 8

If Yes,
Q91a Age of onset ____________ years

Associated with No Yes u/k
Q91b Delirium 0 1 8
Q91c Delusions 0 1 8
Q91d Depressed Mood 0 1 8

If dementia absent, go to Mild Cognitive Disorder.

2. Alzheimer’s Disease Diagnosis (NINCDS - ADRDA criteria)

If DSM-IV diagnosis of Dementia, does participant meet following criteria:
1. **Probable AD**

<table>
<thead>
<tr>
<th>Q92a</th>
<th>Progressive worsening of memory and/or language, motor skills or perception.</th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q92b</td>
<td>Onset between 40 &amp; 90 years.</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q92c</td>
<td>Absence of systemic disorders or other brain diseases that may account for cognitive deficits.</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

**Supported by** (not essential)

<table>
<thead>
<tr>
<th>Q92d</th>
<th>Family history of similar disorders</th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q92e</td>
<td>Normal LP</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q92f</td>
<td>Nil or non-specific EEG abnormality</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q92g</td>
<td>CT/MRI atrophy, especially if progressive</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

2. **Possible AD**

<table>
<thead>
<tr>
<th>Q92h</th>
<th>If (a) &amp; (b) above, but systemic or neurologic disorder not sufficient to cause dementia</th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
</table>

**OR**

<table>
<thead>
<tr>
<th>Q92i</th>
<th>Onset, presentation, or course atypical</th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
</table>

```
Q93a  Does participant meet criteria for AD. - Probable 0 1 8
Q93b  (or) - Possible 0 1 8
```

3. **Other Disorders causing Dementia**

Encircle the appropriate items below & state whether the item is likely to be contributing to the dementia, or to be the major causative factor. (see back of page for diagnosis).

<table>
<thead>
<tr>
<th>Q94a</th>
<th>Cerebrovascular disease</th>
<th>Absent</th>
<th>Major</th>
<th>Yes sec</th>
<th>Yes not related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q94b</td>
<td>Major Depression</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Q94c</td>
<td>Drug/substance toxicity, delirium</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Q94d</td>
<td>Alcohol Abuse/Dep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Q94e</td>
<td>Parkinson's Disease</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Q94f</td>
<td>Thyroid Disease</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Q94g</td>
<td>B12 deficiency</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
If yes to items above, specify basis of diagnosis.

________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________

If yes to A, E or M, go to the Criteria for these disorders.

4. Vascular Dementia (NINDS-AIREN Criteria)

4.1 Probable V-D

<table>
<thead>
<tr>
<th>Q95a1</th>
<th>1. Dementia present</th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Memory impaired, plus</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Two or more other cognitive domains impaired</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Q95a2  | Cardiovascular disease present. | 0  | 1   | 8  |
| Q95a3  | a) Focal signs on neuro exam consistent with CVD | 0  | 1   | 8  |
Q95a  b) Neuroimaging evidence (CT/MRT)  
(from one of the following)  
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q95b1 multiple large infarcts</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q95b2 single strategic impact</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q95b3 multiple lacunes</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q95b4 extensive white matter lesions</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Q95b  multiple large infarcts  
Q95c single strategic impact  
Q95d multiple lacunes  
Q95e extensive white matter lesions

Q95c  2. Relationship between CVD & Dementia  
(from one of the following)  
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q95c1 Onset of dementia within 3 months of stroke</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q95c2 Abrupt deterioration</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q95c3 Fluctuating, step-wise progression</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Q95d  3. Participant does not have a gradual & early onset of memory deficits & slow progression of deficits in language, praxia, and gnosia without corresponding brain lesions

4.2 Possible VaD

As above, but one of the following is “Yes”

Q96a Brain atrophy  
Q96b Absence of clear temporal relationship  
Q96c Subtle onset and variable course with evidence of CVD

Q97a Does participant meet criteria for VaD?  
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q97a Probable</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Q97b Possible  

5. Dementia with Lewy Bodies  (McKeith et al, 1994)

Q98a Dementia present  
Q98b Fluctuating cognitive impairment affecting memory & other higher cortical functions  
Q98c At least one of the following:  
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>u/k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q98c1 Varied/auditory hallucinations with or without delusions</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q98c2 Mild spontaneous EPS or neuroleptic-sensitivity</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Q98c3 Repeated unexplained falls and/or transient clouding or LOC</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Q98d Clinical features persistent over many months  
Q98e No medical cause of delirium
Q98f No history or clinical evidence of cerebral ischaemic changes

Q99 Does participant meet criteria for DLB?

6. Dementia with Parkinson’s Disease

Q100a Does participant have PD? No Yes u/k

At least 2 of the following [if not treated with L-Dopa]

| Q100a1 | Tremor at rest | 0 | 1 | 8 |
| Q100a2 | Rigidity       | 0 | 1 | 8 |
| Q100a3 | Shuffling gait | 0 | 1 | 8 |
| Q1004  | Bradykinesia  | 0 | 1 | 8 |
| Q100a5 | Postural instability | 0 | 1 | 8 |

Q100b Does participant have one of the following features:

| Q100b1 | Non-response to L-Dopa | 0 | 1 | 8 |
| Q100b2 | Gaze palsy             | 0 | 1 | 8 |

Q100c Was participant free of EPSE – inducing medication for past 6 months?

| Q100d | Did the PD begin one year of more before dementia recognized? | 0 | 1 | 8 |

Q101 If yes to 1, 3 & 4, diagnose PD with dementia

Q102 If yes to all four items, diagnose Atypical PD with dementia

Q103 If only one item of (1) endorsed, diagnose ‘Associated EPS’

7. Fronto-Temporal Dementia  {Consensus Criteria}

Q104a Insidious onset and slow progression of deficits

Q104b1 (A) Early behaviour disorder characterized by loss of personal
Or social awareness, disinhibition, mental rigidity, stereotyped
behaviour, impulsivity, &/or lack of insight
(or)

Q104b2 (B) Progressive speech impairment

Q104c Neuroimaging evidence (CT/MRI and/or SPECT/PET)
of predominant frontal and/or anterior temporal lobe abnormality

Q104d Neuropsychology: significant failure on “frontal tests” in the
absence of severe amnesia, aphasia or perceptuo-spatial disorder.

Supportive Features

Q105a Onset < 65 years
Q105b  Positive Family History  0  1  8
Q105c  Motor neurone disease (bulbar palsy, muscular weakness & wasting, fasciculations)  0  1  8

Q106  Does participant meet criteria for FTD?  0  1  8

8. Amnestic Disorder  (DSM-IV)

Q107a  Memory impairment  0  1  8
Q107b  Causes significant impairment of social/occupational functioning & decline from previous level  0  1  8
Q107c  Not exclusively due to delirium or dementia  0  1  8
Q107d  Direct physiological consequence of medical condition  0  1  8

Q108  Does participant meet criteria for Amnestic Syndrome  0  1  8

9. Mild Neurocognitive Disorder  (DSM-IV)

Q109a  Two or more of the following impairments, lasting > 2 weeks  0  1  8
Q109b1 Memory (reduced learning or recall of information)  0  1  8
Q109b2 Executive functioning  0  1  8
Q109b3 Attention or speed of information processing  0  1  8
Q109b4 Perceptual – motor abilities  0  1  8
Q109b5 Language (e.g. comprehension, word finding)  0  1  8
Q109c  A neurological or general medical disorder is judged to be aetiologically related  0  1  8
Q109d  Neuropsychological testing supports abnormality or decline in performance  0  1  8
Q109e  Deficits cause distress or impairment in social/occupational/other functions  0  1  8
Q109f  Does not meet criteria for delirium, dementia amnestic syndrome, and not better accounted for by another mental disorder (e.g. Major Depression, or Substance-Related Disorder)  0  1  8

Q110  Does participant meet criteria for a Mild N-C Disorder?  0  1  8

10. Other Cognitive Disorder  (DSM-IV)

Q111  Participant has mild neurocognitive impairment due to medical condition  0  1  8
Q112  Does not meet criteria for any of the above  0  1  8

Q113  Does participant meet criteria for Other Cognitive Disorder?  0  1  8
11. Age Associated Memory Impairment (Crook et al. 1986)

Q114 Participant complains of memory loss (include loss reflected in everyday problems such as remembering names, misplacing objects, remembering multiple items in shopping lists, problems remembering telephone numbers or postcodes, difficulty recalling information quickly). Onset of memory loss must be described as gradual (see Q20).

Q115 Memory performance below 6 on the immediate CVLT

Q116 Spot-The-Word score over 49

Q117 MMSE score 24 or above

Q118 No evidence of delirium, confusion (see Q22a)

Q119 No neurological disorder that could produce cognitive deterioration as determined by history, clinical neurological examination, and, if indicated, neuroradiologic examination. eg. AD, Parkinson's disease, stroke, intracranial haemorrhage, local brain lesions including tumors, and normal pressure hydrocephalus

Q120 No history of any infective or inflammatory brain disease

Q121 No evidence of significant cerebral vascular pathology as determined by neurological examination

Q122 No history of repeated minor head injury or a period of unconsciousness lasting an hour or more

Q123 No current psychiatric diagnosis of depression, mania or major psychiatric disorder (see q23a to q26i, q28a)

Q124 No diagnosis or history of alcoholism or drug abuse

Q125 No evidence of depression as determined by clinical examination for DSM_IV depression

Q126 No evidence of medical disorder that could produce cognitive deterioration including renal, respiratory, cardiac, and hepatic disease, diabetes mellitus unless well controlled, endocrine, metabolic, or haematologic disturbances; and malignancy not in remission for more than two years. Determination should be based on complete medical history, clinical examination and appropriate lab tests

Q127 No evidence of any psychotrophic drug or any other drug that may significantly affect cognitive functioning during the month prior to psychometric testing (see q67)

Q128 Participant meets all criteria and thus meets criteria for AAMI

<table>
<thead>
<tr>
<th>MCI Criteria</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

180
1. Participant is not normal and not demented
   
   If q1 = 1, go to q2

2. Is cognitive decline:
   
   2a. Self and/or informant report and impairment on objective cognitive tasks?
   2b. Evidence of decline over time on objective cognitive tasks
   2c. Preserved basic activities of daily living/
       Minimal impairment in complex instrumental functions

3. Diagnosis: Does participant have MCI? (If 2a or 2b=1; and 2c =1)
   
   If q3 =1, go to q4

4. MCI SUBTYPES
   
   Does the participant have:
   
   4a. Memory impairment
   
   If q4a=0, go to q8
   If q4a=1, go to q5

5. AMNESTIC SUBTYPE
   
   5a. Frontal executive function impairment
   5b. Language impairment
   5c. Visuospatial function impairment

   If only one of q5a or q5b or q5c =1, go to q6
   If two or more of q5a or q5b or q5c=1, go to q7

6. Diagnosis: Amnestic single domain
   
   7. Diagnosis: Amnestic multiple domain

8. NON-AMNESTIC SUBTYPE
   
   8a. Frontal executive function impairment
   8b. Language impairment
   8c. Visuospatial function impairment

   If only one of q8a or q8b orq8c =1, go to q9
   If two or more of q8a or q8b or q8c =1, go to q10

9. Diagnosis: Non-amnestic single domain

10. Diagnosis: Non-amnestic multiple domain

Q135 Report by participant or informant that cognitive (memory and/or other) function has declined 0 1 8
Q136 Onset is gradual and has been present for at least six months 0 1 8
Q137 Difficulties in one of the following areas: memory and learning; attention and concentration; thinking, (e.g. Problem solving, abstraction); language (e.g. Comprehension, word finding); visuospatial functioning 0 1 8
Q138 There is an abnormality of performance on quantitative cognitive assessments for which age and education norms are available for relatively healthy individuals. Performance must be below 1SD on one of the following tests: SDMT, CVLT immediate, and MMSE adjusted for education.

<table>
<thead>
<tr>
<th>Test</th>
<th>Education level 1</th>
<th>Education level 2</th>
<th>Education level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT</td>
<td>36</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>CVLT immediate</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>MMSE</td>
<td>27</td>
<td>28</td>
<td>29</td>
</tr>
</tbody>
</table>

Q139 None of the present existing: dementia, MCD (i.e. no objective evidence from physical and neurological examination or lab tests and no history of cerebral disease, damage, or dysfunction or of systemic physical disorder known to cause cerebral dysfunction) depression, anxiety, or other significant psychiatric disorders, organic amnestic syndrome, delirium, postencephalic syndrome; post concussional syndrome, cognitive impairment due to psycho-active substance abuse or the effects of any centrally active drug. 0 1 8

Q140 Participant meets all criteria and thus meets criteria for Aacd 0 1 8

14. Mild Cognitive Difficulties (CMHR impairment)

Q141 Participant has a MCD due to one or more of Memory impairment 0 1 8
Q142 Aphasia 0 1 8
Q143 Apraxia 0 1 8
Q144 Agnosia 0 1 8
Q145 Executive functioning disturbance 0 1 8
Appendix B. Overall Diagnostic Criteria for Cognitive Disorders Across Waves
Overall Diagnostic Criteria for Cognitive Disorders Across Waves

*Diagnostic criteria for amnestic MCI (waves 1 and 2)*
1. Memory complaint preferably corroborated by an informant
2. Objective memory impairment
3. Normal general cognitive function (MMSE 26 or above and overall IQ not significantly affected)
4. Intact activities of daily living

*Diagnostic criteria for MCI (waves 3)*
1. Not normal, absence of dementia
2. Cognitive decline
   a) subjective (self and/or informant report)
   b) objective
3. Some decline in function
4. Preserved basic ADL/minimal impairment in complex IADLs

*Diagnostic criteria for AAMI (all waves)*
1. Subject complaints of memory loss
2. Memory performance below 6 on the immediate California Verbal Learning Test
3. Spot-The-Word score over 49
4. MMSE score 24 or above
5. No evidence of delirium, confusion
6. No neurological disorder that could produce cognitive deterioration as determined by history, clinical neurological examination and, if indicated, neuroradiologic examination
7. No history of any infective or inflammatory brain disease
8. No evidence of significant cerebral vascular pathology as determined by neurological examination
9. No history of repeated minor head injury or a period of unconsciousness lasting an hour or more
10. No current psychiatric diagnosis of depression, mania or major psychiatric disorder
11. No diagnosis or history of alcoholism or drug abuse
12. No evidence of depression as determined by clinical examination for DSM-IV depression
13. No evidence of medical disorders that could produce cognitive deterioration
14. No evidence of any psychotropic drug or any other drug that may significantly affect cognitive functioning during the month prior to psychometric testing

*Diagnostic criteria for AACD (all waves)*
1. Report by subject or informant that cognitive (memory and/or other) function has declined
2. Onset is gradual and has been present for at least 6 months
3. Difficulties in one of the following areas: memory and learning; attention and concentration; thinking; language; visuospatial functioning
4. There is an abnormality of performance on quantitative cognitive assessments for which age and education norms are available for relatively healthy individuals. Performance must be below 1 SD on one of the following tests: Symbol-Digit Modalities Test, California Verbal Learning Test and MMSE adjusted for education
5. None of the present existing: dementia, mild cognitive disorder (i.e., no objective evidence from physical and neurological examination or lab tests and no history of cerebral disease,
damage or dysfunction or of systemic physical disorder known to cause cerebral dysfunction); depression; anxiety or other significant psychiatric disorders; organic amnestic syndrome, delirium, post-encephalitic syndrome; post-concussional syndrome; cognitive impairment due to psychoactive substance abuse or the effects of any centrally active drug.

**DSM-IV-TR Diagnostic criteria for MND (all waves)**

1. Two or more of the following impairments, lasting more than 2 weeks
   a. Memory (reduced learning or recall of information)
   b. Executive functioning
   c. Attention or speed of information processing
   d. Perceptual-motor abilities
   e. Language (e.g., comprehension, word finding)
2. A neurological or general medical disorder is judged to be aetiologically related
3. Neuropsychological testing supports abnormality or decline in performance
4. Deficits cause distress or impairment in social/occupational/other functions
5. Does not meet criteria for delirium, dementia, amnestic syndrome, and not better accounted for by another mental disorder

**DSM-IV-TR Diagnostic criteria for other cognitive disorder (all waves)**

1. Subject has mild neurocognitive impairment due to medical condition
2. Does not meet criteria for MND
Appendix C. Brief Patient Health Questionnaire (BPHQ)
Brief Patient Health Questionnaire (BPHQ)

This questionnaire is an important part of providing you with the best health care possible. Your answers will help in understanding problems that you may have.

Name_________________________ Age_________ Sex: ☐ Female ☐ Male Today’s Date_________

1. Over the last 2 weeks, how often have you been bothered by any of the following problems?
   - a. Little interest or pleasure in doing things.................................☐ Not at all ☐ Several days ☐ More than half the days ☐ Nearly every day
   - b. Feeling down, depressed, or hopeless..................................................☐
   - c. Trouble falling or staying asleep, or sleeping too much.........................☐
   - d. Feeling tired or having little energy..................................................☐
   - e. Poor appetite or overeating.................................................................☐
   - f. Feeling bad about yourself — or that you are a failure or have let yourself or your family down...............................☐
   - g. Trouble concentrating on things, such as reading the newspaper or watching television...........................................☐
   - h. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual.................................☐
   - i. Thoughts that you would be better off dead or of hurting yourself in some way..................................................☐

2. Questions about anxiety.
   - a. In the last 4 weeks, have you had an anxiety attack — suddenly feeling fear or panic?..........................☐ NO ☐ YES

   If you checked “NO”, go to question #3.
   - b. Has this ever happened before?............................................................................☐
   - c. Do some of these attacks come suddenly out of the blue — that is, in situations where you don’t expect to be nervous or uncomfortable?..................................................☐
   - d. Do these attacks bother you a lot or are you worried about having another attack?..........................☐
   - e. During your last bad anxiety attack, did you have symptoms like shortness of breath, sweating, your heart racing or pounding, dizziness or faintness, tingling or numbness, or nausea or upset stomach?.................................................................................................☐

3. If you checked off any problems on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult ☐
## Goldberg and Depression Scale (GADS)

**Depression.** Think about how you have been feeling recently:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you been lacking in energy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you lost interest in things?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you lost confidence in yourself?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you felt hopeless?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had difficulty concentrating?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you lost weight (due to poor appetite)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you been waking early?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you felt slowed up?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you tended to feel worse in the morning?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Anxiety.** Think about how you have been feeling recently:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you felt keyed up or on edge?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you been worrying a lot?</td>
<td></td>
<td></td>
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<tr>
<td>Have you been irritable?</td>
<td></td>
<td></td>
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<tr>
<td>Have you had difficulty relaxing?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you been sleeping poorly?</td>
<td></td>
<td></td>
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<tr>
<td>Have you had headaches or neckaches?</td>
<td></td>
<td></td>
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<tr>
<td>Have you had any of the following: trembling, tingling, dizzy spells, sweating, diarrhoea, or needing to pass water more often than usual?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you been worrying about your health?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had difficulty falling asleep?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix E. Phi Coefficients for Covariates in Model 3
**Phi coefficient result analysing the association between covariates in model 3**

<table>
<thead>
<tr>
<th></th>
<th>Exercise</th>
<th>Employment</th>
<th>Anx Med</th>
<th>Dep Med</th>
<th>Partner Status</th>
<th>Smoke</th>
<th>High Blood pressure</th>
<th>Diabetes</th>
<th>Stroke</th>
<th>Heart Disease</th>
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<tr>
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<td>.064</td>
<td>.067</td>
<td>.068</td>
<td>.080</td>
<td>.113</td>
<td>.064</td>
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<td>Employment</td>
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<tr>
<td>Anx med</td>
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<td>.039</td>
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<tr>
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<td>.059</td>
<td>.075</td>
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<tr>
<td>Partner status</td>
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<td>-.015</td>
<td>-.015</td>
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<td>Smoke</td>
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<tr>
<td>High Blood Pressure</td>
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<td>.063</td>
<td>.057</td>
<td>.035</td>
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<td>-.047</td>
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<tr>
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<td>.039</td>
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<td>.019</td>
<td>.001</td>
<td>.151</td>
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<tr>
<td>Stroke</td>
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<td>.003</td>
<td>.131</td>
<td>.044</td>
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<td></td>
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<tr>
<td>Heart Disease</td>
<td>.078</td>
<td>.081</td>
<td>.048</td>
<td>.033</td>
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<td>-.010</td>
<td>.210</td>
<td>.094</td>
<td>.155</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* Anx med = Anxiety medication; Dep med = Depression medication. Cohens criteria for effect size: .10 (small effect), .30 (medium effect) and .50 (large effect).
Appendix F. Positive And Negative Affect Scale (PANAS)
PANAS Questionnaire

This scale consists of a number of words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. **Indicate to what extent you feel this way right now, that is, at the present moment OR indicate the extent you have felt this way over the past week (circle the instructions you followed when taking this measure).**

|--------------|--------------|----------|---------|---------|----------|----------|----------|-------------|---------|--------------|---------|------------|---------|-----------|-------------|---------|-----------|---------|---------|--------|--------|

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