Affective symptoms over the life course and cognitive ageing

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STATEMENT

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

Signature: ……. Date: ……

DECLARATION

The thesis conforms to an 'papers style format' in which chapters 2 to 6 report empirical work written in a style that is appropriate for publication in peer-reviewed journals in the field. The first chapter is a general introduction outlining the existing literature and summarising the work undertaken in this thesis. The final chapter presents discussions of the field and the research undertaken.

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SUMMARY

Affective symptoms over the life course and cognitive ageing

Affective symptoms, such as depression and anxiety, are commonly comorbid with dementia. Estimates report that up to 40% of people with dementia also present with symptoms of depression. Research has also shown that a longitudinal association between affective symptoms and cognitive function may exist over time. However, the majority of research has focussed on older samples (aged 60+ at baseline) with short periods of follow up (<10 years). Less is known about how the association between affective symptoms and cognitive function operates over a longer period of time, including much earlier in the life course. The studies within this thesis aim to test the nature of this complex association, using a life course approach.

The first study in this thesis used a systematic review and meta-analysis method and concluded that depression in older adulthood was associated with a faster subsequent cognitive decline. The second study used secondary data from the National Survey of Health and Development (NSHD), a nationally representative birth cohort of over 5,000 people born in England, Scotland and Wales, during one week of 1946. This study found that adolescent, but not adult, affective symptoms significantly predicted poorer baseline memory and information processing speed scores, but not rate of decline over time. The third study also used data from NSHD to test bidirectionality between affective symptoms and cognitive function. This study found that affective symptoms significantly predicted subsequent level of memory and processing speed over a 16 year period, but that this association did not operate in the opposite direction. The fourth study used data from the National Child Development Study (NCDS), a population representative birth cohort of over 18,000 people born in England, Scotland and Wales, during one week of 1958. This study revealed that accumulation of

persistent affective symptoms was a better predictor of midlife memory function than sensitive periods. The fifth and final study in the thesis also used data from NCDS to explore inflammation as a potential mediator in the association between affective symptoms and cognitive function. This study showed that C-Reactive protein (CRP) fully explained the association between adult affective symptoms and memory function, suggesting that inflammation is an important explanatory factor of this relationship.

Taken together, these findings suggest that chronic and persistent affective symptoms across the life course play an important but complex role in contributing to cognitive function across mid to later life, with particularly strong effects observed on memory function. In addition, inflammation may be one important explanatory mediator of the association between affective symptoms and midlife memory function.

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CHAPTER 1

General Introduction

The general introduction provides a brief overview of cognitive function and cognitive ageing, including definitions of key terms used throughout the thesis, societal and economic costs of cognitive ageing, and the importance of using a life course approach to study this phenomenon. Secondly, the introduction reviews evidence regarding associations between affective symptoms and cognitive ageing, including literature surrounding the nature of this association, primary hypotheses proposed to explain such associations, and plausible biological and social mechanisms which can potentially underlie this association. Finally, the primary overarching aims of the research in this thesis are outlined, and the specific objectives and methods used for each empirical chapter (Chapters 2-6) are also provided.

1.1. Cognitive function and cognitive ageing

1.1.1. Definitions.

Cognitive function encompasses many different but inter-related processes, including memory (working memory and long term memory), information processing speed, attention, executive functioning, and many others. These key cognitive domains are outlined and defined below.

Memory comprises multiple different components. Working memory refers to the active manipulation or reorganisation of information held in the short term memory. Long term memory is a multidimensional construct, which encompasses different functions, including episodic, semantic, procedural, and prospective memory (Glisky, 2007). Episodic memory refers to memory for specific events and experiences, with contextual information playing an important role. Semantic memory is memory for general knowledge, including abstraction such as what words mean. Episodic and semantic memory are both declarative functions, as they are explicit rather than implicit.

Procedural memory is implicit memory for acquired skills, such as riding a bike. Prospective memory refers to memory for the intention to complete future tasks. Memory function is important for effective everyday functioning, and memory loss can cause considerable distress and anxiety (Vinkers, Gussekloo, Stek, Westendorp, & van der Mast, 2004).

Information processing refers to how information is taken in, made sense of, and responded to. Information processing speed is the pace at which these processes are completed, and reflects the efficiency of cognitive performance. Information processing speed may underlie efficiency of other cognitive domains (Salthouse, 1996), and as such this cognitive domain is particularly important for effective daily functioning.

Attention is involved in some form in many other cognitive domains and processes and refers to the capacity for processing information in the environment (Glisky, 2007). Attention comprises multiple sub-processes specialised for different functions, including selective attention, divided attention, and sustained attention. Selective attention refers to the ability to attend to relevant stimuli in the environment, while simultaneously ignoring irrelevant stimuli. Divided attention, also known as multitasking, refers to the ability to process two or more competing stimuli simultaneously. Sustained attention is the ability to maintain focus on a stimulus over a period of time. This requires both the ability to focus on the task (concentration) and the ability to monitor the appearance of a stimulus (vigilance). Attention is particularly important for the effective functioning of other cognitive domains.

Executive function is important in goal-directed activities, and consists of a range of complex processes, including planning, organising, and evaluating behaviours. It is the capacity to control and monitor behaviour and subsequently adjust responses on

the basis of environmental cues. Effective executive functioning is necessary for decision making and planning, correcting errors, solving novel problems, and inhibition of responses. Higher executive functioning predicts better quality of life (Brown & Landgraf, 2010; Davis, Marra, Najafzadeh, & Liu-Ambrose, 2010), and greater success in school (Borella, Carretti, & Pelegrina, 2010; Duncan et al., 2007; Gathercole, Pickering, Knight, & Stegmann, 2004) and work (Bailey, 2007).

Finally, *overall cognitive state* refers to a composite assessment of overall cognitive functioning. This is usually derived as a composite score combining a selection of cognitive domains, representing an individual's global cognitive state. Overall cognitive state is important to study, because low scores on tests of cognitive state have been shown to predict functional impairment and dependence (Gill, Williams, Richardson, & Tinetti, 1996; Wang, Belle, Kukull, & Larson, 2002). Overall cognitive state is described in more detail in the first empirical chapter of this thesis (chapter 2).

These cognitive functions follow distinct developmental patterns across the life course, with rapid cognitive development occurring in the first five years of life, and continuing to increase through to early adulthood (Richards & Hatch, 2011). There are two distinct categories of cognitive functions which follow different developmental trajectories from early adulthood to later life. Crystallised cognitive function refers to the ability to use skills and acquire knowledge, and encompasses general knowledge, vocabulary, and numerical abilities. These crystallised cognitive functions are resistant to age-related cognitive decline, and can improve with age from early adulthood through to later life as a result of lifelong learning (Anstey & Low, 2004). In contrast, fluid cognitive function is independent from pre-existing knowledge or experience (Anstey & Low, 2004). Fluid cognitive functions include memory, information processing, executive function and attention. These processes are particularly sensitive

to age-related cognitive decline, which can be observed from relatively early in the life course, from early to middle adulthood onwards (Salthouse, 2009; Salthouse, 2004). Cognitive ageing is characterised by decline in these fluid functions over time; however the extent and rate of decline is highly variable between individuals. This can range from mild age-related cognitive change, through to mild cognitive impairment, through to clinically diagnosable conditions that impact cognitive functioning, such as dementia. It can be challenging and complex to distinguish between normative and pathological ageing along this cognitive continuum (Brayne, 2007). In this thesis, particular attention will be paid to overall cognitive state, memory and information processing speed, and the life course factors which can be associated with these domains.

1.1.2. Societal and economic costs of cognitive ageing.

Due to population growth and increasing life expectancies, the proportion of older adults in the UK population is rising (ONS, 2017). Cognitive ageing is therefore a social and healthcare priority in the UK. It is estimated that there are 850,000 people living with dementia in the UK, and this is projected to increase (Prince et al., 2014). Poorer cognitive ageing outcomes have a considerable detrimental impact on individuals, families and society. This can include negative effects on an individual's psychological and emotional health, functional outcomes, social life, and financial state (Alzheimer's Society, 2018). Poorer cognitive ageing also has profound effects on close persons, including family and friends, due to emotional stress, burdens associated with caregiving, and increased financial costs (Dunkin & Anderson-Hanley, 1998; Etters, Goodall, & Harrison, 2008; Papastavrou, Kalokerinou, Papacostas, Tsangari, & Sourtzi, 2007). Finally, there are also important economic impacts of poorer cognitive ageing on society. In the UK, approximately 40% of admissions to institutional care are due to cognitive decline (Deary, Corley, et al., 2009). In the UK, the cost of dementia is

estimated to be £26 billion (Lewis, Karlsberg Schaffer, Sussex, O'Neill, & Cockcroft, 2014), and this is forecasted to increase to £55 billion by 2040 (Prince et al., 2014). Given rapid population ageing and the detrimental outcomes associated with cognitive ageing for individuals, families, society, and the economy, this is increasingly a matter of great importance for public health.

In the absence of a cure for dementia or any disease modifying treatment, increasing resources are being invested in preventative methods (Livingston et al., 2017). It has been estimated that delaying the onset of dementia by just one year has the potential to reduce worldwide incidence by 9 million cases over the next 4 decades (Barnes & Yaffe, 2011). Experimental and epidemiological studies have identified a range of biological, socio-behavioural and environmental factors which can play an important role in the pathogenesis of dementia and poorer cognitive ageing outcomes (Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). Due to the long preclinical period of dementia, it is of utmost importance to adopt a life course approach in the identification of potentially modifiable risk factors.

1.1.3. Life course approach to study cognitive ageing.

Cognitive ageing has been studied from a variety of different perspectives, including socio-behavioural and biomedical approaches. Biomedical approaches to cognitive ageing address biological mechanisms of cognitive ageing across cellular, molecular, and physiological levels. For example, advanced modern neuroimaging techniques can provide insight into neural mechanisms underlying cognitive ageing. Specifically, structural and functional neuroimaging techniques can develop existing understanding of neural underpinnings of cognitive impairments in older adulthood and the role of neuropathology in cognitive ageing across the population spectrum from

normal cognitive ageing to pathological cognitive ageing (Grady, 2012; Hedden & Gabrieli, 2004). Related to this, genetic testing is increasingly being used to investigate variability and individual differences in the ageing process. It has been proposed that heritability of cognitive function is about 50%, suggesting that more than half of the variance in adult cognitive function can be explained by genetic factors (Bouchard Jr & McGue, 2003; Carmelli, Swan, LaRue, & Eslinger, 1997; Finkel, Pedersen, Plomin, & McClearn, 1998; Mattay, Goldberg, Sambataro, & Weinberger, 2008; Plomin & McClearn, 2001; Plomin & Spinath, 2002). This is not fixed over the life course, with evidence showing that heritability of cognitive function is around 30% in early childhood, rising to 80% in later life (Deary, Johnson, & Houlihan, 2009). Genetics, therefore, seem to play an important role in cognitive function over the life course. As such, there is growing interest in studying the genetic underpinnings of cognitive ageing and how these can develop across the life course. Socio-behavioural methods and approaches are also commonly used to investigate how lifestyle factors, particularly those which are potentially modifiable, are associated with individual differences in cognitive ageing (Barnes & Yaffe, 2011; Livingston et al., 2017). Specifically, this approach focusses on how demographic, social, and behavioural factors can contribute to cognitive reserve and promote healthy cognitive ageing.

The life course approach to the study of cognitive ageing is valuable because it can integrate socio-behavioural and biomedical perspectives. Specifically, the life course approach highlights lifelong changes or trajectories of cognitive ageing across individual and system levels. As such, use of the life-course approach can facilitate integration of multidisciplinary methods in the study of cognitive ageing. Use of a life course approach allows investigation into how early life determinants and processes which operate across various life stages can contribute to adult health and ageing

outcomes (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003). The availability of biological and social information across multiple life stages provides a unique opportunity to test this, for example by exploring cumulative effects of an exposure over the life course, joint action of early and later exposures, or sensitive periods of an exposure on adult health outcomes (Power, Kuh, & Morton, 2013). This life course approach is particularly useful in the context of ageing, as age-related cognitive decline is a lifelong process which becomes evident from early adulthood (Salthouse, 2009; Salthouse, 2004). Additionally, pathological brain changes associated with cognitive ageing may also become apparent from early adulthood (Salthouse, 2009). As such, it is important to establish how determinants over multiple periods of life from childhood through to older adulthood can influence cognitive trajectories, rather than focussing exclusively on determinants present during later life once cognitive decline and associated brain changes are already well established.

For this reason, birth cohort data are an important and powerful resource for addressing these questions. Birth cohort data can contain social, behavioural, and biomedical data measured longitudinally from birth across multiple life stages. This facilitates the integration of socio-behavioural and biomedical approaches to study cognitive ageing across the entire life course. This is important, because results from birth cohort studies show that focusing on determinants of cognitive ageing only in midlife or older adulthood may offer incomplete or partial explanations, because early life factors and trajectories also play an important role in predicting ageing outcomes, as well as interacting with more proximal health indicators to shape outcomes (Power et al., 2013). There are four national birth cohorts in Great Britain: 1. National Survey of Health and Development (NSHD); 2. National Child Development Study (NCDS); 3. 1970 Birth Cohort Study (BCS70); and 4. Millennium Cohort Study (MCS). This thesis

utilises data from the two oldest British birth cohorts: NSHD and NCDS. NSHD comprises a representative social-class weighted sample of 5,362 people born during 1 week of 1946. This cohort includes repeated measures of cognitive function in childhood (ages 8, 11, and 15) and from mid to later adulthood (ages 43, 53, 60-64, and 69), including verbal memory (assessed using word list recall tests) and information processing speed (assessed using letter cancellation tasks). NCDS includes a nationally representative sample of 18,558 individuals born during a single week of 1958. This comprised 98.2% of all births in England, Scotland and Wales during that week. Cognitive data is available in this cohort in childhood (ages 7, 11, and 16) and midlife (age 50), including measures of immediate and delayed verbal memory (measured using word list recall test with an immediate and delayed component), verbal fluency (measured using animal naming test), and information processing speed and accuracy (measured using letter cancellation task). Data included in NSHD and NCDS are complementary and offer a unique opportunity to study life course determinants of cognitive ageing.

1.2. Affective problems and cognitive ageing

1.2.1. Affective problems: prevalence and socio-economic costs.

Affective problems refer to a set of psychiatric mood disorders, including depression and anxiety, and their symptoms. The Office for National Statistics (ONS) reported that 17% of adults in England met the diagnostic criteria for an affective disorder in 2014 (McManus, Bebbington, Jenkins, & Brugha, 2016). According to official UK statistics, affective symptoms are prevalent within all age groups, including in childhood from ages 5-10 (4%), in early adolescence from ages 11-16 (9%), in later

adolescence from ages 17-19 (15%), in adulthood from ages 25-64 (18%), and in older adults age 65+ (9%) (McManus et al., 2016; Sadler et al., 2018).

Mental health problems are the largest cause of disability in the UK, ahead of both cancer and cardiovascular disease, accounting for 22.8% of total disease burden (Department of Health, 2011). Specifically, affective disorders are associated with increased physical morbidity and mortality and have been linked to an increased risk of dementia (Da Silva, Gonçalves-Pereira, Xavier, & Mukaetova-Ladinska, 2013), stroke (Surtees et al., 2008), and heart disease (Hemingway & Marmot, 1999). Affective symptoms in older adults may also be a contributing factor to falls, frailty, and greater disability (Cronin-Stubbs et al., 2000; Iaboni & Flint, 2013; Strawbridge, Shema, Balfour, Higby, & Kaplan, 1998). Individuals with affective symptoms also show lower adherence to management regimes for comorbid physical conditions (Ciechanowski, Katon, & Russo, 2000; Gonzalez et al., 2008; Krousel-Wood et al., 2010). This results in more missed medical appointments and more hospital admissions, increasing associated costs. Economic costs of mental illness are vast in the UK, estimated at £105.2 billion annually (Department of Health, 2011). This estimate includes direct costs of health and social care services, indirect costs through reduced quality of life and poorer physical health, and lost productivity in the workplace (through both presenteeism and absenteeism). In England, it is estimated that £7.5 billion is spent on depression and £8.9 billion on anxiety disorders annually, including direct service costs and lost employment and earnings, but not public services or informal care costs (Department of Health, 2011). In addition, looking after a loved one with an affective disorder also brings risks of mental and physical health problems to carers (Shah, Wadoo, & Latoo, 2010). Poor health in carers is linked with greater use of health and social care services, such as increased admissions, delayed discharge, or unplanned

readmission to hospital (Hirst, 2004). As such, protecting mental health is important to improve quality of life, decrease caregiver burden, reduce demand on NHS services, cut social and healthcare costs associated with mental health, and increase the number of people who are able to continue working for longer.

1.2.2. Affective problems and cognitive ageing: state of the art and methodological limitations.

Research suggests that affective problems, such as depression and anxiety, frequently occur in individuals with late-life cognitive problems, including dementia (Potter & Steffens, 2007). Several studies have investigated prevalence rates of depression in dementia patients, but there is variation in prevalence rates reported. Approximately 30-50% of people diagnosed with dementia also present with symptoms of depression (Zubenko et al., 2003), though some studies report much higher estimates of up to 75% (Jost & Grossberg, 1996). Some evidence suggests that depression in people with dementia is particularly common during the early stages of dementia, and is also prevalent once dementia symptoms have become more advanced and at this later stage is often observed in parallel with agitation symptoms (Lyketsos & Lee, 2004).

In addition to cross-sectional evidence, a growing body of longitudinal research has found associations between affective problems and cognitive ageing over time. Several systematic reviews and meta-analyses have been conducted to address this research question. Specifically, depression has been associated with an increased risk of developing subsequent dementia (Da Silva et al., 2013; Diniz, Butters, Albert, Dew, & Reynolds, 2013; Jorm, 2001; Livingston et al., 2017; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). For example, Jorm (2001) conducted a review and meta-analysis of seven case-control and six prospective cohort studies testing associations between the life history of depression and risk of dementia. The study revealed that depression was

significantly associated with an increased risk of developing dementia, specifically concluding that depression approximately doubles this risk.

Additionally, Ownby et al (2006) reviewed nine case-control and eleven cohort studies with the total sample of 102,172 participants, testing associations between presence of depression (both retrospectively and prospectively measured) and risk for developing Alzheimer's disease. Overall, pooled odds ratios from the meta-analysis revealed that presence of depression was significantly positively associated with risk for developing Alzheimer's disease. Specifically, the odds of developing Alzheimer's disease are around two times higher in people with depression than those without. In addition, meta-regression analyses showed that the interval between diagnosis of depression and Alzheimer's disease was positively associated with increased risk of developing dementia. The authors concluded that depression may act as a remote risk factor for Alzheimer's disease, rather than as a prodrome. It is, however, acknowledged that due to the small number of studies included in the meta-regression analysis, these results should be interpreted with caution and replicated in future research for confirmation.

Da Silva et al (2013) conducted a systematic review of 51 case-control and cohort studies (with the total sample of 464,724 participants) investigating associations between affective disorders and risk of developing dementia. Overall, this review concluded that depression is associated with increased risk. The review also reported that greater severity of affective symptoms at baseline and the frequency of affective episodes experienced are both associated with a higher risk of dementia. Results revealed inconsistent evidence regarding how age of onset of depression may affect dementia risk. Equally, Da Silva et al (2013) reviewed studies which tested sex

differences in associations between affective symptoms and risk of dementia, but revealed that the evidence was mixed.

Diniz et al (2013) conducted a systematic review and meta-analysis of 23 population-based prospective cohort studies testing associations between late-life depression and risk of Alzheimer's disease (N= 28,746), vascular dementia (N= 14,901), and all-cause dementia (N= 49,612). Results revealed that people with depression had 1.85 higher odds of developing all-cause dementia, 1.65 higher odds of developing Alzheimer's disease, and 2.52 higher odds of developing vascular dementia then people without depression. In addition, the review concluded that risk for vascular dementia was significantly higher than for Alzheimer's disease in adults with depression during later life. This review did not include studies looking at depression earlier in the life course, so it is unclear how early onset depression can differentially affect risk for Alzheimer's disease and vascular dementia. Integrating these results with those from Ownby et al (2006), there is evidence that depression in both earlier and later adulthood may be associated with increased risk of dementia.

Research investigating longitudinal associations between anxiety and dementia is scarcer than for depression. However, there have been several systematic reviews aiming to explore these associations (Gimson, Schlosser, Huntley, & Marchant, 2018; Gulpers et al., 2016). One such review concluded that anxiety symptoms are associated with an increased risk of incident cognitive impairment and dementia in community-based samples (Gulpers et al., 2016). In contrast to evidence from Ownby et al (2006), this review observed strongest associations in later ages. In addition, evidence from a recent systematic review has shown that clinically relevant anxiety symptoms present during midlife are associated with increased risk of dementia across a follow up period of over a decade (Gimson et al., 2018).

Taken together, these reviews demonstrate that there is reasonably strong evidence to suggest that depression can increase risk of dementia. In addition to this, affective disorders have also been shown to increase the risk of progression from mild cognitive impairment to dementia (Alexopoulos, Young, & Meyers, 1993; Kral & Emery, 1989; Potter & Steffens, 2007). The number of Alzheimer's disease cases attributable to depression is estimated to be 3.6 million worldwide, comprising over 10% of all Alzheimer's disease cases (Barnes & Yaffe, 2011). A reduction of 25% of depression cases could potentially prevent as many as 827,000 cases of Alzheimer's disease globally (Barnes & Yaffe, 2011).

To date, research has focussed largely on associations between affective symptoms and dementia, with less attention paid to affective symptoms and cognitive decline in cognitively healthy older adults. However, this focus on transition to dementia as an outcome without consideration of cognitive function short of clinically diagnosable dementia may have methodological flaws. Specifically, there is a long preclinical period of several decades for dementia. It is therefore possible that individuals who transition to dementia at follow up may have already had underlying neuropathological changes indicative of dementia without presentation of clinically observable symptoms at the baseline assessment. As such, any associations apparent between affective symptoms and transition to dementia could simply be due to reverse causality, whereby dementia neuropathology leads to affective symptoms rather than vice versa.

In addition, evidence has also shown that even before any pathological cognitive changes, mild cognitive decline can have a substantial impact on both individuals and society. Specifically, cognitive decline can predict greater functional disability and dependence in older ages (Millan-Calenti et al., 2012). Additionally, cognitive decline

remains one of the most feared elements of the ageing process (Deary, Corley, et al., 2009; Plassman et al., 2010). As such, it is clear that greater understanding of the life course factors associated with cognitive decline short of dementia is both necessary and important. A better understanding of associations between affective symptoms and cognitive ageing over time may be potentially critical for the development of stronger life course predictive models, which may have important implications for designing preventative intervention studies.

There have been a few studies investigating associations between affective symptoms and cognitive decline in healthy older adults, but due to mixed and conflicting findings as a result of differences in methodology, design, sampling, and measures used, it is difficult to draw a clear and robust conclusion from this work. Some research has shown that affective symptoms are associated with poorer cognitive outcomes and faster cognitive decline (Chang & Tsai, 2015; Chen & Chang, 2016; Geerlings, Schmand, Braam, & Jonker, 2000; Johnson, Hall, & O'Bryant, 2013; Paterniti, Verdier-Taillefer, Dufouil, & Alperovitch, 2002; Rajan, Wilson, Skarupski, Leon, & Evans, 2014; Reyes-Ortiz et al., 2008; Royall & Palmer, 2013). However these conclusions have not been consistently replicated (Bassuk, Berkman, & Wypij, 1998; Brailean et al., 2017; Bunce, Batterham, Mackinnon, & Christensen, 2012; Gale, Allerhand, & Deary, 2012; Ganguli, Du, Dodge, Ratcliff, & Chang, 2006; Neubauer, Wahl, & Bickel, 2013). There is therefore good reason to hypothesise that affective symptoms can play an important role in predicting later cognitive function and decline in cognitively healthy people; however the absence of any systematic synthesis of the research means that this is still unknown. In addition to this, our understanding of the nature of this association is also limited. Evidence from previous research suggests that risk of poorer cognitive ageing outcomes in later life may be proportionate to the

cumulative effects, symptom severity, or age of onset of affective symptoms. However, to date limited research has aimed to directly address these questions.

Accumulation of affective problems.

It is possible that the frequency of affective problems over the life course may influence risk of subsequent cognitive decline and dementia. Paterniti et al (2002) reported that persistent, rather than episodic, episodes of depression were associated with cognitive decline. This study, however, only assessed cognitive function at a four-year follow up, so these findings cannot extend to depressive symptoms present prior to late life. (Kessing & Andersen, 2004) utilised a case register study design to address this research question and found that a greater frequency of depressive episodes conferred a significantly increased risk of dementia. Specifically, there was a 13% increase in rate of dementia with every depressive episode which resulted in hospital admission. Additionally there was a 6% increase in dementia rate with every episode of bipolar disorder. This has also been replicated in a longitudinal study in which participants were followed for 24.7 years (Dotson, Beydoun, & Zonderman, 2010). Specifically, a monotonic increase in dementia and Alzheimer's disease was observed as a function of the number of depressive episodes over the period of assessment. It was reported that one episode of depression was associated with an 87-97% increased risk of subsequent dementia, and two or more episodes resulted in a near doubling of this risk. There have also been several cross-sectional studies utilising a sample of euthymic phase affective problem patients, which have reported that the number of affective episodes was significantly related to severity of cognitive dysfunction (Kessing, 1998; Kessing, Dam, Jørgensen, & Bolwig, 1996; Tham et al., 1997). These findings suggest that greater accumulation of episodes over the life course may increase the strength of the

relationship between affective problems and cognitive ageing, although there has been some evidence to the contrary.

Timing of affective problems.

Age of onset of affective problems (i.e. early or late-onset specifiers) has been used to investigate whether affective problems are a real aetiological risk factor for subsequent cognitive conditions, an early clinical manifestation of dementia (prodromal), or a psychological reaction to the disease process. Results have been varied, rendering a straightforward conclusion problematic. Several studies have presented evidence that late-onset affective problems alone are associated with an increased risk of cognitive decline (Brommelhoff et al., 2009; Steffens et al., 1997), while conversely others have reported that early-onset affective problems can increase this risk (Geerlings, den Heijer, Koudstaal, Hofman, & Breteler, 2008; Pálsson, Aevarsson, & Skoog, 1999; Speck et al., 1995), with one systematic review showing that associations are stronger when the interval between depression diagnosis and dementia is longer (Ownby et al., 2006). Several additional studies have also offered evidence to suggest that the risk of developing cognitive conditions was increased when affective problems presented both in years proximal to dementia, and also many years prior (25 years prior to dementia diagnosis) (Green et al., 2003).

Studies using prospective as well as cross-sectional designs, have investigated the association between late-life depression and dementia. Several studies reported that late-life depression was associated with approximately a 2 to 5-fold increased risk of later dementia (Andersen, Lolk, Kragh-Sørensen, Petersen, & Green, 2005; Byers, Covinsky, Barnes, & Yaffe, 2012; Chen et al., 2008; Gatz, Tyas, St. John, & Montgomery, 2005; Saczynski et al., 2010), and Wilson et al (2002) also concluded that

risk of pathological cognitive ageing increased with each additional symptom of depression. However, some studies have only reported evidence for an association between late-life depression and dementia within specific sub-groups, such as in men only (Fuhrer, Dufouil, & Dartigues, 2003), sub-groups with the *APOE4* gene (Irie et al., 2008), and more highly educated samples (Geerlings et al., 2000). There have also been two studies which found no association at all (Becker et al., 2009; Lindsay et al., 2002), although this lack of evidence may have been related to a lack of power in one (Becker et al., 2009). These contradictory findings across studies may reflect methodological differences in terms of attrition rates, methods of measuring affective problems, sub-populations assessed, and definitions or operationalisation of key measures. Additionally many studies did not specifically report frequency, severity, or duration of affective episodes.

Research has also begun to use longitudinal methodology to explore the relationship between earlier-life (defined as before age 60) affective problems and dementia. Early onset depression has been proposed to be associated with a 2 to 4-fold increased risk of dementia in late life (Byers & Yaffe, 2011). Dal Forno et al (2005) analysed depression at multiple pre-set time lengths prior to onset of dementia. They concluded that depression was associated with a 2-fold increased risk of dementia only when interval between depression onset and dementia diagnosis was greater than 4 years, suggesting that depression was unlikely to be exclusively a prodromal feature of dementia. Dotson et al (2010) also examined recurrent depression over several decades, and concluded that cumulative depression episodes over the life course can increase the risk of subsequent late-life dementia. Beyond this, Barnes et al (2012) found that age of onset can have differential patterns of risk depending on dementia sub-type. Specifically, they reported that depression with an earlier onset and accumulation over

the entire life course may be associated with an increased risk of vascular dementia, whereas an increased risk of Alzheimer's disease may be dependent to a greater degree on late-life exposure to depression.

Severity of affective problems.

There is also evidence to suggest that greater severity of depressive symptomology is associated with a higher risk of developing dementia (Saczynski et al., 2010) and Alzheimer's disease (Gatz et al., 2005), suggesting that severity is likely to play an important role within the lifelong relationship between affective problems and cognitive ageing. Similarly, it was reported in the Cardiovascular Health Study (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006) that the presence of a greater severity of depressive symptoms independently predicted a more than doubled risk of developing mild cognitive impairment (MCI) after a 6 year follow up. Beyond this, in a prospective cohort study Yaffe et al (1999) concluded that a greater number of depressive symptoms was significantly related to increased risk of a dementia diagnosis after a 4 year follow up. Individuals with 3-5 depressive symptoms were reported to have a two-fold increased risk of dementia compared with individuals exhibiting 0-2 symptoms. Similarly, individuals who reported 6 symptoms had a three-fold increased risk of dementia. Wilson et al (2002) reported that for each additional symptom of depression, global cognitive decline increased by approximately 24% and risk of Alzheimer's disease increased by 19% at a 7 year follow up. However, much of this evidence focuses primarily on late-life depression and limited evidence is available regarding the influence of severity of affective problems at an earlier stage in the life course with a longer follow up period (>10 years).

1.2.3. Affective problems and cognitive ageing: Competing hypotheses.

Three primary hypotheses have been proposed to explain observed associations between affective symptoms and cognitive ageing. It remains contentious whether affective problems: 1. act as a real etiological factor for dementia; 2. are an early prodromal feature of dementia; or 3. share a common cause, e.g. genetic or neurophysiological.

It has been proposed that affective problems over the life course can act as an etiological factor for poorer cognitive outcomes. This hypothesis was supported by a meta-analysis, which showed that the interval length between diagnoses of depression and dementia was positively associated with risk of developing Alzheimer's disease, suggesting that depression can act as a remote risk factor for dementia (Ownby et al., 2006). However, Brommelhoff et al (2009) argued that only a small minority of the studies included in this review showed that an onset of depression more than 10 years prior to emergence of cognitive deficits was associated with an increased risk of late-life Alzheimer's disease (Pálsson et al., 1999; Speck et al., 1995), so as such these conclusions should be interpreted with caution.

The second potential explanation for the observed link between affective problems and pathological cognitive ageing is that affective problems may act as a prodromal feature of dementia. Several studies have reported an increased risk of dementia only for affective episodes in which first onset was proximal to dementia diagnosis (Berger, Fratiglioni, Forsell, Winblad, & Bäckman, 1999; Chen, Ganguli, Mulsant, & DeKosky, 1999; Wetherell, Gatz, Johansson, & Pedersen, 1999; Yaffe et al., 1999). This provides support for the hypothesis that affective problems may manifest as an early clinical presentation of dementia. However, in a recent review, Da

Silva et al (2013) argued that the risk of developing dementia is not limited to late life depression. Although dementia pathology can begin to build up in midlife, Da Silva et al (2013) propose that it is unlikely that depression would manifest as a symptom of dementia related neuropathological changes this early in life. For this reason, the authors concluded that increased risk of dementia as a result of affective problems cannot be explained exclusively by the prodromal hypothesis. As such, observed associations between affective symptoms and risk of dementia may be due to reverse causality, whereby affective symptoms may arise as a response to emerging cognitive impairment and its functional consequences.

It is also possible that affective problems and cognitive ageing may share common risk factors (Jorm, 2001). One such example of a mechanism which may act as a common substrate is vascular disease (Singh-Manoux et al., 2010), which may be involved in the clinical expression of both Alzheimer's disease and depression (see Taylor, Aizenstein, & Alexopoulos, 2013 for a comprehensive review of the vascular depression hypothesis). There has been some suggestion that a reciprocal relationship between vascular disease and depression may exist, whereby each condition is related to a higher risk of subsequently developing the other (Alexopoulos, 2006; Alexopoulos et al., 1997; Newberg, Davydow, & Lee, 2006). Additionally, vascular disease contributes to the clinical manifestation and presentation of symptoms of late-life cognitive conditions, such as dementia (Luchsinger et al., 2005; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005).

These hypotheses are not mutually exclusive. Unfortunately, due to the relatively short follow-up periods (>10 years) in many prior studies in the area (Singh-Manoux et al., 2010), a straightforward conclusion regarding explanations for association between affective problems and cognitive ageing is not yet achievable.

Given that dementia has a relatively long preclinical period, studies with short follow-ups are unable to distinguish between prodromal symptoms of preclinical dementia and etiological risk factors. Longitudinal life course studies in which lengthy follow ups are possible are therefore essential to further elucidate the temporal relationship between affective problems and cognitive ageing.

1.2.4. Plausible underlying mechanisms of the association: inflammatory processes.

It is likely that associations between affective problems and cognitive ageing are underpinned by multiple interacting biological mechanisms, including inflammatory processes, genetic factors, and neuroendocrine factors. Chronic inflammation may be particularly important for this association (Byers & Yaffe, 2011). Specifically, chronic depressive symptoms are associated with an increase in cytokines, which can reduce anti-inflammatory regulation and increase CNS pro-inflammatory changes, which have been associated with development of dementia (Sorrells & Sapolsky, 2007; Yaffe et al., 2003). It is also known that pro-inflammatory cytokines can impair serotonin metabolism, reduce neurogenesis in the hippocampus, and ultimately increase risk of dementia (Caraci, Copani, Nicoletti, & Drago, 2010; Maes et al., 2009). Cross-sectional research has shown that level of depression is significantly associated with plasma levels of inflammatory markers, such as C-Reactive Protein (CRP) (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Raison, Capuron, & Miller, 2006), and prospective longitudinal cohort studies have also provided evidence that depressive symptoms can be positively associated with levels of inflammation over time (Copeland, Shanahan, Worthman, Angold, & Costello, 2012). Beyond this, longitudinal studies have also shown that levels of inflammation during midlife are associated with risk of dementia after a follow up period of 25 years, and with risk of cognitive decline over time in

well-functioning older people (Koyama et al., 2013; Kuo et al., 2005; Schmidt et al., 2002; Yaffe et al., 2003). Taken together, this evidence suggests that inflammation may play an important role in the association between affective symptoms and poorer cognitive ageing, though this hypothesis has not been directly tested using birth cohort resources.

1.3. Research aims

This thesis has an overarching aim to investigate associations between affective symptoms over the life course, from childhood through to later adulthood, and cognitive function and ageing from middle to later adulthood in a population without dementia. Specifically, this work sought to clarify and extend previous research by using a life course approach to test these associations and to explore inflammation as a plausible biological mechanism which may underlie associations between affective symptoms and cognitive function. The conceptual framework for this thesis is presented in Figure 1.4.1.

Chapter 2 presents a systematic literature review and meta-analysis of the available literature investigating associations between affective symptoms over the life course and cognitive decline. The primary aims of this review are: 1. to investigate whether affective symptoms (both as a binary and a continuous measure) are associated with a faster subsequent cognitive decline; 2. to highlight methodological limitations of the previous research into this area in order to inform and guide the following empirical studies included in this thesis.

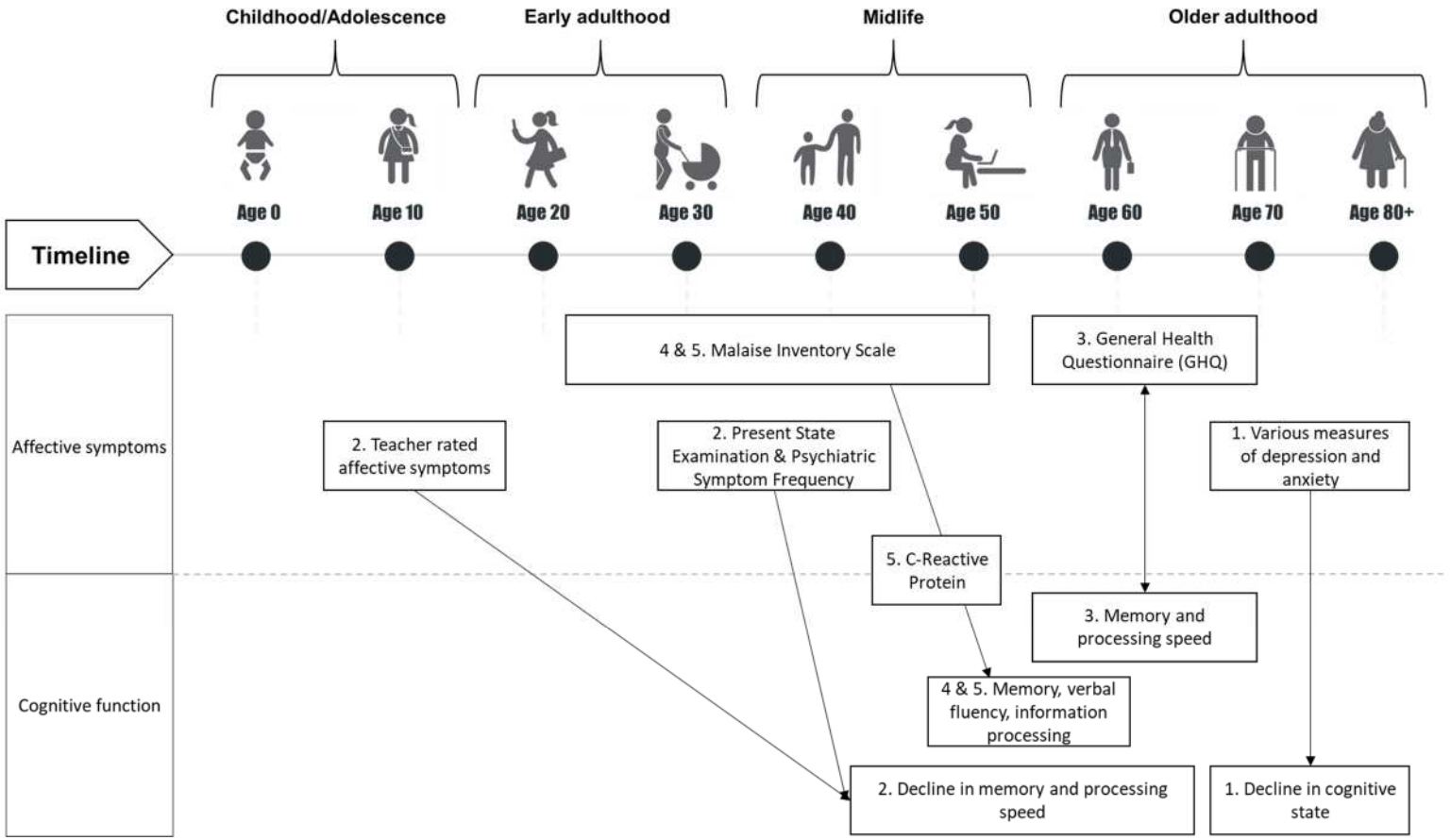
Chapters 3 and 4 present studies that used data from the National Survey of Health and Development (NSHD), a nationally representative sample of 5,362 people born in England, Scotland and Wales during 1 week of 1946. Study 2 focuses on two

primary aims: 1. to model verbal memory and processing speed trajectories from mid- to later adulthood, as in previous research (Davis et al., 2017; Rawle, Davis, et al., 2018); 2. to test how affective symptoms in adolescence & adulthood are associated with adult cognitive function at baseline (age 43) and decline (age 43 to 69). The primary aim of Study 3 is to test bidirectional relationships between affective symptoms and cognition function over a period of 16 years from middle to later adulthood (age 53 to 69).

Chapters 5 and 6 present two studies that used data from the National Child Development Study (NCDS), a population based birth cohort of 18,558 people born in mainland UK during 1 week of 1958. Chapter 5 comprised three main aims: 1. to investigate whether timing or accumulation of affective disorders predicts midlife cognitive outcomes; 2. to derive longitudinal trajectories of affective symptoms over adulthood (age 23 to 50); 3. to test how trajectories of affective symptoms are associated with cognitive function in mid-life. The aim of Chapter 6 was to test whether inflammation can act as a mediator in the association between adult affective symptoms and cognitive outcomes in midlife.

1.4. Tables and figures

Figure 1.4.1: Conceptual framework of thesis



CHAPTER 2

Study 1: Affective problems and decline in cognitive state in older adults: a systematic review and meta-analysis.

Study 1 is published in *Psychological Medicine* as:

John, A., Patel, U., Rusted, J., Richards, M., & Gaysina, D. (2018). Affective problems and decline in cognitive state in older adults: a systematic review and meta-analysis. *Psychological Medicine*, *49*(3), 353-365.

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2.1. Abstract

Evidence suggests that affective problems, such as depression and anxiety, increase risk for late-life dementia. However, the extent to which affective problems influence cognitive decline, even many years prior to clinical diagnosis of dementia, is not clear. The present study systematically reviews and synthesises the evidence for the association between affective problems and decline in cognitive state (i.e., decline in non-specific cognitive function) in older adults. An electronic search of PubMed, PsycInfo, Cochrane, and ScienceDirect was conducted to identify studies of the association between depression and anxiety separately and decline in cognitive state. Key inclusion criteria were prospective, longitudinal designs with a minimum follow-up period of 1 year. Data extraction and methodological quality assessment using the STROBE checklist were conducted independently by two raters. A total of 34 studies (n = 71 244) met eligibility criteria, with 32 studies measuring depression (n = 68 793), and five measuring anxiety (n = 4698). A multi-level meta-analysis revealed that depression assessed as a binary predictor (OR 1.36, 95% CI 1.05–1.76, p = 0.02) or a continuous predictor (B =−0.008, 95% CI −0.015 to −0.002, p = 0.012; OR 0.992, 95% CI 0.985–0.998) was significantly associated with decline in cognitive state. The number of anxiety studies was insufficient for meta-analysis, and they are described in a narrative review. Results of the present study improve current understanding of the temporal nature of the association between affective problems and decline in cognitive state. They also suggest that cognitive function may need to be monitored closely in individuals with affective disorders, as these individuals may be at particular risk of greater cognitive decline.

2.2. Introduction

Decline in cognitive state is a central feature of ageing, and severe deterioration in cognitive function has frequently been associated with poorer quality of life and worse performance on physical tasks (Tabbarah, Crimmins, & Seeman, 2002). Accelerated decline in cognitive state also has an influential and adverse impact upon the psychological, social, emotional and financial status of the individual, which can subsequently contribute to heightened levels of burden and distress (Wilson et al., 2007). Cognitive symptoms are common in affective disorders, particularly impairments in memory, executive control, feedback sensitivity and affective processing (Clark, Chamberlain, & Sahakian, 2009). These cognitive symptoms are associated with pathophysiology across a distributed neural circuit, which is made up of various regions across the prefrontal cortex, as well as subcortical regions and also temporal lobe structures (Clark et al., 2009). Both affective disorders, such as depression and anxiety, and poor cognitive function are common in older adulthood (Alexopoulos & Abrams, 1991; Rovner, Broadhead, Spencer, Carson, & Folstein, 1989). It is estimated that after age 70, the combination of low mood and poor cognition doubles with every 5 years. By age 85, around one in four of individuals experience both these comorbid conditions (Arve, Tilvis, Lehtonen, Valvanne, & Sairanen, 1999). Due to the high prevalence of these conditions in older adulthood, this is a research area of clinical relevance and importance.

Previous research has proposed that affective problems, such as depression and anxiety, may be associated with accelerated cognitive ageing (Da Silva et al., 2013; Gulpers et al., 2016). However, there are significant gaps in our understanding of this link. For instance, the precise temporal order of the association between affective problems and decline in cognitive state is currently unclear. It is possible that affective

problems may act as an early risk factor for decline in cognitive state, or alternatively that affective problems may be a prodromal symptom of oncoming cognitive impairment. Additionally, previous studies, including several meta-analyses, have been largely diagnosis driven, with a primary focus on dementia as an outcome (Bennett & Thomas, 2014; Byers & Yaffe, 2011; Cherbuin, Kim, & Anstey, 2015; Da Silva et al., 2013; Jorm, 2001; Ownby et al., 2006). Less is known about the impact of affective problems on decline in cognitive state across the entire population spectrum. The focus on the transition to dementia as an outcome may be problematic, as it is now believed that there is a long pre-clinical period of several decades before cognitive impairment becomes evident (Morris, 2005). It is possible that participants who transition to dementia at follow-up assessment may have already developed substantial cerebral pathology by the time of baseline assessment, even if they had not yet presented with any cognitive symptoms. In this case, associations between affective disorders and development of dementia may be the result of reverse causality. The present study focuses on the association between affective disorders and decline in cognitive state in healthy older adults in order to minimise effects of possible reverse causality.

Cognitive state refers to a composite measure of overall cognitive function. It has been studied extensively in previous research (Esslinger et al., 2011; Kave, Eyal, Shorek, & Cohen-Mansfield, 2008; Nordin, Rosendahl, & Lundin-Olsson, 2006; Sohrabi et al., 2008), using assessments of overall cognitive status, such as the Mini-Mental State Examination (MMSE) or composite assessments of multiple cognitive domains (e.g. memory, information processing speed, executive function). Therefore, decline in cognitive state is defined in the present review as a decline in overall cognitive function, rather than decline in specific cognitive domains. There is evidence from longitudinal research that low scores on cognitive state tests may predict onset of

functional impairment (Gill et al., 1996; Moritz, Kasl, & Berkman, 1995), and functional dependence over time (Agüero-Torres, Thomas, Winblad, & Fratiglioni, 2002; Gill, Hardy, & Williams, 2002; Wang et al., 2002). For this reason, it is important to investigate how affective problems influence decline in cognitive state over time.

There are large individual differences in the extent of cognitive decline experienced by healthy older adults; however, the decline in cognitive state occurs at a steady and gradual rate over time. On average there is a decline of around 1–2 standard deviations in fluid cognition from age 20 to 70, after which average decline increases to around 0.5 S.D. every 10 years (Anstey & Low, 2004). This stable decline is often maintained over time until symptoms of dementia begin to manifest, at which point a sharper decline in cognitive state may be observed (Rubin et al., 1998). As such, studies in which substantial cognitive decline is apparent within a short time frame of under 1 year may be more indicative of pathological ageing (e.g. oncoming dementia), rather than healthy ageing. Since the present study aims to examine the longitudinal association between affective disorders and decline in cognitive state in cognitively healthy individuals, it includes only longitudinal studies with sufficient time between baseline and follow-up assessments (i.e., minimum 1 year) for a substantial decline to occur within these populations. There are several studies that have investigated the association between affective problems and decline in cognitive state (Bassuk et al., 1998; Brailean et al., 2017; Bunce et al., 2012; Chang & Tsai, 2015; Chen & Chang, 2016; Gale et al., 2012; Ganguli et al., 2006; Geerlings et al., 2000; Johnson et al., 2013; Kohler et al., 2010; Neubauer et al., 2013; Paterniti et al., 2002; Rajan et al., 2014; Reyes-Ortiz et al., 2008; Royall & Palmer, 2013). However, it is difficult to draw a straightforward conclusion from this work due to conflicting findings. Specifically, some studies report a significant association between affective problems and decline in

cognitive state (Chang & Tsai, 2015; Chen & Chang, 2016; Geerlings et al., 2000; Johnson et al., 2013; Kohler et al., 2010; Paterniti et al., 2002; Rajan et al., 2014; Reyes-Ortiz et al., 2008; Royall & Palmer, 2013), while conversely others report that affective problems do not predict decline (Bassuk et al., 1998; Brailean et al., 2017; Bunce et al., 2012; Gale et al., 2012; Ganguli et al., 2006; Neubauer et al., 2013). These contradictory results are likely attributable to inconsistencies in methodologies and study design, such as length of follow-up, sampling, definitions used, differences in assessment tools and also the primary aim of each study (Bennett & Thomas, 2014).

To date, however, there have been no systematic reviews or meta-analyses addressing associations between affective problems and subsequent decline in cognitive state, prior to the onset of dementia. Due to inconsistencies in findings, as well as the lack of attempts to synthesise these data, it is still unclear whether affective problems across the life course are associated with a decline in cognitive state, prior to the onset of dementia and cognitive impairment. The primary aim of the present study therefore was to systematically review and synthesise current evidence regarding the longitudinal association between affective problems (depression and anxiety separately) and subsequent decline in cognitive state, with consideration of several potential moderators, including mean age of sample at baseline, length of follow-up, quality of study and publication year. The conceptual framework for the research question of this chapter is presented in Fig. 2.6.1, testing whether measures of depression and anxiety in older adulthood are associated with subsequent decline in cognitive state.

2.3. Method

Search strategy.

This review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). A systematic literature search was conducted using PubMed, PsycInfo, Cochrane, and ScienceDirect databases for studies investigating the association between affective problems and decline in cognitive state. All studies published up to November 2016 were included in the search. There was no restriction on the start date. Our search terms comprised three search blocks (Table 2.6.1). The first search block included keywords relating to affective problems. The second search block contained keywords describing the decline in cognitive state. To reduce the number of irrelevant hits, a third search block was added, which contained keywords related to methodology, to ensure all studies with cross-sectional designs were excluded from search results. In addition, reference lists of relevant papers were scanned for studies of interest.

Inclusion/exclusion criteria.

Stringent inclusion/exclusion criteria were applied to studies identified through the initial search.

Design criteria.

Original studies written in English up to November 2016 were included. Only studies using longitudinal, prospective designs with human participants were included in order to test for the association between affective disorders and decline in cognitive state over time. Cross-sectional, case-control, experimental, including intervention and treatment, studies were excluded. Studies with a follow-up period of 1 year or greater

were included, as it is possible that substantial decline in cognitive state may not be observed over very short follow-up periods in a general population. Included studies used samples drawn from a general population, whereas studies using specific clinical populations only, for example, a sample of stroke patients, were excluded. This criterion was used because inclusion of clinical samples may increase the heterogeneity of data synthesis and reduce the comparability of studies. Studies with a sample size of 100 or less were also considered ineligible, due to insufficient statistical power.

Outcome-related criteria.

Samples with cognitive impairment or dementia present at baseline were excluded. In addition to this, studies with any measure of change in cognitive state from baseline to follow-up were selected for inclusion. Other outcomes, such as the transition to dementia or cognitive performance at follow-up without consideration of change from a baseline measure were omitted. This was because the present study aimed to look at the association between affective disorders and cognitive decline within healthy ageing populations, rather than samples with dementia. Additionally, studies assessing specific cognitive domains, such as attention or visuospatial ability exclusively, rather than cognitive state, were also excluded to reduce heterogeneity.

Predictor-related criteria.

Both diagnostic and dimensional measures of depression and anxiety at baseline assessment were judged as eligible. Studies with retrospective assessments of affective problems were excluded, as such assessments may be less reliable. Both binary indicators of affective problems, defined as either a diagnosis or as a score above a threshold level, or continuous symptoms scores, as assessed by a validated scale of affective problems were included in this review.

Screening procedure.

All studies identified through our search strategy were screened for eligibility using a three-step process. All references were first reviewed by title. Next, the remaining references were screened by abstract. Finally, all remaining studies were read in full and final eligibility determinations were made on this basis. All studies were reviewed for inclusion by one rater, and 10% of all studies were additionally screened by an independent rater, in order to assess the consistency of screening. Any disagreements were resolved during consensus meetings.

Data extraction.

Data from the relevant studies were extracted using a detailed coding form. Information extracted included: Study information (Authors, publication year, DOI); Sample information (Country, mean age at baseline, gender composition, ethnicity, year of data collection, number of follow-ups, time between lags, total length of follow-up, sample size at baseline, sample size at final follow-up); Instrument information (Type of affective problem, measure used to assess affective problem, measure used to assess decline in cognitive state); Statistical information (Statistical test used, effect sizes, covariates adjusted for in statistical model). Where results for more than one follow-up were reported, the longest follow-up was selected for our analysis, as longer follow-up times allow a greater period for the decline in cognitive state to occur. Similarly, where multiple models were reported with various adjustments made, the most conservative model (with the greatest amount of adjustments) was selected. In cases where insufficient statistical information was available, original authors were contacted directly via email. All studies were evaluated for methodological quality using

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Elm, Altman, Egger, Pocock, & Gøtzsche, 2007).

Statistical analysis and data synthesis.

All analyses were conducted in R Studio (Studio, 2012), using the metafor package. Separate meta-analyses were run for studies in which affective problems were assessed as a binary predictor (using a defined threshold), and studies where affective problems were assessed as a continuous predictor (using a symptom score). In addition, separate analyses were conducted for studies that used depression or anxiety as predictors of decline in cognitive state.

Odds ratios (ORs) were used as a common effect size across studies with a binary measure of affective problems. When ORs were not reported in original studies, these were estimated from available data using standard computational techniques (Borenstein, Hedges, & Rothstein, 2009; Field & Gillett, 2010; Lipsey & Wilson, 2000). Log ORs were then computed for subsequent analysis. Standardised regression coefficients were used as a common effect size across studies with a continuous measure of affective problems. If unstandardised effect sizes were reported, or measures were not standardised to a z score before analysis, coefficients were converted to standardised coefficients using standard computational methods (Duncan, 2014; Kim & Ferree Jr, 1981). In cases where insufficient information was reported in the study to calculate the standardised coefficients, authors were contacted directly via email. We also converted the estimated regression coefficients into ORs to facilitate the comparison with the analyses using a binary predictor of depression.

Multi-level meta-analyses were conducted to account for multiple effect sizes within studies (Van Den Noortgate & Onghena, 2003). Heterogeneity across studies

was assessed using the Q statistic, with $p < 0.1$ suggesting significant heterogeneity between studies, and the I^2 statistic, in which 25, 50 and 75% represent low, medium and high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003).

Additional meta-regression analyses were also conducted to assess the effects of potential moderators, including the length of follow-up, age of sample at baseline, publication year, method of affective problem assessment (diagnosis or self-report) and quality of studies. All moderators were entered initially as continuous variables, except for the assessment method of affective problems which was coded as a binary variable. For significant moderators, binary variables were created using the average values and sub-group analyses were run using these variables.

Publication bias was assessed using Begg's funnel plot and Begg's rank correlation test (Egger, Davey-Smith, & Altman, 2008; Song, Eastwood, Gilbody, Duley, & Sutton, 2000).

2.4. Results

Literature search.

Our search identified 25 844 references. After exclusion of duplicates, 20 954 unique citations remained. At stage 1, citations were screened by title and 981 were determined to be eligible (interrater reliability = 96%). In stage 2, remaining citations were screened by abstract and 185 were judged as relevant (inter-rater reliability = 91%). Finally, all 185 citations were selected for full text screening, after which 84 references remained (inter-rater reliability = 94%). At this stage, a further 36 studies were excluded, as they were addressing decline in specific cognitive outcomes, rather than cognitive state. Of the 48 studies remaining, initially there were 18 with insufficient information for calculation of effect sizes. Authors were contacted directly by email about this and four responded to provide the relevant information. This left a total of 34 studies with sufficient information to calculate effect sizes, with 32 studies investigating the link between depression and a decline in cognitive state (n = 68 793), and five studies investigating anxiety and decline in cognitive state (n = 4698; Fig. 2.6.2 and Table 2.6.2).

Depression studies.

Of the depression studies, 17 used a binary measure of depression (k = 34) and 16 measured depression as a continuous variable (k = 36). Depression studies had a mean follow-up length of approximately 6.61 years (S.D. = 4.41). The mean age of participants was 72.15 at baseline (S.D. = 7.56) and the gender composition of the sample was approximately 59.48% female. The majority of studies took place in the USA (n = 14), followed by the Netherlands (n = 4) and Taiwan (n = 3). Studies also took place in Australia, Canada, France (n = 2 for each), Germany, England, Italy,

Singapore and Japan, Hawaii and the mainland-USA (n = 1 for each). Overall, the majority of studies used the Center for Epidemiologic Studies Depression Scale (CES-D) to assess depression present at baseline (n = 16), followed by the Geriatric Depression Scale (GDS) (n = 7), the Diagnostic Interview Schedule (DIS) (n = 3), the Neuroticism scale from the NEO Personality Inventory, the Duke Depression Evaluation Schedule (DDES), the Goldberg Depression Scale, Neuropsychiatric Inventory, Hamilton Rating Scale for Depression (HDRS), the Symptom Checklist (n = 1 for each). Only one study reported separate effect sizes for more than one follow-up period (Bassuk et al., 1998). This study reported effect sizes at 3 years after baseline (n = 2030), 6 years after baseline (n = 1447) and 12 years after baseline (n = 756). The effect size with the longest follow-up (12 years) was selected for inclusion in the meta-analysis.

Anxiety studies.

Of the five anxiety studies, two used a binary indicator of anxiety (k = 2) and three used a continuous measure of anxiety (k = 3). Anxiety studies had a mean follow-up time of 5.9 years (S.D. = 4.36). On average, participants were 76.56 years old at baseline (S.D. = 4.23) and were predominantly female (60.14% female). The majority of studies took place in Australia (n = 2), followed by the USA, the Netherlands and Israel (n = 1 for each). Anxiety was assessed using Sinoff's Short Anxiety Screening Test (SAST), Hospital Anxiety and Depression Scale-Anxiety (HADS-A), Neuropsychiatric Inventory, Goldberg Anxiety Scale and the Neuroticism scale from the NEO Personality Inventory (n = 1 for each). All anxiety studies had a score of 60% or greater on the STROBE checklist (maximum score = 81%, median score = 78%).

Depression and decline in cognitive state.

Meta-analysis of studies with depression as a binary predictor.

There were 34 relevant effect sizes across 17 studies with a binary measure of depression (Bassuk et al., 1998; Brodaty et al., 2012; Chang & Tsai, 2015; Downer, Vickers, Al Snih, Raji, & Markides, 2016; Dufouil, Fuhrer, Dartigues, & Alperovitch, 1996; Ganguli et al., 2006; Geerlings et al., 2000; Han, McCusker, Cole, Abrahamowicz, & Čapek, 2008; Kohler et al., 2010; Niti, Yap, Kua, & Ng, 2009; Paterniti et al., 2002; Raji, Reyes-Ortiz, Kuo, Markides, & Ottenbacher, 2007; Reyes-Ortiz et al., 2008; Rosenblatt, Mehta, Romanoski, Eaton, & Lyketsos, 2003; Sawyer, Corsentino, Sachs-Ericsson, & Steffens, 2012; Wilson et al., 2016; Yaffe et al., 1999). A multi-level meta-analysis of 34 effect sizes revealed that depression was associated with an increased risk of subsequent decline in cognitive state (OR 1.36, 95% CI 1.05–1.76, p = .02; Fig. 2.6.3).

Assessment of heterogeneity, meta-regression and sub-group analyses.

Significant heterogeneity was observed across the studies with depression as a binary predictor (Q = 106.83, df = 33, $p < 0.0001$, $I^2 = 69.08\%$). An omnibus meta-regression analysis including publication year, mean age at baseline, length of follow-up, method of depression assessment (diagnosis or self-report) and quality of study revealed that these variables together were able to explain a significant amount of heterogeneity in the model (QM= 13.32, df = 5, $p = 0.02$). However, even after accounting for these factors, significant heterogeneity remained in the model (QE = 93.51, df = 28, $p < 0.0001$). To further explore the effect of publication year, age at baseline, length of follow-up, depression assessment and quality on heterogeneity, individual meta-regressions were conducted for each of these potential modifiers. These analyses revealed that mean age at baseline ($p = 0.13$), publication year ($p = 0.19$),

quality of the study ($p = 0.09$) and depression assessment ($p = 0.91$) did not significantly explain the between-study variability.

Meta-regression analyses including the length of follow-up showed significant between-study variability, whereby studies with shorter follow-up periods had significantly greater effect sizes than studies with longer follow-up periods (B = −0.03, S.E. = 0.009, $p = 0.002$). Additionally, meta-regression analyses including the method of cognitive assessment (MMSE v. neuropsychiatric batteries) showed significant between-study variability (B = −0.2, S.E. = 0.08, $p = 0.01$). To further explore precisely how these significant factors were involved in this association sub-group meta-analyses were conducted.

To explore how length of follow-up affected the association, effect sizes were divided by the mean follow-up length in years (M = 6.35 (S.D. = 4.25) years), resulting in two groups of longer (k = 7, M= 10.79 (S.D. = 2.45) years) and shorter follow-up periods (k = 10, M= 3.25 (S.D. = 1.48) years). Multi-level sub-group meta-analyses revealed that depression was significantly associated with decline in cognitive state in studies with shorter follow-up periods (OR 1.43, 95% CI 1.03–2.00, $p = 0.03$) and was approaching significance in studies with longer follow-up periods (OR 1.15, 95% CI 0.98–1.36, $p = 0.08$). However, the overall effect size was larger for studies with shorter follow-up periods than those with longer follow-up periods. Studies with longer follow-up periods did not differ significantly from studies with shorter follow-up periods on quality (t (14.29) = 1.08, $p = 0.3$), publication year (t (15.38) = 0.1, $p = 0.92$), mean age at baseline (t (10.67) = −0.41, $p = 0.69$), or depression assessment (t (14.07) = −0.5, $p = 0.63$).

The meta-regression analysis including the method of cognitive assessment suggested that effect sizes were significantly smaller for studies using the MMSE than studies using neuropsychiatric batteries (B = −0.2, S.E. = 0.08, $p = 0.01$). However, there were only four studies using neuropsychiatric battery assessments of cognitive state, so results need to be treated with caution.

Meta-analysis of studies with depression as a continuous predictor.

A multi-level meta-analysis of the 36 effect sizes across 16 studies with a continuous measure of depression was conducted (Bunce et al., 2012; Chen & Chang, 2016; Chiao & Weng, 2016; Dotson, Resnick, & Zonderman, 2008; Gale et al., 2012; Geerlings et al., 2000; Han, McCusker, Abrahamowicz, Cole, & Capek, 2006; Johnson et al., 2013; Neubauer et al., 2013; Panza et al., 2009; Rajan et al., 2014; Royall & Palmer, 2013; Turner, Capuano, Wilson, & Barnes, 2015; Van Den Kommer et al., 2013; Vinkers et al., 2004; Robert S Wilson, Begeny, Boyle, Schneider, & Bennett, 2011). This analysis revealed that depression was significantly associated with a decline in cognitive state (B = −0.008, 95% CI −0.015 to −0.002, $p = 0.012$; Fig. 2.6.4; OR 0.992, 95% CI 0.985–0.998).

Assessment of heterogeneity and meta-regression analyses.

Significant heterogeneity was observed across studies with depression as a continuous predictor (Q = 93.86, df = 35, $p < 0.0001$, $I^2 = 69.74\%$). In order to try and explain some of this heterogeneity, an omnibus meta-regression analysis was conducted, including mean age at baseline, length of follow-up, quality and publication year as potential moderators. This analysis revealed that together these variables were not able to explain a significant amount of the heterogeneity in the model (QM = 8.97, df = 4, $p = 0.06$), but even after accounting for these factors, significant heterogeneity

remained within the model (QE = 84.9, df = 31, $p < 0.0001$). In order to explore the influence of age at baseline, follow-up length, quality and publication year in more depth, individual meta-regressions were conducted for each potential modifier. These analyses revealed that mean age at baseline ($p = 0.27$), length of follow-up ($p = 0.1$), publication year ($p = 0.18$), method of cognitive assessment ($p = 0.47$) and quality ($p = 0.11$) could not significantly explain between-study variability individually.

Publication bias.

Publication bias is unlikely for meta-analyses of depression studies measured as a continuous variable, as Begg's rank correlation test was non-significant ($p = 0.07$). Begg's funnel plot also appears relatively symmetrical (online Supplementary Fig. S1). There may have been some publication bias present in the meta-analysis of studies with depression as a binary predictor, as although Begg's funnel plot appears symmetrical (online Supplementary Fig. S1), Begg's rank correlation test was significant ($p = 0.02$). Results should, therefore, be interpreted with caution.

Anxiety and decline in cognitive state.

Due to the limited number of studies with anxiety which met our inclusion criteria, meta-analyses for these studies were not possible. Instead, these studies are described in the form of a narrative review. Of the five relevant anxiety studies, two used a binary indicator of anxiety (Brodaty et al., 2012; Sinoff & Werner, 2003) and three used a continuous measure of anxiety (Bierman, Comijs, Rijmen, Jonker, & Beekman, 2008; Bunce et al., 2012; Robert S Wilson et al., 2011).

Two of these studies reported that anxiety was a significant predictor of decline in cognitive state (Sinoff & Werner, 2003; Robert S Wilson et al., 2011). Specifically, Sinoff and Werner (2003) reported that in a sample of 100 people, anxiety (assessed

using Sinoff's Short Anxiety Screening Test – SAST) had a strong direct and indirect effect on predicting future decline in cognitive state over 3.2 years (B = 0.23, 95% CI −0.03 to –3.95, $p < 0.05$). Similarly, Wilson et al (2011) found that in 785 older adults, higher levels of anxiety symptoms (assessed using the anxiety subscale from the 48-item Neuroticism scale) were significantly associated with more rapid decline in cognitive state over a 3.4-year period (B = −0.003, S.E. = 0.001, $p = 0.01$).

Conversely, three of the eligible studies found no association between anxiety symptoms and a decline in cognitive state (Bierman et al., 2008; Brodaty et al., 2012; Bunce et al., 2012). Bierman et al (2008) found no evidence that anxiety (assessed using the anxiety sub-scale from the Hospital Anxiety and Depression Scale – HADS-A) predicted a linear decline in cognitive state in a sample of 2351 people over a period of 9 years. Instead, a significant negative quadratic trend for cognition was reported. The authors state that this is suggestive of a curvilinear association between anxiety levels and cognitive performance. Specifically, milder anxiety symptoms may be associated with an improvement on the MMSE until it reaches an optimal level, beyond which the beneficial influence reduces, so more severe anxiety is related to poorer cognitive function. The authors posit that the Yerkes and Dodson law regarding the association between arousal and cognitive performance (Mendl, 1999; Yerkes & Dodson, 1908) may also apply to anxiety symptoms. Brodaty et al (2012) found that in a sample of 480 non-impaired people, the odds of decline in global cognitive state over a period of 2 years were not significantly higher for participants with anxiety (assessed using Neuropsychiatric Inventory) at baseline than those without (OR 1.63, 95% CI 0.5–5.8, $p = 0.45$). They did, however, find a significant effect of anxiety at baseline on the decline in executive function (OR 3.54, 95% CI 1.3–9.9, $p = 0.016$). Finally, Bunce et al (2012) found no evidence that anxiety (assessed using the Goldberg Anxiety Scale) affected

change in cognitive state over a period of 12 years in a sample of 836 community-dwelling individuals over the age of 70 (B = −0.14, S.E. = 0.19, p = 0.46).

2.5. Discussion

The aim of the current study was to systematically investigate associations between affective problems (depression and anxiety) present at baseline and subsequent decline in cognitive state. Our findings revealed that individuals with depression (measured as a binary or continuous predictor) were at an increased risk of a greater decline in cognitive state. These findings are consistent with previous reviews which have indicated an association between affective problems and development of dementia (Bennett & Thomas, 2014; Byers & Yaffe, 2011; Cherbuin et al., 2015; Da Silva et al., 2013; Gulpers et al., 2016; Jorm, 2001; Ownby et al., 2006). Our results extend these findings by linking affective problems to a greater decline in cognitive state in samples without dementia at baseline.

Strengths and limitations.

Several limitations of the current study must be acknowledged. They are subject to the limitations of the included studies. Our analyses suggest that there are several key methodological differences between studies which significantly affect the results produced. For example, our results suggest that effects may differ based on length of follow-up. As shown, this is unrelated to differences in publication year, age at baseline, or method of depression assessment (self-report or diagnosis). It is possible that this is more likely attributable to additional unobserved heterogeneity.

This review only included studies of decline in cognitive state as an outcome. For this reason, it is not clear whether affective problems may differentially influence decline in different cognitive domains. Additionally, the majority of included studies assessed cognitive state using the MMSE. This measure has been criticised for lacking sensitivity to subtle changes in cognition and for ceiling and floor effects (Tombaugh &

McIntyre, 1992). Consistent with this, the meta-analysis of studies using depression as a binary predictor revealed that effect sizes are significantly smaller for studies using the MMSE than studies using neuropsychiatric batteries. It is therefore possible that the widespread use of the MMSE may have resulted in an underestimation of the association between affective disorders and decline in cognitive state in healthy older adults over time. One further limitation is that excluding cognitive impairment and dementia at baseline does not completely rule out the possibility of reverse causality.

Beyond this, included studies used different approaches and instruments to assess affective problems. Research suggests that there is low overlap among different scales of depression and anxiety, with content analysis suggesting that different types of assessments may capture different symptoms (Fried, 2017). It is therefore possible that studies included in this review are not entirely comparable on the basis that the methods of assessing depression are heterogeneous and may each be capturing different kinds of symptoms. Beyond this, there were also very few studies which met our inclusion criteria which examined the association between anxiety and decline in cognitive state, meaning that a quantitative meta-analysis was not possible. Moreover, an additional limitation is that as there were no studies investigating comorbidity between anxiety and depression. Finally, many of the studies did not report separate effect sizes for different types of symptoms of affective problems (e.g. negative affect symptoms, somatic symptoms, etc.), meaning we could not look at how different symptoms of affective problems may influence decline in cognitive state in the current study.

Plausible mechanisms.

Three major hypotheses have been proposed to explain this observed association. The first states that affective problems may act as an aetiological risk factor

for the subsequent decline in cognitive state, perhaps by lowering the threshold for manifesting decline (Bennett & Thomas, 2014; Butters et al., 2008). The second hypothesis proposes that affective problems may act as a prodromal feature of dementia. Specifically, affective problems may manifest as an early clinical presentation of this disorder. Affective problems and decline in cognitive state may therefore be different symptoms of the same underlying condition (Bennett & Thomas, 2014; Panza et al., 2010). The third hypothesis posits that affective problems and decline in cognitive state are separate processes but may share common risk factors and underlying neurobiological substrates (Bennett & Thomas, 2014; Djernes, 2006; Enache, Winblad, & Aarsland, 2011). These hypotheses are not necessarily mutually exclusive and it is likely that multiple pathways and mechanisms underlie this relationship.

There are several biological and behavioural pathways which may be involved in the association between affective problems and decline in cognitive state. These include vascular disease, increased cortisol production leading to atrophy of the hippocampus (Geerlings & Gerritsen, 2017), increased deposition of β-amyloid plaques (Byers & Yaffe, 2011), inflammatory changes (Byers & Yaffe, 2011) and a decline in the levels and activities of neurotrophic factors (Royall, Al-Rubaye, Bishnoi, & Palmer, 2017). A multiple pathways model has also been proposed by Butters et al (2008), which posits that depression-associated cerebrovascular disease and glucocorticoid neurotoxicity may operate to decrease levels of brain and cognitive reserve, as well as interact with pathology of Alzheimer's disease, giving rise to the clinical manifestation of Alzheimer's disease and accelerated cognitive decline. Additional potential lifestyle and behavioural pathways associated with affective problems include educational attainment, social support, early life adversity and health behaviours such as exercise regime, alcohol consumption, smoking status and medication status. It is more likely

that a complex interaction of biological and sociobehavioural mechanisms are involved in linking affective problems with cognitive decline, rather than one single aetiological determinant (Da Silva et al., 2013).

Implications and future directions.

Future research should focus on investigating whether effective treatment and management of affective problems may reduce risk of decline in cognitive state. Additionally, future reviews could focus on how affective problems are associated with decline in specific cognitive domains, such as memory, executive function and information processing speed. This information can help to elucidate the pattern of decline characteristic of individuals with a history of affective problems. The present review could not address the issue of comorbidity between depression and anxiety and how comorbidity is associated with subsequent decline in the mental state. Indeed, comorbidity of depression and anxiety disorders is common. It is estimated that around 50–60% of individuals who have experienced depression also have a history of anxiety disorder (Fava et al., 2000; Kessler et al., 1996). Additionally, it is believed that comorbidity of anxiety and depression may be related to higher symptom severity and persistence, as well as poorer functional outcomes (Kaufman & Charney, 2000; Roy-Byrne et al., 2000). For this reason, it is important for future research to address how comorbid depression and anxiety is associated with future cognitive decline, and whether comorbidity of these conditions may result in poorer cognitive outcomes than depression or anxiety in isolation. One additional question which remains unresolved is whether affective problems act as a risk factor for the accelerated decline in cognitive state or whether they are an early biomarker representing prodromal dementia. While we excluded studies where cognitive impairment was present at baseline, it is also known that dementia has a preclinical period of many decades (Sperling, Jack, & Aisen,

2011). It is therefore possible that participants in included studies may have already built up substantial dementia pathology at baseline, even if cognitive symptoms were not yet apparent. Associations could therefore be due to reverse causality from subtle cognitive changes short of dementia. Future research should focus on distinguishing more clearly between these possibilities.

As average life expectancy lengthens and rapid demographic ageing occurs in populations worldwide, there is a dramatic predicted increase in the number of older adults living in our society (Lutz, Sanderson, & Scherbov, 2008; Oeppen & Vaupel, 2002). By 2030, it is estimated that approximately one in five people in England will be over the age of 65 (House of Lords, 2013). Given the predicted increase in population size of adults over the age of 65, as well as the poor outcomes and economic costs associated with a decline in cognitive state and impairment, it is important to identify life course risk factors for poorer late-life cognitive outcomes, for potential early intervention. These findings may have value in identifying individuals who may be at a greater risk of deterioration in cognitive function over time. It is possible that effective management and treatment of depression may reduce risk and improve cognitive outcomes within these individuals. However, there has also been some evidence to suggest there may be persisting neurocognitive disturbances even after remission of depression (Frasch et al., 2000; Paelecke-Habermann, Pohl, & Leplow, 2005; Weiland-Fiedler et al., 2004). Additionally, cognition may be an important treatment target for depression (Kaser, Zaman, & Sahakian, 2017). Due to the high prevalence of depression in the population, these results are of great public health importance.

In conclusion, demographic ageing is occurring rapidly worldwide and the number of people living with dementia is expected to grow substantially in prevalence over the next thirty years. As such, focussing research on potentially modifiable life

course risk factors, such as affective problems, is of increasing importance. This review highlights the importance of affective problems, particularly depression, in this context.

2.6. Tables & figures

Figure 2.6.1: Conceptual framework of Chapter 2

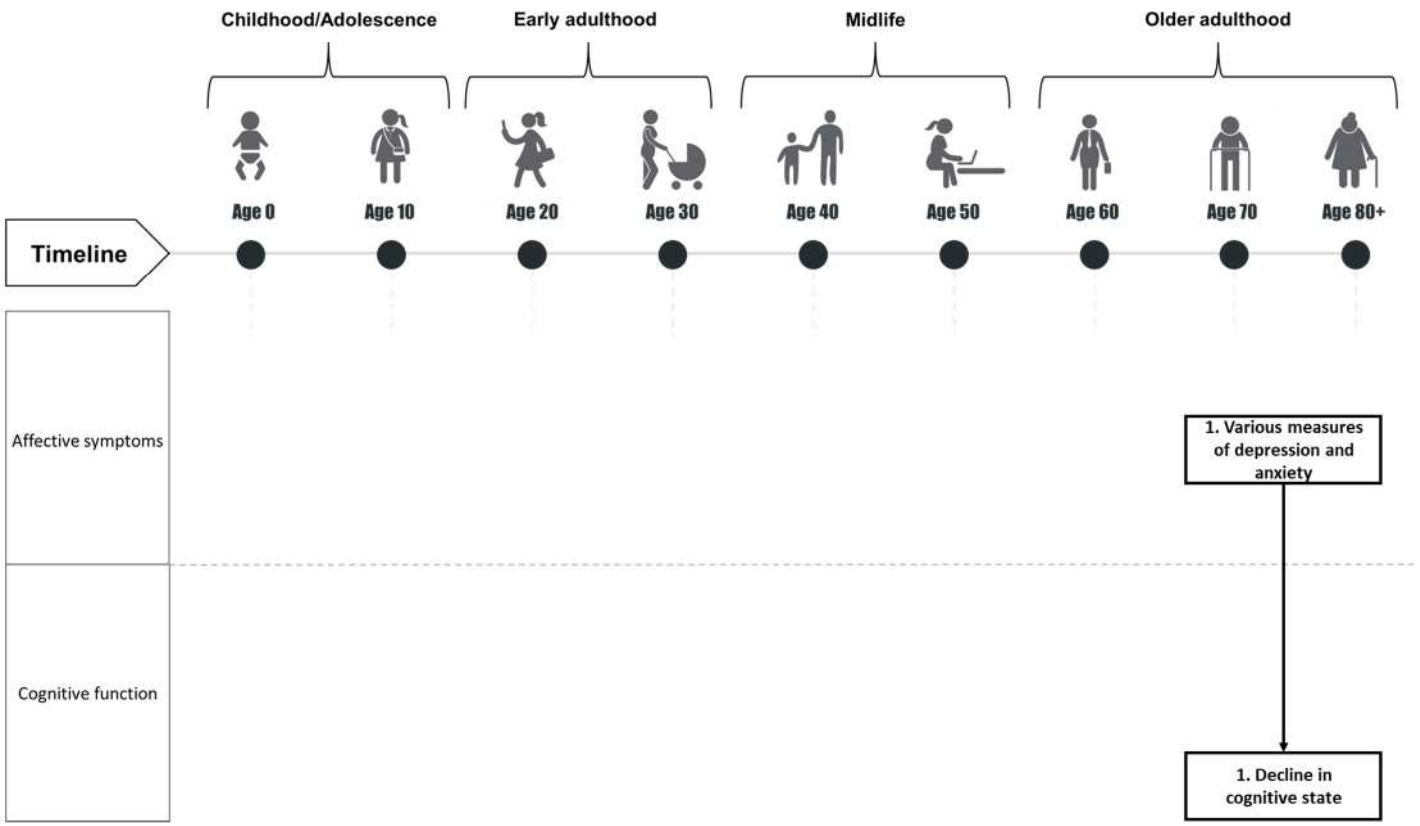


Table 2.6.1: Key terms used for systematic search

Search Block 1 (Affective problems)	Search Block 2 (Cognitive decline)	Search Block 3 (Study design)
Depress* OR MDD OR Dysthymi* OR Anxi* OR GAD OR worr* OR Phobia OR Panic OR Agoraphobia OR "Obsessive compulsive" OR OCD OR PTSD OR "Post traumatic stress" OR "Post-traumatic stress" OR mood OR affective OR psychiatric OR neuropsychiatric	"Cognitive function" OR "Cognitive impairment" OR "Cognitive decline" OR "Cognitive deficit" OR "Cognitive loss" OR "Cognition loss" OR "Cognitive ability" OR "Cognitive abilities" OR "Cognitive status" OR "Cognitive change" OR "Cognition change" OR "Cognitive performance" OR "Cognitive dysfunction" OR "Cognitive complaints" OR "Cognitive capability" OR "Cognitive ageing" OR "Cognitive aging" OR Memory OR Attention OR "Reaction time" OR "Speed of processing" OR "Processing speed" OR Intelligence OR "General mental ability" OR GMA OR "Executive function" OR "Neuropsychological testing" OR "Mini mental state exam" OR MMSE OR "Mental status"	Longitudinal OR prospective OR follow-up OR cohort OR "life course" OR lifespan OR "life span" OR lifelong OR "life long"

Table 2.6.2: Studies included in the systematic literature review and meta-analyses

Study ID	Author	Year	Country	% Female	Mean age at baseline	Mean length of follow-up	Measure of cognition	Type of affective problem	Measure of affective problem
1	Bassuk	1998	USA	63	73.72	12	Short Portable Mental Status Questionnaire (SPMSQ)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
2	Brodaty	2012	Australia	59	78.41	2	Mean of other cognitive domain scores	Depression	Neuropsychiatric Inventory
2	Brodaty	2012	Australia	59	78.41	2	Mean of other cognitive domain scores	Anxiety	Neuropsychiatric Inventory
3	Chang	2015	Taiwan	49	63.34	4	Short Portable Mental Status Questionnaire (SPMSQ)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)

Study ID	Author	Year	Country	% Female	Mean age at baseline	Mean length of follow-up	Measure of cognition	Type of affective problem	Measure of affective problem
4	Downer	2016	USA	58	73.18	14	Mini Mental state Examination (MMSE)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
5	Dufouil	1996	France	60	74.78	3	Mini Mental state Examination (MMSE)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
6	Ganguli	2006	USA	61	74.60	12	Mini Mental state Examination (MMSE)	Depression	Modified Center for Epidemiologic Studies Depression Scale (CES-D)
7	Geerlings	2000	The Netherlands	51	69.39	3	Mini Mental state Examination (MMSE)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D) (>16 vs. <16)
8	Han	2008	Canada	66	79.11	1	Mini Mental state Examination (MMSE)	Depression	Hamilton Depression Rating Scale (HDRS)

Study ID	Author	Year	Country	% Female	Mean age at baseline	Mean length of follow-up	Measure of cognition	Type of affective problem	Measure of affective problem
9	Kohler	2010	The Netherlands	48	69.40	6	Mini Mental state Examination (MMSE)	Depression	Revised 90-item version of the Symptom Checklist (SCL-90)
10	Niti	2009	Singapore	64	65.40	1.5	Mini Mental state Examination (MMSE)	Depression	Chinese version of the 15 item Geriatric Depression Scale (GDS)
11	Paterniti	2002	France	43	64.96	4	Mini Mental state Examination (MMSE)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
12	Raji	2007	USA	59	72.70	7	Mini Mental state Examination (MMSE)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
13	Reyes-Ortiz	2008	USA	57	72.70	11	Mini Mental state Examination (MMSE)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
14	Rosenblatt	2003	USA	63	40.30	11.5	Mini Mental state Examination (MMSE)	Depression	Diagnostic Interview Schedule (DIS)

Study ID	Author	Year	Country	% Female	Mean age at baseline	Mean length of follow-up	Measure of cognition	Type of affective problem	Measure of affective problem
15	Sawyer	2012	USA	69	70.18	4	Mini Mental state Examination (MMSE)	Depression	Duke Depression Evaluation Schedule (DDES)
16	Sinoff	2003	Israel	63	77.64	3.1	Mini Mental state Examination (MMSE)	Anxiety	Sinoff's Short Anxiety Screening Test (SAST)
17	Wilson	2016	USA	74	76.30	8	Battery of 19 cognitive performance tests	Depression	Subset of questions from the Diagnostic Interview Schedule
18	Yaffe	1999	USA	100	72.94	4	Mini Mental state Examination (MMSE)	Depression	Geriatric Depression Scale (GDS)
19	Bierman	2008	The Netherlands	53	69.49	9	Mini Mental state Examination (MMSE)	Anxiety	Hospital Anxiety and Depression Scale-Anxiety (HADS-A)
20	Bunce	2012	Australia	49	76.55	12	Mini Mental state Examination (MMSE)	Depression	Goldberg Depression Scale

Study ID	Author	Year	Country	% Female	Mean age at baseline	Mean length of follow-up	Measure of cognition	Type of affective problem	Measure of affective problem
20	Bunce	2012	Australia	49	76.55	12	Mini Mental state Examination (MMSE)	Anxiety	Goldberg Anxiety Scale
21	Chen	2016	Taiwan	45	70.95	14	Short Portable Mental Status Questionnaire (SPMSQ)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
22	Chiao	2016	Taiwan	57	71.04	14	Short Portable Mental Status Questionnaire (SPMSQ)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
23	Dotson	2008	USA	40	75.38	4.4	Mini Mental State Exam (MMSE), and Blessed Information Memory and Concentration Scale (BIMCS)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)

Study ID	Author	Year	Country	% Female	Mean age at baseline	Mean length of follow-up	Measure of cognition	Type of affective problem	Measure of affective problem
24	Gale	2012	England	55	64.07	6	Principal components analyses of 5 cognitive outcomes	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
25	Geerlings	2000	The Netherlands	51	69.39	3	Mini Mental state Examination (MMSE)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D) score (per point increase)
26	Han	2006	Canada	66	79.11	1	Mini Mental state Examination (MMSE)	Depression	HDRS
27	Johnson	2013	USA	69	73.50	2	Mini Mental state Examination (MMSE) & Clinical Dementia Rating (CDR-SB)	Depression	Geriatric Depression Scale (GDS30)

Study ID	Author	Year	Country	% Female	Mean age at baseline	Mean length of follow-up	Measure of cognition	Type of affective problem	Measure of affective problem
28	Neubauer	2013	Germany	60	75.70	1	Mini Mental state Examination (MMSE) and Syndrome Short Test (SKT)	Depression	Geriatric Depression Scale (GDS30)
29	Panza	2009	Italy	36	71.90	3.5	Mini Mental state Examination (MMSE)	Depression	Italian version of the Geriatric Depression Scale (GDS)
30	Rajan	2014	USA	63	72.41	9	Cognitive battery of four tests	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
31	Royall	2013	Japan, Hawaii, and the mainland-US		77.80	10	Cognitive Abilities Screening Instrument (CASI)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)

Study ID	Author	Year	Country	% Female	Mean age at baseline	Mean length of follow-up	Measure of cognition	Type of affective problem	Measure of affective problem
32	Turner	2015	USA	70	73.90	5	Measure derived from 19 cognitive tests	Depression	Center for Epidemiologic Studies Depression Scale (CES-D) & Geriatric Depression Scale (GDS)
33	Van den Kommer	2013	The Netherlands	53	69.25	13	Mini Mental state Examination (MMSE)	Depression	Center for Epidemiologic Studies Depression Scale (CES-D)
34	Vinkers	2004	The Netherlands	63	85.00	4	Mini Mental state Examination (MMSE)	Depression	Geriatric Depression Scale (GDS)
35	Wilson	2011	USA	76	80.70	3.4	Derived from 19 cognitive tests	Depression	48-item Neuroticism scale from the NEO Personality Inventory-Revised. Depression sub-scale
35	Wilson	2011	USA	76	80.70	3.4	Derived from 19 cognitive tests	Anxiety	48-item Neuroticism scale from the NEO Personality Inventory-Revised. Anxiety sub-scale

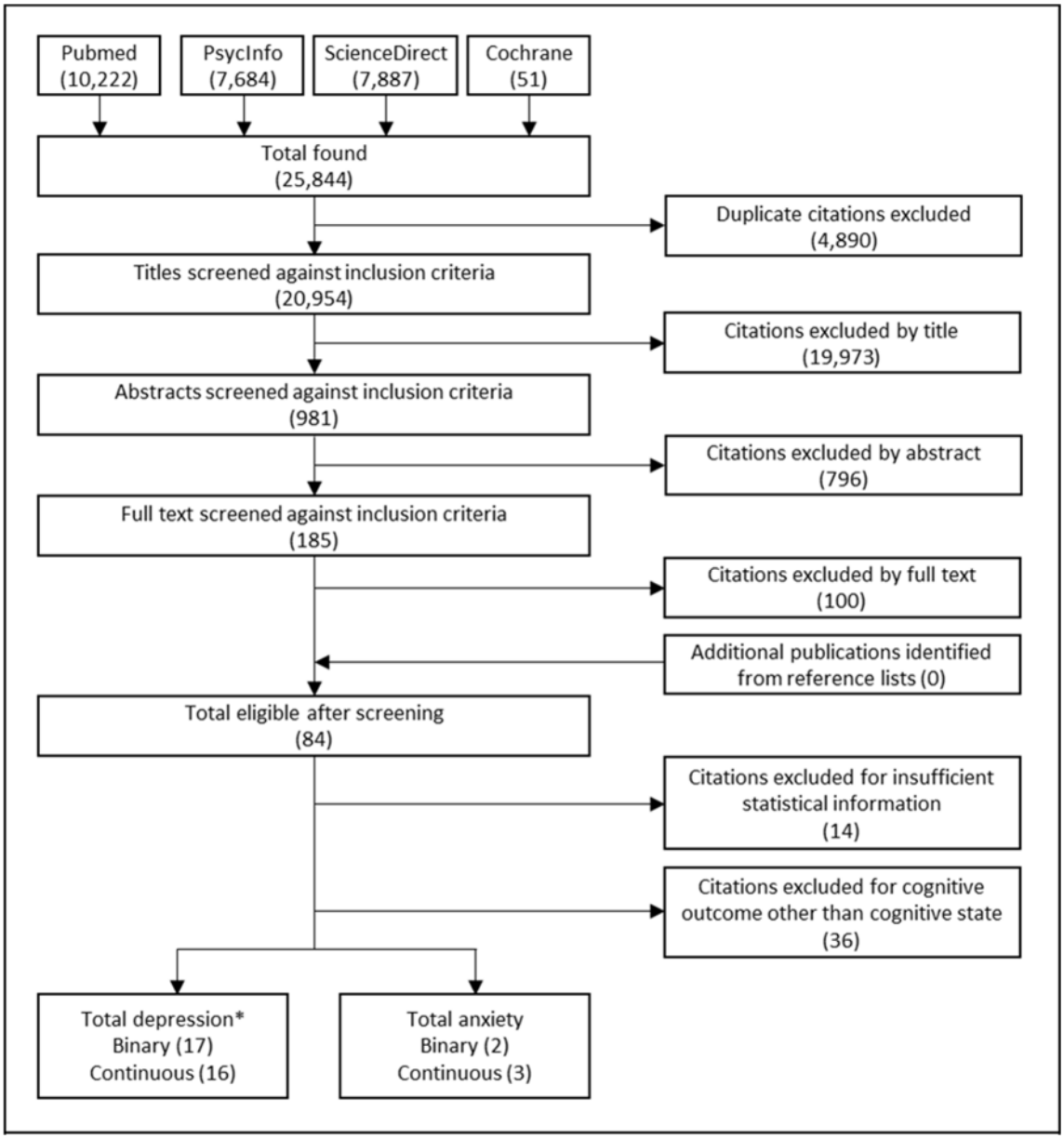


Figure 2.6.2: Flowchart of study selection

Note: *One study assessed both binary and continuous assessments of depression, meaning that although there are 17 studies using binary measures of depression and 16 studies using continuous measures of depression, in total there are only 32 studies reporting on depression and cognitive decline.

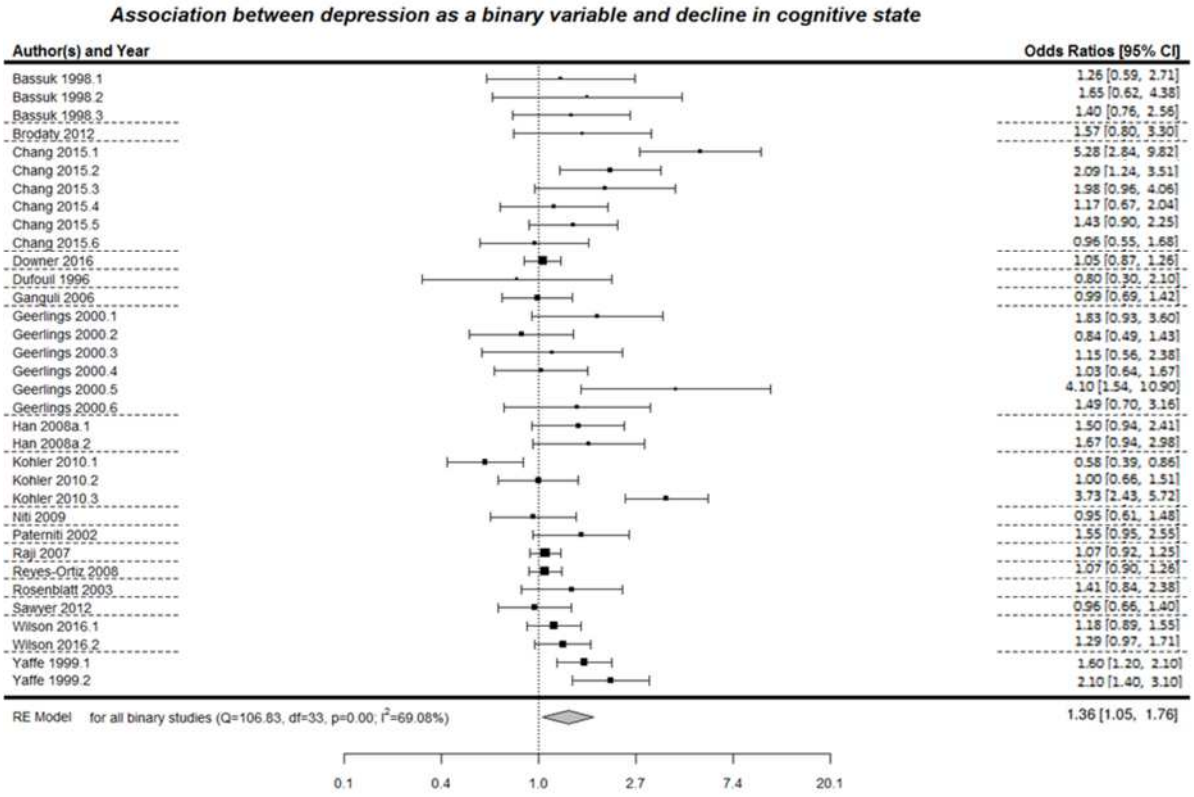


Figure 2.6.3: Forest plot of the association between binary depression and decline in cognitive state

Notes for multiple effect sizes within studies: Bassuk* (1: High SPMSQ at baseline; 2: Medium SPMSQ at baseline; 3: High or medium SPMSQ at baseline), Chang (1: Males with persistent depressive symptoms; 2: Males with increasing depressive symptoms; 3: Males with decreasing depressive symptoms; 4. Females with persistent depressive symptoms; 5: Females with increasing depressive symptoms; 6: Females with decreasing depressive symptoms), Geerlings* (1: CES-D threshold in high education sample; 2: CES-D threshold in low education sample; 3: Felt depressed some of the time vs never in high education sample; 4: Felt depressed some of the time vs never in low education sample; 5: Felt depressed most of the time vs never in high education sample; 6: Felt depressed most of the time vs never in low education sample), Han (1: Major depression vs no depression; 2: Minor depression vs no depression), Kohler (1:

Low depression vs no depression; 2: Middle depression vs no depression; 3: High depression vs no depression), Wilson* (1: Major depression vs no depression; 2: Elevated depression symptoms vs no depression), Yaffe (1: 3-5 depressive symptoms vs 0-2 depressive symptoms; 2: >6 depressive symptoms vs 0-2 depressive symptoms).

* represent effect sizes within studies where there may be some overlap in sample.

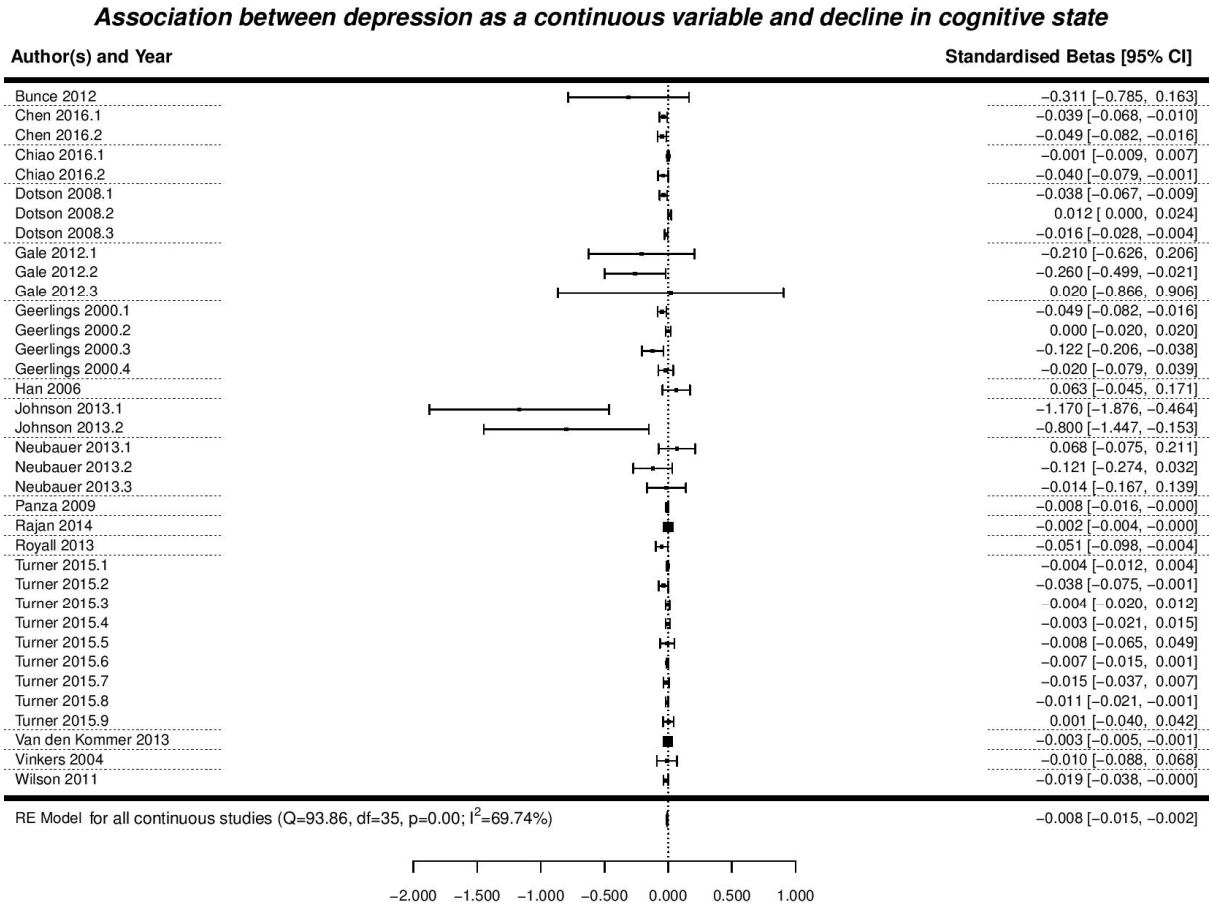


Figure 2.6.4: Forest plot of the association between continuous depression and decline in cognitive state

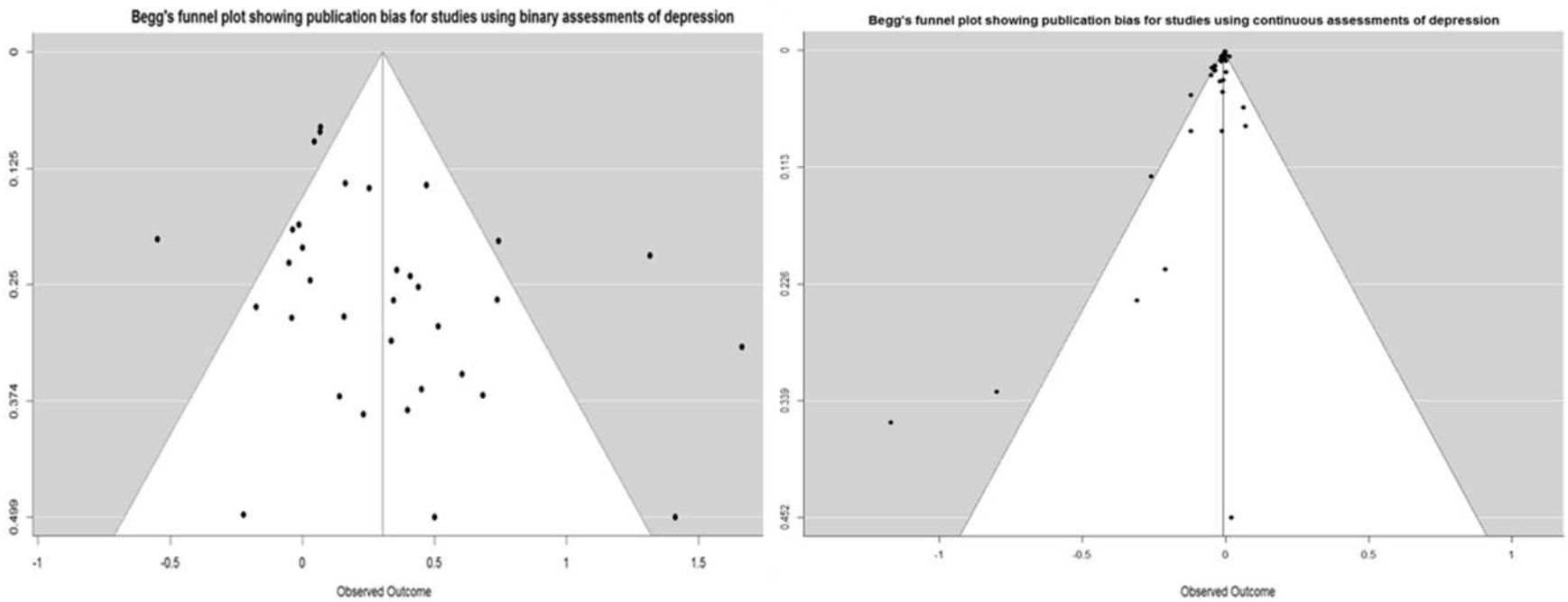
Notes for multiple effect sizes within studies: Chen 2016 (1: Cognition starting high and declining; 2: Cognition starting low and declining), Chiao 2016* (1: Negative affect; 2: Lack of positive affect), Dotson 2008* (1: Baseline CES-D on MMSE; 2: Average CES-D on BIMCS; 3: Average CES-D on MMSE); Gale 2012 (1: Age 50-60; 2: Age 60-80; 3: Age 80-90), Geerlings 2000* (1: CES-D Score per point increase, education>8 years; 2: CES-D Score per point increase, education<8 years; 3: Negative affect score per point increase, education>8 years; 4: Negative affect score per point increase, education<8 years), Johnson 2013* (1: MMSE; 2: CDR-SB), Neubauer 2013* (1: Depression at T1 predicting cognition change from T1 to T2; 2: Depression at T2 predicting cognition change from T2 to T3; 3: Depression at T3 predicting cognition

change from T3 to T4), Turner 2015* (1: CES-D; 2: CES-D Positive affect; 3: CES-D Negative affect; 4: CES-D Somatic complaints; 5: CES-D Interpersonal problems; 6: GDS; 7: GDS Positive affect; 8: GDS Negative affect; 9: GDS Positive and negative affect).

* represent effect sizes within studies where there may be some overlap in sample.

2.7. Supplementary material

Supplementary Figure 1: Begg's funnel plot for publication bias of studies using depression as a predictor of cognitive decline



Supplementary Figure 1: Begg's funnel plot for publication bias of studies using depression as a predictor of cognitive decline

CHAPTER 3

Study 2: Effects of affective symptoms in adolescence and adulthood on trajectories of cognitive function from middle to late adulthood.

Study 2 is accepted for publication in *Journal of Affective Disorders*.

3.1. Abstract

Little is known about the link between affective symptoms and cognitive function across the life course. This study aims to investigate whether affective symptoms in adolescence and adulthood predict trajectories of cognitive function from middle to late adulthood. Data from the MRC National Survey of Health and Development (NSHD), a cohort of 5362 individuals born in mainland UK in 1946, were utilised. Linear mixed models were used to model cognitive trajectories (memory and information processing speed) over a three decade period (from 43 to 69) and to test effects of affective symptoms in adolescence (ages 13-15) and adulthood (ages 36 and 43) on baseline cognitive function (age 43) and decline in cognitive function (from 43 to 69). Models were adjusted for sex, childhood cognition, childhood socioeconomic position, and education. A quadratic model best fitted memory and information processing speed data. Models revealed that adolescent affective symptoms were associated with lower memory ($b = -1.11$, $SE = 0.53$, $p = .04$) and information processing speed ($b = -18.17$, $SE = 7.53$, $p = .02$) at baseline, but not with rates of decline over time from 43 to 69. There were no significant associations between adult affective symptoms and cognitive trajectories. Missing data is a potential limitation of this study. This was dealt with using maximum likelihood estimation and multiple imputation. Findings suggest that adolescent, but not adult, affective symptoms are important predictors of cognitive function in midlife, but not rate of cognitive decline. This highlights the importance of early intervention to manage mental health in adolescence to protect later cognitive function.

3.2. Introduction

Affective symptoms are common during adolescence and adulthood, with one in six adults and adolescents in the UK reporting symptoms of depression and anxiety (McManus et al., 2016; Patalay & Fitzsimons, 2017). Recent longitudinal studies have confirmed long-lasting effects of affective disorders and symptoms on a wide range of outcomes later in life, including lower educational attainment (Richards & Abbott, 2009), poorer physical and mental health (Colman, Wadsworth, Croudace, & Jones, 2007; Keenan-Miller, Hammen, & Brennan, 2007), and premature mortality (Archer, Kuh, Hotopf, Stafford, & Richards, 2018). Affective symptoms have also been shown to lead to worse cognitive outcomes, including dementia and faster cognitive decline (Da Silva et al., 2013; James et al., 2018; John, Patel, Rusted, Richards, & Gaysina, 2018; Livingston et al., 2017). However, the majority of existing studies have focused only on the link between affective symptoms and cognitive function in late adulthood (John et al., 2018; Singh-Manoux et al., 2010). Therefore, less is known about the effects of affective symptoms in adolescence and early adulthood on cognitive ageing from middle to late adulthood. The period of middle adulthood could be particularly important for prevention of dementia in relation to depression, before dementia pathology has built up to the clinical threshold for a diagnosis (Exalto et al., 2014). For example, previous research has shown that post-menopausal women may be at increased risk of depression, and this transition is also known to be an important period of increased vulnerability to cognitive impairment and decline (Weber, Maki, & Mcdermott, 2014). Specifically, research has shown that higher cognitive function from childhood through to midlife is associated with later menopause (Kok et al., 2006; Kuh et al., 2005; Richards, Kuh, Hardy, & Wadsworth, 1999) and that later menopause may

be associated with better verbal memory (Richards, Cooper, Kuh, Moore, & Hardy, 2018).

Using data from the Medical Research Council National Survey of Health and Development (MRC NSHD), Richards et al (2014) tested six life course profiles of affective symptoms (from age 13 to 60-64) in relation to cognitive performance at age 60-64 and decline from 53 to 60-64 (Richards et al., 2014). No associations were found between affective symptoms and cognitive outcomes. Additionally, using NSHD data, Xu et al (2013) investigated adolescent mental health and memory function and decline from age 43 to 60-64. They reported that adolescent self-organisation, but not conduct problems or emotional problems, was associated with lower memory scores at age 43, but not decline from age 43 to 60-64 (Xu et al., 2013). It is possible, however, that participants may have still been relatively young for detection of significant cognitive decline in both of these studies. Indeed, recent evidence shows that in the NSHD cohort, rate of decline in verbal memory accelerates after age 60 (Davis et al., 2017). Therefore, the aim of the present study was to extend existing research by testing associations of affective symptoms in adolescence and adulthood with trajectories of verbal memory and information processing speed from middle to late adulthood (from age 43 through age 69). The conceptual framework for this chapter is presented in Figure 3.6.1. The previous chapter showed that depression in older adulthood may be associated with decline in cognitive state. This chapter extends those findings by testing whether affective symptoms much earlier in the life course (i.e. adolescence and early adulthood) are associated with cognitive trajectories from midlife to early old age.

3.3. Method

Participants.

Participants were from the MRC NSHD, a nationally representative sample of 5362 individuals born in England, Scotland and Wales during one week of 1946. Since birth, the cohort members have been followed up 24 times, most recently in 2015. At age 69, 80% of participants who were currently alive and with a known address in the UK, took part (N=2148). Of the target sample (N=2698) who were eligible but did not take part (N=550), 298 (54%) refused to take part temporarily, 155 (28%) did not respond, 55 (10%) completed postal questionnaire only, 31 (6%) withdrew from the study, and 11 (2%) were unable to give informed consent. Detailed information about participation patterns, respondent profiles and data collection methods have been published elsewhere (Kuh et al., 2011a, 2016; Wadsworth, Kuh, Richards, & Hardy, 2006). All participants provided written informed consent at each wave of data collection. Ethical approval for the latest data collection was obtained from NRES Queen Square REC and Scotland A REC.

Measures.

Cognitive function.

Repeated assessments of verbal memory and information processing speed were available at ages 43, 53, 60-64, and 69 (Davis et al., 2017; Rawle, Davis, et al., 2018; Richards, Shipley, Fuhrer, & Wadsworth, 2004). Information processing speed was measured using a letter cancellation task, which required cohort members to cross out as many randomly distributed target letters as possible from a grid of other letters within a timed period of 1 minute. Scores ranged from 0-600. Memory function was assessed using a 15-item word recall task, which required participants to recall as many words as

possible from a list shown visually at the rate of 1 word per second. Scores ranged from 0-45.

Previously, linear mixed models (linear and quadratic trends) were fit to verbal memory and information processing speed data available from age 43 to age 69 (Davis et al., 2017; Rawle, Davis, et al., 2018). The quadratic model was the best fit for both cognitive domains (Davis et al., 2017; Rawle, Davis, et al., 2018), and therefore used in the present study to test for associations between affective symptoms in adolescence and adulthood (ages 13-15, 36 and 43) and cognitive trajectories.

Affective symptoms.

Affective symptoms were assessed at ages 13, 15, 36, 43, 53, 60-64, and 69 (Richards et al., 2014). For the present study, measures of affective symptoms at ages 13, 15, 36, and 43 were included in order to ensure forward temporal associations. Psychological problems in adolescence (age 13 and age 15) were reported by teachers using a forerunner of the Rutter A scale (Richards & Abbott, 2009). Previous research used exploratory factor analysis on this scale at ages 13 and 15 (Xu et al., 2013), and ten items which loaded strongly onto the factor representing emotional problems at ages 13 and 15 were included in the present study. Confirmatory factor analyses of these items were run to derive latent affective symptoms scores at both ages, and then the mean of these factor scores was calculated to represent the measure of adolescent affective symptoms.

In adulthood, affective symptoms were assessed using the Present State Examination (PSE) at age 36 (Wing, Cooper, & Sartorius, 1974), and the Psychiatric Symptom Frequency scale (PSF) at age 43 (Lindelow, Hardy, & Rodgers, 1997). Latent

trait scores of PSE at age 36, and PSF at age 43 were derived previously (Colman, Ploubidis, Wadsworth, Jones, & Croudace, 2007).

The original latent scores were categorised into three percentile groups (1st-50th, 51st-90th, 91th-100th percentiles), which represented no/low, moderate and severe symptoms, as previously described using NSHD data (Archer et al., 2018), as a measure of symptom severity. Both continuous and categorical measures of affective symptoms were used for the analyses.

Covariates.

Key covariates were selected based on previous research: sex, childhood socioeconomic position (SEP) (Kaplan et al., 2001), childhood cognition (McGurn, Deary, & Starr, 2008), and educational attainment (Brayne et al., 2010). Childhood SEP was represented by father's occupation. This was coded to correspond to social classes I-V in the Classification of Occupations (1970). Participants were classified by the following: professional; intermediate; skilled non-manual; skilled manual; partly skilled; unskilled. In order to maximise sample size, if SEP at age 4 was missing, this was substituted with SEP at age 11. If SEP at age 4 and 11 were both missing, SEP at age 15 was used. Educational attainment was represented by the highest qualification achieved by age 26. This measure was coded according to the UK Burnham scale and then grouped into 3 categories, including: no educational qualifications; vocational or GCSE; A-Level or higher. Childhood cognition at age 8 was represented by a composite score of four tests of verbal and nonverbal ability, including reading comprehension, word reading, vocabulary, and picture intelligence (Hatch et al., 2007; Richards et al., 2004). In order to maximise sample size, if cognitive function at age 8 was missing it

was substituted with z scores of cognitive function at age 11. Where cognitive data was not available at age 8 or 11, z scores of cognitive function at age 15 were used.

Additional covariates were: psychiatric medication use (Rawle, Cooper, Kuh, & Richards, 2018) and externalising problems (Archer et al., 2018; Richards & Abbott, 2009). At ages 36, 43, 53, 60-64, and 69, participants were asked about use of antidepressant and anxiolytic medications. A binary variable was derived, representing participants who were prescribed these medications during at least one time-point between ages 36 and 69 compared with participants who were never prescribed these medications. Externalising problems were measured with the teacher rated forerunner of the Rutter A scale at ages 13 and 15 (Xu et al., 2013).

Statistical Analyses.

Main analyses.

STATA version 14 (StataCorp, 2015) was used for all the analyses. Linear mixed models were fitted to model memory and information processing speed trajectories from middle to late adulthood. Intercepts (age 43) and slopes (from age 43 through age 69) were random and an unstructured covariance structure was assumed. These models of cognitive trajectories using NSHD data have been described previously (Davis et al., 2017; Rawle, Davis, et al., 2018). Latent scores of affective symptoms in adolescence (ages 13-15), and adulthood (36 and 43) were used to predict cognitive trajectory intercepts and slopes. In order to test for the effect of affective symptom severity on cognitive trajectories, the ordinal measure based on percentile scores of affective symptoms representing no/low, moderate and severe symptoms, were added into the models.

Initial models were unadjusted (Model 1) and subsequent models were adjusted for key covariates: adjusted for sex (Model 2); adjusted for sex, childhood cognition, childhood socioeconomic position, and education by age 26 (Model 3). Because there was no significant interaction at the 5% level between sex and affective symptoms at any of the time-points assessed (age 13-15, 36 and 43) for memory or information processing speed (Supplementary Table 1), sex was used as a covariate, rather than a moderator, in all subsequent analyses. Additionally, the models were adjusted for the use of psychiatric medication (Model 4) and adolescent externalising problems (Model 5).

Sensitivity analyses.

The main analyses included participants with cognitive data available in at least one time point between ages 43 and 69 (including participants who might die during this period) with, missing data being accounted for using maximum likelihood estimation. A sensitivity analysis was conducted in order to test whether results might be affected by mortality. For this, the main models we reran on the sub-sample of people who were alive by age 69.

In our main analyses, the sample size was restricted to those with data on all on predictors and covariates available. Therefore, in order to maximise our sample size and to determine that effects observed were not attributable to the method used to account for missing data, an additional sensitivity analysis was conducted, in which a multiple imputation approach was employed using MICE in R (Azur, Stuart, Frangakis, & Leaf, 2011; Buuren & Groothuis-Oudshoorn, 2011). Sixteen imputations were conducted across 11 sweeps over the life course. Multiple imputation techniques have been used frequently with NSHD data (Almoosawi, Prynne, Hardy, & Stephen, 2013; Jones et al.,

2015; Silverwood et al., 2013). The inclusion of a larger number of auxiliary variables in the model maximises the plausibility of the missing at random (MAR) assumption (Coley et al., 2011). To determine whether method used to account for missing data had an effect on our results, all main models were re-run on the imputed sample.

3.4. Results

Available study sample and demographic information.

Table 3.6.1 shows demographic information for the samples included in the main analyses with key covariates. A total of 3395 people had both cognitive measures available in at least one time-point: Verbal memory N = 3404; Information processing speed N = 3447 (Supplementary Table 2). Of this sample, 2648 (78%) people had complete information on affective symptoms at each time-point assessed. Of this number, 2543 (96%) people also had complete information for covariate data (Supplementary Figure 1). The sample size was slightly larger for those with verbal memory data (N = 2546) or information processing speed data (N = 2570) than for those with both (N = 2543).

The sample with cognitive data (both verbal memory and information processing speed) in at least one time-point and complete predictor and covariate data (N = 2543) was compared with the sample with cognitive data in at least one time-point and missing predictor and covariate data (N = 852). The sample with missing data did not differ from the sample with complete information on sex ($X^2 = 1.29$, $p = .26$), education ($X^2 = 4.68$, $p = .10$), childhood socioeconomic position ($X^2 = 9.07$, $p = .11$), childhood cognition (t = -0.96, $p = .34$), adolescent affective symptoms (t = -0.03, $p = .97$), information processing speed scores at any age (Age 43: t = 1.58, $p = .11$; Age 53: t = 1.95, $p = .051$; Age 60-64: t = 1.23, $p = .22$; Age 69: t = 1.36, $p = .17$), or verbal memory scores at any age (Age 43: t = 1.44, $p = .15$; Age 53: t = 1.17, $p = .24$; Age 60-64: t = 1.19, $p = .23$; Age 69: t = 1.24, $p = .21$). However, participants with missing predictor and covariate data had significantly higher level of affective symptoms in adulthood (Age 36: t = 3.06, $p = .002$; Age 42: t = 3.58, $p < .001$).

Effects of adolescent and adult affective symptoms on cognitive trajectories.

Fully adjusted models (Model 3, best fit according to AIC and BIC statistics) revealed that adolescent affective symptoms were significantly associated with cognitive function at baseline (Verbal Memory: b = -1.11, SE = 0.53, p = .04; Information Processing Speed: b = -18.17, SE = 7.53, p = .02), but not with rate of decline (Verbal Memory: b = 0.01, SE = 0.01, p = .30; Information Processing Speed: b = 0.09, SE = 0.13, p = .50). There were no significant associations between affective symptoms at ages 36 or 43 and cognitive trajectories between the ages of 43 and 69 (intercept or slope) in unadjusted or adjusted models (Table 3.6.2 & Table 3.6.3).

In order to investigate the effect of symptom severity, an ordinal variable based on percentile cuts of the latent score of adolescent affective symptoms (0-50th, 51-90th, 91-100th percentile) was included in the models. Fully adjusted models revealed that both groups with moderate and with severe adolescent symptoms differed significantly in baseline memory performance from the group with no/low symptoms. Effect sizes were largest for the highest percentile group of people with the most severe affective symptoms in adolescence (Moderate symptoms: b = -0.87, SE = 0.42, p = .04; Severe symptoms: b = -1.88, SE = 0.81, p = .02). Adolescent affective symptom percentile groups were not significantly associated with the rate of memory decline between the ages of 43 and 69 (b = 0.01, SE = 0.01, p = .14) (Table 3.6.4, Figure 3.6.2).

In information processing speed models, the moderate symptom group did not differ significantly from the no/low symptom group on baseline information processing speed performance (b = -9.25, SE = 5.97, p = .12), but the group with the most severe symptoms were significantly poorer in baseline information processing speed than the no/low symptom group (b = -23.42, SE = 11.55, p = .04). Adolescent affective symptom

percentile groups were not significantly associated with the rate of processing speed decline between the ages of 43 and 69 (b = 0.04, SE = 0.10, *p* = .72) (Table 3.6.4, Figure 3.6.2).

When psychiatric medication use and externalising behaviour in adolescence were controlled for, results were essentially unchanged for both memory and information processing speed (Supplementary Tables 3 & 4).

Sensitivity analyses.

As a sensitivity analysis, participants who died before age 69 were excluded (N = 1028), and main models were re-run on the sample of people who were still living up to 2015 (N = 4334). From previous research using this data, it is already known that both affective symptoms (Archer et al., 2018) and cognitive function (memory and processing speed) (Davis et al., 2016; Kuh et al., 2009) are associated with mortality.

Fully adjusted models revealed that adolescent affective symptoms significantly predicted baseline level of processing speed (b = -16.76, SE = 7.98, *p* = .04), but not decline of processing speed between the age of 43 and 69 (b = 0.05, SE = 0.14, *p* = .71). Affective symptoms at ages 36 and 43 did not significantly predict trajectories of processing speed (intercept or slope). Models including verbal memory showed a slightly different pattern. No effects were observed for affective problems at any age across adolescence and adulthood on memory trajectories (intercept or slope) over the period tested (Supplementary Tables 5 & 6).

Finally, main models were re-run on the imputed sample (N = 3404) to maximise sample size and to determine whether effects observed were due to the method used to account for missing data. Effect sizes from the models using the imputed sample were substantially identical to those produced from the main models

(Supplementary Tables 7 & 8). Affective symptoms in adolescence significantly predicted lower cognitive scores at baseline (Memory: b = -1.03, SE = 0.47, p = .03; Information processing speed: b = -16.81, SE = 6.65, p = .01), but not decline over the time period tested. Adult affective symptoms did not predict cognitive trajectories.

3.5. Discussion

Adolescent affective symptoms predicted lower memory and information processing speed scores in middle adulthood (at age 43). However, adolescent affective symptoms did not predict rate of cognitive decline over the period of three decades. Overall, in this study no effects were observed for adult affective symptoms at ages 36 and 43 on cognitive function or decline from middle to late adulthood. Previous research has reported that affective symptoms in adolescence can have a profound and long-lasting effect on outcomes later in life, including educational attainment (Fletcher, 2010) and premature mortality (Archer et al., 2018). Findings from the current study extend this to include lower memory and information processing speed level in midlife, but not a faster rate of decline from fourth through sixth decade of life.

There was a dose-response between affective symptoms and memory at age 43. Those with moderate and severe symptoms during adolescence differed significantly in baseline memory function at age 43 from a group with no/low adolescent symptoms, but effect sizes were largest for the group with severe adolescent symptoms. These results also revealed that participants with moderate adolescent affective symptoms did not differ significantly in baseline information processing speed performance from participants with no/low adolescent symptoms. However, participants with severe adolescent affective symptoms did show significantly poorer information processing speed performance at baseline than participants with no/low adolescent symptoms. This suggests that effects of adolescent affective symptoms on baseline information processing speed performance may have been largely driven by cohort members with more severe adolescent affective symptoms.

After excluding participants who died before age 69 from the analysis, results revealed that adolescent, but not adult, affective symptoms significantly predicted baseline processing speed scores, but not decline over fourth to sixth decade. However, after excluding deceased individuals from the analysis, the effect of adolescent affective symptoms on memory was no longer significant. Previous research using NSHD has shown that affective symptoms during adolescence are associated with premature mortality (Archer et al., 2018). It is therefore not entirely surprising that when the sample is restricted to only participants who are alive in 2015, the effects of adolescent affective symptoms on cognitive outcomes is attenuated, as cohort members with the most severe adolescent affective symptoms are more likely to have already died by the time of cognitive assessment in adulthood.

These findings are consistent with those of Richards et al (2014), who reported no associations between lifetime latent profiles of affective symptoms on cognitive decline. The present study also found no effects of affective symptoms during adulthood on cognitive performance and no effects of affective symptoms at any time-point on rate of cognitive decline over the time period tested. However, in contrast to Richards et al (2014), in the present study there were significant associations between adolescent affective symptoms and memory and information processing speed level. This may be due to differences in the baseline cognitive performance age between the studies. Richards et al (2014) used cognitive scores at age 60-64 to determine effects of lifetime affective symptoms on cognitive performance, whereas the present study used cognitive scores at age 43 as the baseline. The latter is potentially a more stable baseline uncontaminated by differential age-related decline and prodromal pathological confounders emerging from mid-life. Additionally, the inclusion of additional waves

with cognitive data at ages 43 and 69 may explain why these findings in adolescence differ from those of Richards et al (2014).

Importantly, we did not see any effects of adult affective symptoms (age 36 and 43) on performance or rate of decline in either of the cognitive outcomes assessed. This suggests that adolescence is an important sensitive period, during which the presence of more severe affective symptoms may have more profound and lasting long term effects on cognitive health than affective symptoms present during adulthood. Adolescence may therefore be a sensitive period, during which the presence of more severe affective symptoms can impact cognitive health across the life course. It is known that adolescence is an important period of continued brain maturation, characterised by major changes in both brain structure and function (Eiland & Romeo, 2013; Whittle et al., 2014) with long-lasting effects on cognition function and ageing (Andersen, 2003; Spear, 2000). Early developmental changes that accompany the experience of stress or depression during adolescence may therefore be the source of cognitive impairment observed later in life.

Strengths and limitations.

Key strengths of the present study include prospectively assessed measurements of affective symptoms available across the life course, spanning from multiple time points in adolescence through to midlife. Additionally, there are multiple repeated assessments of memory and information processing speed from midlife to older adulthood which are consistent over time, allowing for longitudinal modelling of cognitive trajectories.

One potential limitation of the present study is that the NSHD has been collecting data from cohort members for over 70 years, and as such missing data are

inevitable. It is therefore possible that characteristics which predict attrition may also be predictive of greater cognitive decline, and as such these individuals may be under-represented in the study. In this analysis, we dealt with missing data using maximum likelihood estimation, minimising issues associated with using a complete case analysis. In order to determine whether this method influenced results, models were re-run on a sample derived from a multiple imputation approach. Results from models including the imputed sample were substantially identical to those without, suggesting that the method used to account for missing data did not have a considerable impact on these results. Limitations of the psychometric instruments used to assess cognitive and affective symptoms should also be acknowledged. Specifically, although necessarily so, different measures of affective symptoms were used in adolescence and adulthood which may limit comparability of these measures. Additionally, in adolescence, affective symptoms were reported by teachers, whereas for all other time points they were reported directly by the cohort member. Beyond this, cognitive measures were assessed using single assessments, rather than a more comprehensive cognitive battery, and only memory and information processing speed were measured repeatedly over time, although these are key cognitive domains that are sensitive to age- and morbidity-associated decline. Finally, cognitive assessments were only available in adulthood at ages 43, 53, 60-64 and 69, and subsequently associations between affective problems and cognitive function before middle adulthood were not explored.

It is also important to note that affective symptoms were only considered from ages 13 to age 43 in this study and it is possible that affective symptoms later in the life course may also play an important role in predicting cognitive function and decline. Specifically, research has shown that the menopause transition is associated with approximately a 2- to 4- fold increased risk for major depression and that this effect is

independent of history of depressive episodes (Bromberger et al., 2011). Additionally, early cognitive ability is associated with age at menopause (Kok et al., 2006; Kuh et al., 2005; Richards et al., 1999) and the menopausal transition has been associated verbal memory function (Richards et al., 2018), and with increased vulnerability to cognitive impairment (Weber et al., 2014). The menopausal transition may therefore be an important period within the association between affective disorders and cognitive function/decline. This is an interesting avenue for consideration in future research.

Implications.

With the high prevalence of mental health problems within adolescent populations (24% of girls and 9% of boys report high depressive symptoms by the age of 14 (Patalay & Fitzsimons, 2017), these findings are potentially of great importance for public health. Additionally, there is evidence to suggest that the prevalence of affective symptoms are increasing over time within this adolescent age-group, with depressive symptoms increasing from 13.1% in 2009 to 20.3% in 2014 in adolescent girls (Fink et al., 2015). This high and increasing prevalence is particularly concerning when considered in the context of the results from this study, showing long-lasting effects of adolescent affective symptoms on cognitive health into midlife and beyond, as well as other recent studies demonstrating other negative adult outcomes of adolescent affective symptoms, including educational attainment (Fletcher, 2010) and premature mortality (Archer et al., 2018).

In conclusion, our findings suggest that adolescent affective symptoms are important predictors of cognitive function in midlife, but they do not predict the rate of cognitive decline from middle to late adulthood in cognitively healthy individuals. Taken together, these findings highlight the importance of early intervention to prevent

and manage mental health present during adolescence, in order to protect cognitive function later in the life course.

3.6. Tables & figures

Figure 3.6.1: Conceptual framework of Chapter 3

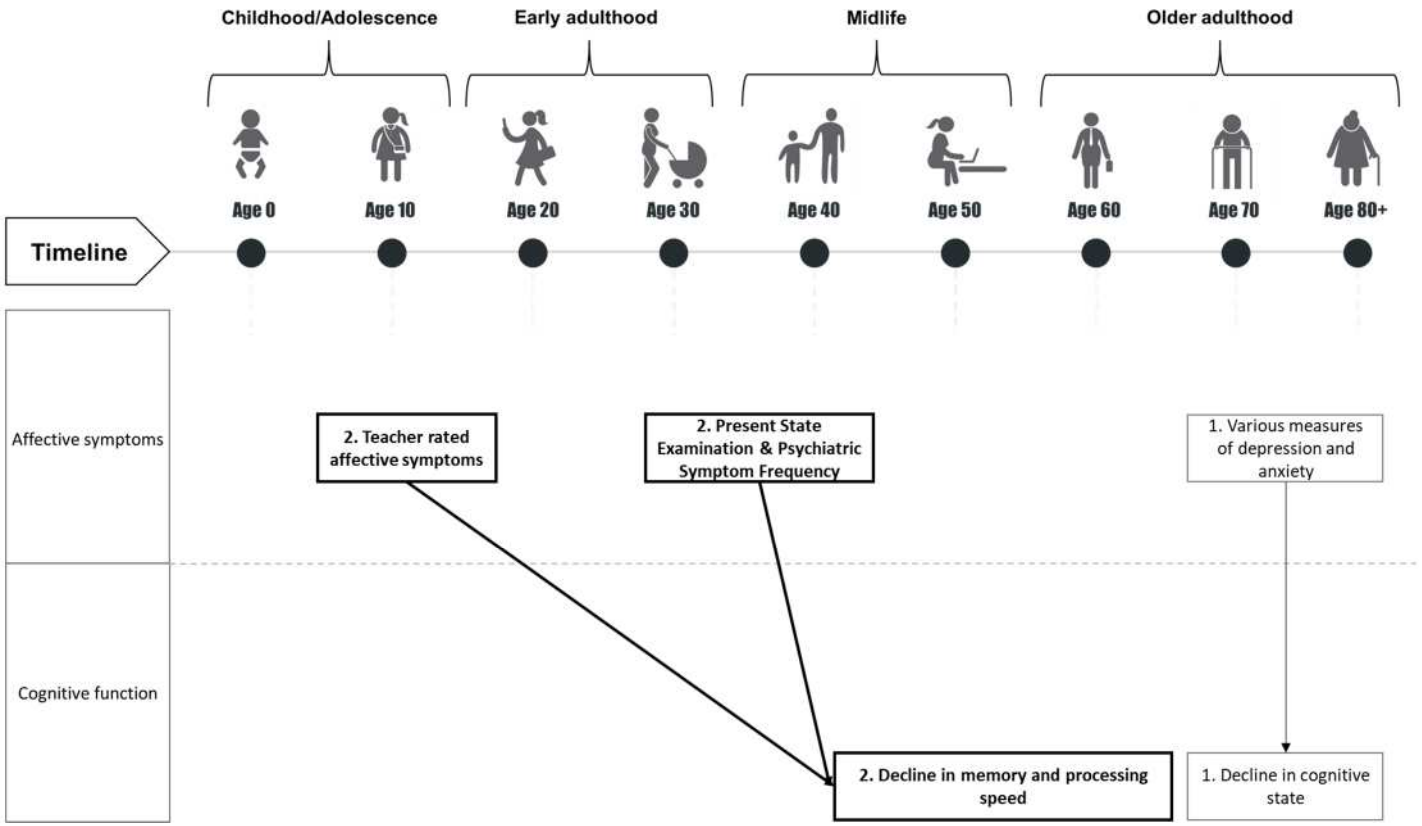


Table 3.6.1: Demographic information for sample included in fully adjusted memory (n=2546) and information processing speed models (n=2570)

Demographic information		**Verbal memory N = 2546**	**Information processing speed N = 2570**
Verbal Memory, Mean (SD)	Age 43	24.65 (6.35)	24.66 (6.35)
	Age 53	23.85 (6.34)	23.85 (6.34)
	Age 60-64	24.17 (6.16)	24.17 (6.16)
	Age 69	22.11 (6.05)	22.11 (6.05)
Processing Speed, Mean (SD)	Age 43	340.94 (75.99)	340.69 (76.15)
	Age 53	279.73 (75.07)	279.55 (75.24)
	Age 60-64	265.74 (71.62)	265.74 (71.62)
	Age 69	261.20 (73.29)	261.08 (73.28)
Continuous Measures of Affective Symptoms, Mean (SD)	Age 13-15	0.02 (0.50)	0.02 (0.49)
	Age 36	0.23 (0.84)	0.23 (0.84)
	Age 43	0.001 (0.64)	0.005 (0.64)
Categorical Measures of Affective Symptoms, N (%)*			
- Low affective symptoms	Age 13-15	1322 (51.92)	1327 (51.63)
	Age 36	1323 (51.96)	1335 (51.95)
	Age 43	1318 (51.77)	1323 (51.48)
- Moderate affective symptoms	Age 13-15	994 (39.04)	1009 (39.26)
	Age 36	987 (38.77)	995 (38.72)
	Age 43	993 (39.00)	1009 (39.26)

Demographic information (cont.)		**Verbal memory N = 2546 (cont.)**	**Information processing speed N = 2570 (cont.)**
- Severe affective symptoms	Age 13-15 Age 36 Age 43	230 (9.03) 236 (9.27) 235 (9.23)	234 (9.11) 240 (9.34) 238 (9.26)
Number of episodes of severe affective symptoms between ages 13-42, N (%)	0 1 2 3	1970 (77.38) 465 (18.26) 97 (3.81) 14 (0.55)	1988 (77.35) 467 (18.17) 100 (3.89) 15 (0.58)
Sex N (%)	Male Female	1262 (49.57) 1284 (50.43)	1278 (49.73) 1292 (50.27)
Childhood Cognition, Mean (SD)	Cognitive score	0.05 (0.83)	0.04 (0.83)
Childhood Social Class, N (%)	Professional Intermediate Skilled non-manual Skilled manual Partly skilled Unskilled	140 (5.50) 430 (16.89) 472 (18.54) 786 (30.87) 556 (21.84) 162 (6.36)	141 (5.49) 434 (16.89) 474 (18.44) 799 (31.09) 560 (21.79) 162 (6.30)
Education, N (%)	None attempted Vocational or GCSE A Level or Higher	934 (36.68) 731 (28.71) 881 (34.60)	950 (36.96) 736 (28.64) 884 (34.40)

Notes: * Low symptoms: 0-50th percentile; Moderate symptoms 51-90th percentile; Severe symptoms: 91-100th percentile.

Table 3.6.2: Affective symptoms (at ages 13-15, 36, and 43) and verbal memory trajectories – Linear mixed models

	Model 1: Unadjusted			**Model 2: Adjusted for sex**			**Model 2: Adjusted for sex, education, childhood cognition and SEP**		
	b	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS									
Affective symptoms in adolescence	**-2.08**	**0.54**	**<.001**	**-2.29**	**0.54**	**<.001**	**-1.11**	**0.53**	**.04**
Affective symptoms at age 36	-0.61	0.33	.07	-0.54	0.33	.11	-0.54	0.33	.10
Affective symptoms at age 43	0.87	0.44	.05	0.60	0.44	.18	0.48	0.43	.26
Gender				**2.13**	**0.22**	**<.001**	**2.13**	**0.18**	**<.001**
Childhood cognition							**2.48**	**0.13**	**<.001**
Childhood socioeconomic position							-0.02	0.01	.10
Education							**1.93**	**0.13**	**<.001**
SLOPE TERMS									
Decline per year (linear)	0.36	**0.06**	**<.001**	**0.36**	**0.06**	**<.001**	**0.35**	**0.06**	**<.001**
Decline per year (quadratic)	-0.004	**0.001**	**<.001**	**-0.004**	**0.001**	**<.001**	**-0.004**	**0.001**	**<.001**
Affective symptoms in adolescence	0.01	0.01	.21	0.01	0.01	.19	0.01	0.01	.30
Affective symptoms at age 36	0.01	0.01	.18	0.01	0.01	.17	0.01	0.01	.31
Affective symptoms at age 43	-0.01	0.01	.08	-0.01	0.01	.07	-0.01	0.01	.12
N	2652			2652			2546		
AIC	49763.34			49673.18			46636.31		
BIC	49839.82			49755.55			46735.63		

Table 3.6.3: Affective symptoms (at ages 13-15, 36, and 43) and information processing speed trajectories – Linear mixed models

	Model 1: Unadjusted			**Model 2: Adjusted for sex**			**Model 2: Adjusted for sex, education, childhood cognition and SEP**		
	b	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS									
Affective symptoms in adolescence	**-19.66**	**7.38**	**.008**	**-21.56**	**7.33**	**.003**	**-18.17**	**7.53**	**.02**
Affective symptoms at age 36	-1.04	4.56	.82	-0.21	4.53	.96	0.05	4.64	.99
Affective symptoms at age 43	2.95	6.02	.62	0.15	5.99	.98	0.46	6.10	.94
Gender				**21.68**	**2.44**	**<.001**	**21.51**	**2.47**	**<.001**
Childhood cognition							**4.50**	**1.75**	**.01**
Childhood socioeconomic position							**-0.36**	**0.14**	**.01**
Education							**8.44**	**1.75**	**<.001**
SLOPE TERMS									
Decline per year (linear)	**-21.68**	**0.84**	**<.001**	**-21.74**	**0.84**	**<.001**	**-22.02**	**0.85**	**<.001**
Decline per year (quadratic)	**0.17**	**0.01**	**<.001**	**0.17**	**0.01**	**<.001**	**0.17**	**0.01**	**<.001**
Affective symptoms in adolescence	0.09	0.13	.46	0.09	0.13	.47	0.09	0.13	.50
Affective symptoms at age 36	-0.002	0.08	.98	-0.001	0.08	.99	-0.002	0.08	.98
Affective symptoms at age 43	-0.04	0.10	.68	-0.05	0.10	.66	-0.05	0.11	.62
	2677			2677			2570		
AIC	93702.93			93627.48			89796.77		
BIC	93779.53			93709.98			89896.25		

Table 3.6.4: Effect of adolescent affective symptom percentiles on baseline memory and information processing speed function at age 43

Severity of adolescent affective symptoms	**Verbal Memory**			**Information Processing Speed**		
	Model 1 **b (SE), *p***	**Model 2** **b (SE), *p***	**Model 3** **b (SE), *p***	**Model 1** **b (SE), *p***	**Model 2** **b (SE), *p***	**Model 3** **b (SE), *p***
No/Low	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Moderate	**-1.11 (0.44), 0.01**	**-1.30 (0.44), 0.003**	**-0.87 (0.42), 0.04**	-8.63 (5.90), 0.14	-10.26 (5.86), 0.08	-9.25 (5.97), 0.12
High	**-3.21 (0.84), <.001**	**-3.51 (0.84), <.001**	**-1.88 (0.81), 0.02**	**-25.53 (11.39), 0.03**	**-27.98 (11.32), 0.01**	**-23.42 (11.55), 0.04**

Figure 3.6.2: Cognitive trajectories from ages 43 to 69 by exposure to affective symptoms in adolescence

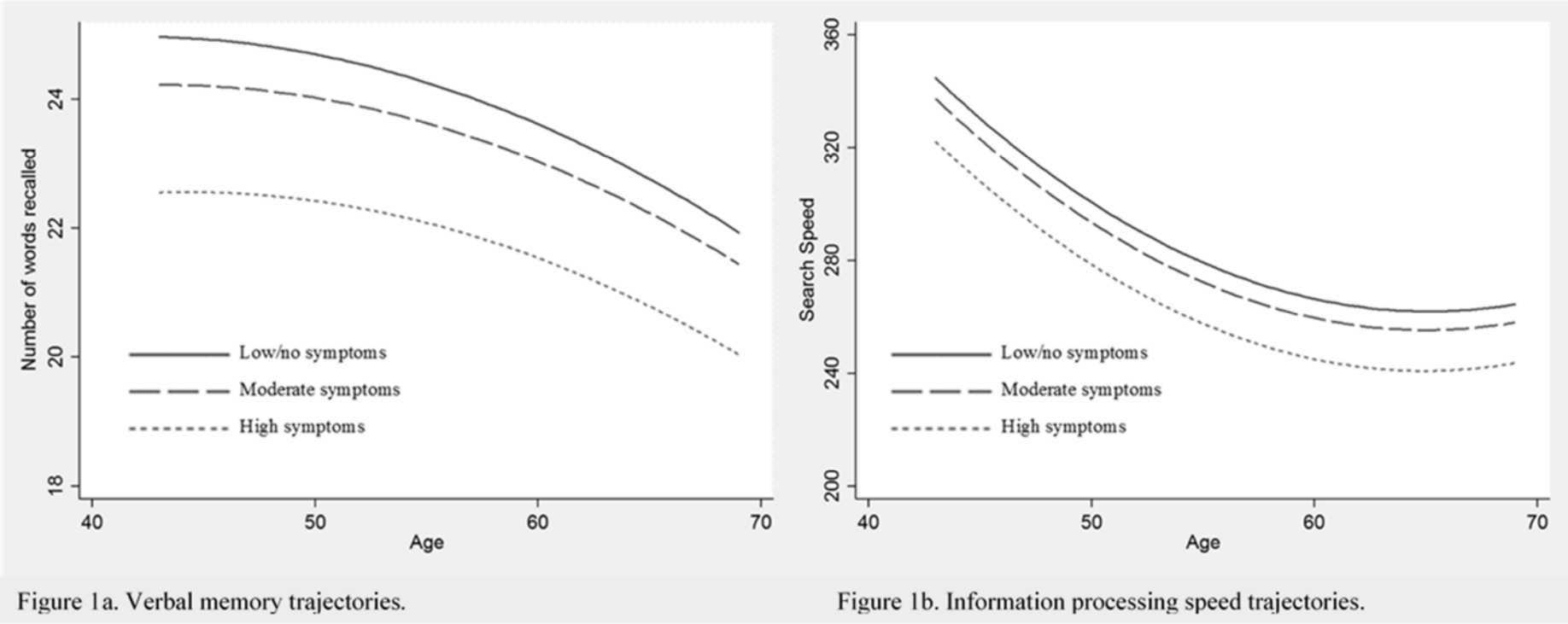


Figure 1a. Verbal memory trajectories.

Figure 1b. Information processing speed trajectories.

Note: Adolescent affective symptoms split into three groups with either 'no/low adolescent affective symptoms', 'moderate adolescent affective symptoms' or 'high adolescent affective symptoms' by dividing participants based on percentiles (0-50th percentile, 51-90th percentile, and 91-100th percentile).

3.7. Supplementary material

Supplementary Table 1: Interaction effects of sex and affective symptoms on verbal memory and processing speed trajectories.

Supplementary Table 2: Number of participants with cognitive data available.

Supplementary Table 3: Affective symptoms and cognitive trajectories, adjusting for anxiolytic and antidepressant medication use.

Supplementary Table 4: Affective symptoms and cognitive trajectories, adjusting for adolescent externalising behaviour.

Supplementary Table 5: Affective symptoms and verbal memory trajectories, excluding participants who died before age 69.

Supplementary Table 6: Affective symptoms and information processing speed trajectories, excluding participants who died before age 69.

Supplementary Table 7: Affective symptoms and verbal memory trajectories using imputed sample (N=3404).

Supplementary Table 8: Affective symptoms and information processing speed trajectories using imputed sample (N=3404).

Supplementary Figure 1: Flow chart of available sample.

Supplementary Table 1: Interaction effects of sex and affective symptoms on verbal memory and processing speed trajectories.

Cognitive domain	Interaction effect	b	SE	p
Verbal Memory	Sex x Age 13-15 affective symptoms	0.05	0.44	.91
	Sex x Age 36 affective symptoms	-0.49	0.27	.08
	Sex x Age 43 affective symptoms	-0.29	0.36	.43
Processing Speed	Sex x Age 13-15 affective symptoms	3.50	4.91	.48
	Sex x Age 36 affective symptoms	-1.19	3.05	.70
	Sex x Age 43 affective symptoms	3.81	4.04	.35

Supplementary Table 2: Number of participants with cognitive data available.

Number of time points with cognitive data available	Number of cohort members	
	Memory	**Processing Speed**
0	1958	1915
1	495	487
2	654	648
3	657	675
4	1598	1637
Total with cognitive data at 1 or more time-points	3404	3447

Supplementary Table 3: Affective symptoms and cognitive trajectories, adjusting for anxiolytic and antidepressant medication use.

	Verbal Memory			Information processing speed		
	b	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS						
Affective symptoms in adolescence	**-1.12**	**0.53**	**.03**	**-18.04**	**7.53**	**.02**
Affective symptoms at age 36	-0.54	0.33	.10	0.47	4.65	.92
Affective symptoms at age 43	0.51	0.43	.24	0.86	6.11	.89
Gender	**2.16**	**0.18**	**<.001**	**21.61**	**2.48**	**<.001**
Childhood cognition	**2.46**	**0.13**	**<.001**	**4.55**	**1.76**	**.01**
Childhood socioeconomic position	-0.02	0.01	.11	**-0.36**	**0.14**	**.01**
Education	**1.93**	**0.13**	**<.001**	**8.38**	**1.75**	**<.001**
Anxiolytic medication use	0.51	0.46	.27	-8.23	6.24	.19
Antidepressant medication use	**-0.79**	**0.34**	**.02**	-0.81	4.52	.86
SLOPE TERMS						
Decline per year (linear)	**0.35**	**0.06**	**<.001**	**-22.02**	**0.85**	**<.001**
Decline per year (quadratic)	**-0.004**	**0.001**	**<.001**	**0.17**	**0.01**	**<.001**
Affective symptoms in adolescence	0.01	0.01	.29	0.09	0.13	.51
Affective symptoms at age 36	0.01	0.01	.32	-0.003	0.08	.96
Affective symptoms at age 43	-0.01	0.01	.13	-0.05	0.11	.62
N	2546			2570		
AIC	46634.28			89798.9		
BIC	46745.28			89910.08		

Supplementary Table 4: Affective symptoms and cognitive trajectories, adjusting for adolescent externalising behaviour.

	Verbal Memory			Information processing speed		
	b	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS						
Affective symptoms in adolescence	**-1.15**	**0.53**	**.03**	**-18.47**	**7.53**	**.01**
Affective symptoms at age 36	-0.53	0.33	.11	0.08	4.64	.99
Affective symptoms at age 43	0.50	0.43	.24	0.60	6.10	.92
Gender	**2.08**	**0.18**	**<.001**	**21.22**	**2.48**	**<.001**
Childhood cognition	**2.46**	**0.13**	**<.001**	**4.39**	**1.76**	**.01**
Childhood socioeconomic position	-0.02	0.01	.11	**-0.36**	**0.14**	**.01**
Education	**1.86**	**0.13**	**<.001**	**8.00**	**1.79**	**<.001**
Adolescent externalising behaviour	**-0.48**	**0.18**	**.008**	-3.04	2.43	.21
SLOPE TERMS						
Decline per year (linear)	**0.35**	**0.06**	**<.001**	**-22.02**	**0.85**	**<.001**
Decline per year (quadratic)	**-0.004**	**0.001**	**<.001**	**0.17**	**0.01**	**<.001**
Affective symptoms in adolescence	0.01	0.01	.30	0.09	0.13	.51
Affective symptoms at age 36	0.01	0.01	.31	-0.001	0.08	.99
Affective symptoms at age 43	-0.01	0.01	.12	-0.05	0.11	.61
N	2546			2570		
AIC	46631.26			89797.21		
BIC	46736.42			89902.54		

Supplementary Table 5: Affective symptoms and verbal memory trajectories, excluding participants who died before age 69.

	Model 1: Unadjusted			**Model 2: Adjusted for sex**			**Model 2: Adjusted for sex, education, childhood cognition and SEP**		
	b	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS									
Affective symptoms in adolescence	**-1.92**	**.57**	**.001**	**-2.14**	**0.58**	**<.001**	-0.99	0.56	.08
Affective symptoms at age 36	-0.48	0.35	.17	-0.41	0.35	.25	-0.38	0.34	.27
Affective symptoms at age 43	**0.96**	**0.46**	**.04**	0.67	0.46	.15	0.37	0.44	.41
Gender				**2.11**	**0.23**	**<.001**	**2.13**	**0.19**	**<.001**
Childhood cognition							**2.52**	**0.14**	**<.001**
Childhood socioeconomic position							-0.02	0.01	.09
Education							**1.92**	**0.14**	**<.001**
SLOPE TERMS									
Decline per year (linear)	**0.40**	**0.06**	**<.001**	**0.40**	**0.06**	**<.001**	**0.39**	**0.06**	**<.001**
Decline per year (quadratic)	**-0.004**	**0.001**	**<.001**	**-0.004**	**0.001**	**<.001**	**-0.004**	**0.001**	**<.001**
Affective symptoms in adolescence	0.01	0.01	.24	0.01	0.01	.23	0.01	0.01	.33
Affective symptoms at age 36	0.01	0.01	.34	0.01	0.01	.33	0.003	0.01	.58
Affective symptoms at age 43	-0.01	0.01	.09	-0.01	0.01	.08	-0.01	0.01	.20
N	2339			2339			2248		
AIC	46098.96			46019.66			43243.58		
BIC	46173.81			46100.26			43340.78		

Supplementary Table 6: Affective symptoms and information processing speed trajectories, excluding participants who died before age 69.

	Model 1: Unadjusted			**Model 2: Adjusted for sex**			**Model 2: Adjusted for sex, education, childhood cognition and SEP**		
	b	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS									
Affective symptoms in adolescence	**-18.49**	**7.81**	**.02**	**-20.45**	**7.76**	**.008**	**-16.76**	**7.98**	**.04**
Affective symptoms at age 36	-3.80	4.75	.42	-3.01	4.72	.52	-2.68	4.84	.58
Affective symptoms at age 43	3.65	6.27	.56	0.70	6.24	.91	0.79	6.36	.90
Gender				**20.72**	**2.56**	**<.001**	**20.70**	**2.60**	**<.001**
Childhood cognition							**4.33**	**1.85**	**.02**
Childhood socioeconomic position							**-0.36**	**0.15**	**.01**
Education							**8.26**	**1.84**	**<.001**
SLOPE TERMS									
Decline per year (linear)	**-21.33**	**0.86**	**<.001**	**-21.39**	**0.86**	**<.001**	**-21.63**	**0.88**	**<.001**
Decline per year (quadratic)	**0.16**	**0.01**	**<.001**	**0.16**	**0.01**	**<.001**	**0.17**	**0.01**	**<.001**
Affective symptoms in adolescence	0.06	0.13	.64	0.06	0.13	.64	0.05	0.14	.71
Affective symptoms at age 36	0.03	0.08	.70	0.03	0.08	.69	0.03	0.08	71
Affective symptoms at age 43	-0.04	0.11	.69	-0.04	0.11	.69	-0.05	0.11	.65
N	2353			2353			2260		
AIC	86913.68			86851.53			83314.71		
BIC	86988.60			86932.21			83412.00		

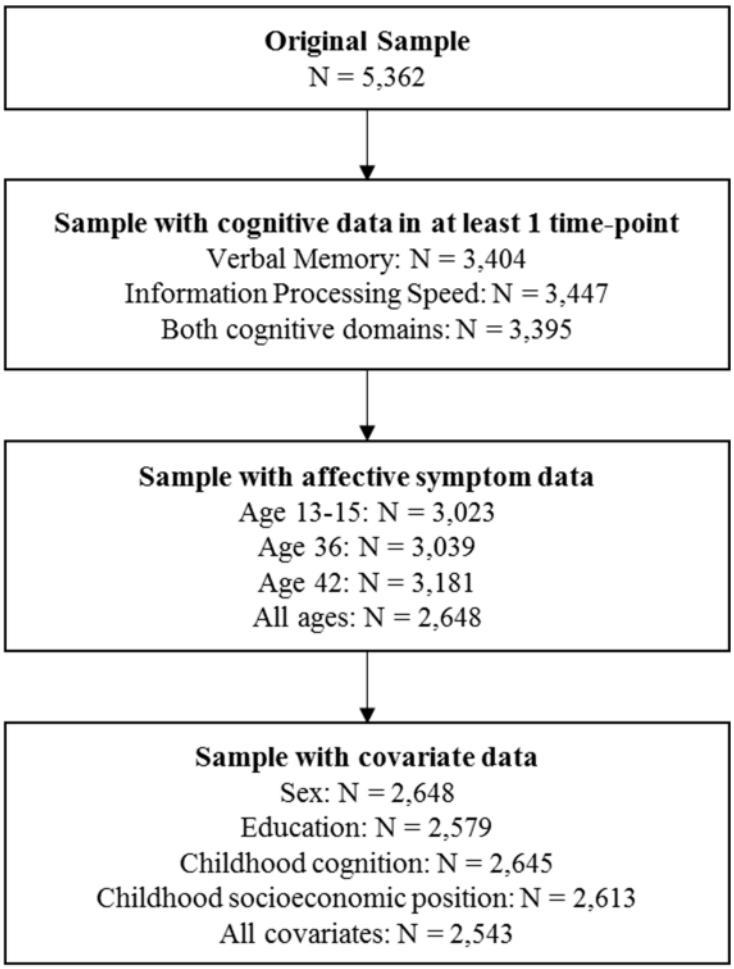
Supplementary Table 7: Affective symptoms and verbal memory trajectories using imputed sample (N=3404).

	Model 1: Unadjusted			**Model 2: Adjusted for sex**			**Model 2: Adjusted for sex, education, childhood cognition and SEP**		
	b	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS									
Affective symptoms in adolescence	**-1.79**	**0.49**	**<.001**	**-1.96**	**0.49**	**<.001**	**-1.03**	**0.47**	**.03**
Affective symptoms at age 36	-0.21	0.30	.48	-0.14	0.30	.63	-0.22	0.29	.45
Affective symptoms at age 43	0.57	0.39	.15	0.30	0.40	.45	0.41	0.38	.28
Gender				**2.08**	**0.19**	**<.001**	**2.20**	**0.16**	**<.001**
Childhood cognition							**1.96**	**0.11**	**<.001**
Childhood socioeconomic position							**-0.19**	**0.07**	**.005**
Education							**2.14**	**0.11**	**<.001**
SLOPE TERMS									
Decline per year (linear)	**0.35**	**0.06**	**<.001**	**0.34**	**0.06**	**<.001**	**0.35**	**0.06**	**<.001**
Decline per year (quadratic)	**-0.004**	**0.001**	**<.001**	**-0.004**	**0.001**	**<.001**	**-0.004**	**0.001**	**<.001**
Affective symptoms in adolescence	0.01	0.01	.20	0.01	0.01	.20	0.01	0.01	.19
Affective symptoms at age 36	0.001	0.005	.83	0.001	0.005	.80	0.0001	0.005	.98
Affective symptoms at age 43	-0.01	0.01	.18	-0.01	0.01	.18	-0.01	0.01	.12
N	3404			3404			3404		
AIC	61548.6			61436.6			60233.0		
BIC	61628.3			61522.5			60337.3		

Supplementary Table 8: Affective symptoms and information processing speed trajectories using imputed sample (N=3447).

	Model 1: Unadjusted			**Model 2: Adjusted for sex**			**Model 2: Adjusted for sex, education, childhood cognition and SEP**		
	b	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
INTERCEPT TERMS									
Affective symptoms in adolescence	**-18.91**	**6.69**	**.005**	**-20.16**	**6.65**	**.002**	**-16.81**	**6.65**	**.01**
Affective symptoms at age 36	-0.61	4.09	.88	0.08	4.07	.98	-0.04	4.06	.99
Affective symptoms at age 43	3.08	5.43	.57	0.50	5.41	.93	0.88	5.40	.87
Gender				**20.20**	**2.18**	**<.001**	**20.99**	**2.16**	**<.001**
Childhood cognition							**3.29**	**1.49**	**.03**
Childhood socioeconomic position							**-2.15**	**0.89**	**.02**
Education							**9.40**	**1.48**	**<.001**
SLOPE TERMS									
Decline per year (linear)	**-22.01**	**0.77**	**<.001**	**-22.07**	**0.77**	**<.001**	**-22.02**	**0.77**	**<.001**
Decline per year (quadratic)	**0.17**	**0.01**	**<.001**	**0.17**	**0.01**	**<.001**	**0.17**	**0.01**	**<.001**
Affective symptoms in adolescence	0.15	0.12	.19	0.15	0.12	.21	0.14	0.12	.22
Affective symptoms at age 36	-0.004	0.07	.96	-0.002	0.07	.97	-0.01	0.07	.90
Affective symptoms at age 43	-0.07	0.09	.49	-0.07	0.09	.48	-0.07	0.09	.45
N	3447			3447			3447		
AIC	115826.7			115744.3			115643.8		
BIC	115906.6			115830.3			115748.2		

Supplementary Figure 1: Flow chart of available sample.



CHAPTER 4

Study 3: Bidirectional relation between affective symptoms and cognitive function from middle to late adulthood: a prospective population-based birth cohort study.

Study 3 is under review in *British Journal of Psychiatry (BJP).*

4.1. Abstract

The aim of this study was to test for possible bidirectional relationships between affective symptoms and cognitive function (memory and information processing speed) from middle to late adulthood. Data were available from the MRC National Survey of Health and Development (NSHD), a prospective birth cohort of 5362 people born in 1946. Affective symptoms and cognition were measured at ages 53, 60-64, and 69. Latent scores of affective symptoms were derived at each time point and cross-lagged models were fitted for affective symptoms with memory and information processing speed separately to model bidirectional relationships. Models were adjusted for sex, childhood socioeconomic position, education, and National Adult Reading Test score. Results revealed an inverse cross-sectional association between affective symptoms and memory (β = -0.18, SE = 0.04, $p < .001$) and information processing speed (β = -0.13, SE = 0.06, $p = .05$) at age 53, but not at ages 60-64 or 69. Affective symptoms at age 53 significantly predicted lower memory at age 60-64 (β = -0.58, SE = 0.27, $p = .03$), and affective symptoms at age 60-64 was associated with lower memory (β = -0.64, SE = 0.29, $p = .03$) and information processing speed (β = -1.27, SE = 0.41, $p = .002$) at age 69. Memory and information processing speed did not predict subsequent affective symptoms. Affective symptoms predict poorer memory and information processing speed over a period of 16-years, but the association does not operate in the opposite direction. Future research should test whether treatment of affective disorders can reduce risk of poorer cognitive outcomes.

4.2. Introduction

Affective disorders are common in midlife, with 19% of women and 14.9% of men between the age 55-64 reporting symptoms of depression (Stansfeld et al., 2014). Additionally, research shows that affective symptoms in older age are highly comorbid with cognitive impairment. It has been estimated that around 32% of people with dementia present with high depressive symptoms compared with only 7% of people in the general population (Lyketsos et al., 2002).

Previous research has also shown that a longitudinal association may exist between affective symptoms and cognitive function over time, although the precise temporal order remains unclear. There has been some evidence that affective symptoms can precede subsequent development of dementia (Da Silva et al., 2013; Gulpers et al., 2016; Jorm, 2001; Ownby et al., 2006), cognitive decline (John et al., 2018), and poorer cognitive level (John et al., 2019). However, other research has suggested that cognitive function can predict subsequent level of affective symptoms (Jajodia & Borders, 2011). A bi-directional longitudinal association between affective symptoms and cognitive function is therefore possible, but evidence is inconsistent. For example, Jajodia and Borders, (2011) reported that in 14000 adults over the age of 50, memory performance predicted increases in depressive symptoms over a follow-up period of 8-years, but not vice versa. Vinkers et al (2004) studied 500 people aged 85 over a 4-year follow-up. Similarly, it was concluded that poorer attention and memory function at baseline were related to faster increases in depressive symptoms. No associations were observed between baseline depression and change in cognitive function. Gale, Allerhand, & Deary (2012) reported that in a sample of 8611 people over the age of 50, higher levels of depression were associated with faster cognitive decline over a follow-up period of 7-years, but only in people aged 60-80 years old. However, cognitive function was not

associated with change in depressive symptoms over time. In these studies, samples were based on people over the age of 50 at baseline, and therefore the analyses was unable to account for earlier life influences which may be pertinent within this association. Additionally, follow-up periods were relatively short (<10 years), so it is unclear how affective symptoms and cognitive function may interact with each other over a longer period of time.

The aim of the present study is to clarify and extend previous research by testing bidirectional relationships between affective symptoms and cognition function (memory and information processing speed) over a period of 16-years: from middle age (53), through late middle age (60-64) to older age (69). The conceptual framework for this chapter is presented in Figure 4.6.1. The previous chapters showed that affective symptoms in older adulthood are associated with subsequent decline in cognitive state and that affective symptoms in adolescence are associated with cognitive intercept, but not slope from midlife to early old age. This chapter extends those findings by testing bidirectional associations between affective symptoms and cognitive function across midlife to early old age.

4.3. Method

Participants.

Data from the MRC National Study of Health and Development (NSHD) were used. The sample originally comprised 5362 males and females born in mainland UK in 1946. Data has been collected from participants at 24 time points, most recently when participants were aged 69. At the latest sweep, 80% (N=2148) of participants who were alive and with a known UK address, participated (Kuh et al., 2016). Reasons for non-participation at age 69 varied; 155 cohort members did not respond to the invitation, 55 people only took part in the postal questionnaire, 298 people refused to participate, 31 people withdrew from the study, and 11 were not able to provide informed consent. Further information about data collection and participation rates in NSHD is available elsewhere (Kuh et al., 2011b, 2016; Wadsworth et al., 2006). Informed consent was provided by participants at every wave and the latest ethical approval was obtained from NRES Queen Square REC and Scotland A REC. Further ethical approval for the current study has been received from the University of Sussex (ER/AJ316/1).

Measures.

Cognitive function.

The current study focuses on measures of verbal memory and information processing speed measured three times, at ages 53, 60-64, and 69. Memory was assessed using a word recall test with 3 administrations. At each administration participants were asked to recall as many words from the list as they could, with possible scores ranging from 0-45. A letter cancellation task was used to capture information processing speed. For this task, participants were asked to cross out the target letters P and W from a letter grid within a 1 minute time limit, as quickly and

accurately as possible, with possible scores ranging from 0-600. These measures have been described in detail elsewhere (Davis et al., 2017; Rawle, Davis, et al., 2018; Richards et al., 2004).

Affective symptoms.

Affective symptoms were measured at multiple time points across the life course (ages 13, 15, 36, 43, 53, 60-64, and 69). For the current study, measures of affective symptoms assessed at ages 53, 60-64, and 69 were included in main analyses. At all three of these latter time points, the 28 item General Health Questionnaire (GHQ-28) was used. Research has shown that the GHQ is a consistent and reliable measure in detecting psychiatric symptoms in a general population across multiple time points with long intervals between testing (Pevalin, 2000).

Covariables.

The covariables selected for the analysis were sex, childhood socioeconomic position (SEP) (Kaplan et al., 2001), education (Hatch, Feinstein, Link, Wadsworth, & Richards, 2007), and score on the National Adult Reading Test (NART) at age 53 (James et al., 2018). Score on the National Adult Reading Test was adjusted for to account for crystallised intelligence and to isolate associations between affective symptoms and fluid cognitive abilities (James et al., 2018). Details about how covariables were derived is presented in Supplementary Material 1A

Statistical Analyses.

The GHQ-28 measure of affective symptoms comprises four sub-scales measuring depression, anxiety, social dysfunction, and somatic symptoms. To take account of the four factor structure within the GHQ at each time point, second order confirmatory factor analysis (CFA) was conducted to derive latent scores of affective

symptoms at each time point. Model fit was assessed and measurement invariance was tested to check that the same latent construct was captured over time (Supplementary Figure 1).

To explore bidirectional relationships between affective symptoms and cognitive function across middle to late adulthood, cross-lagged models were fitted for memory and processing speed separately. This method allows directional relationships between two variables to be estimated across multiple time points. Benefits of cross-lagged methods are that lagged associations between variables can be estimated, while simultaneously allowing for cross-sectional associations and auto-correlations across repeated measures over time (Kearney, 2017). Models included affective symptoms and cognitive function at ages 53, 60-64 and 69. Two main models were fitted, including: Model 1: Unadjusted; Model 2: Adjusted for covariables: sex, childhood socioeconomic position, education by age 26, score on NART. Model fit did not significantly improve when the analysis was stratified by sex (Supplementary Table 1), suggesting that patterns of association did not differ significantly between men and women. For this reason, sex was used as a covariable in all subsequent analyses, rather than as a stratifying variable.

As a sensitivity analysis, main models were re-run on the sample of people who were still alive by age 69, to ensure that our results were not affected by mortality. As an additional sensitivity analysis, main models were re-run excluding participants using anxiolytic and antidepressant medications at ages 36, 43, 53, 60-64, and 69. Finally to maximise sample size available for the analyses, we ran a final sensitivity analysis using multiple imputation with MICE in R (Azur et al., 2011; Buuren & Groothuis-Oudshoorn, 2011) to impute covariate data for the adjusted models. Multiple imputation operates by deriving multiple plausible complete datasets, where missing values are

replaced by imputed values. Results from the generated complete datasets are then pooled into one (Sterne et al., 2009). Due to the multiple estimations, this analysis can create plausible standard error estimates (Patrician, 2002). The multiple imputation approach maximises plausibility of the missing at random assumption, as it allows for the inclusion of auxiliary variables and covariates in the models (Coley et al., 2011). For the current analysis, eighteen imputations were conducted over 12 sweeps in NSHD data. Further information about the multiple imputation process is presented in Supplementary Material 1B.

Mplus version 8 (Muthén & Muthén, 2017) was used for analyses, and missing data were dealt with using full information maximum likelihood (FIML) methods for cognitive and GHQ data, and using multiple imputation for covariables.

4.4. Results

Available sample and missing data.

The available sample included all participants with at least one measure of affective symptoms or cognitive function. Slightly different sample sizes were available for memory and processing speed. Specifically, 3125 survey members had at least one measure of memory or affective symptoms (58.3% of the original birth sample) and of this group, 2028 (64.9%) also had complete information for all covariables. In total, 3127 (58.3%) people had data for processing speed or affective symptoms in at least one time point of the total sample available at birth. Of this group, 2028 (64.9%) also had data for all covariables. For more information about available data, see Figure 4.6.2.

The sample with at least one measure of affective symptoms or cognition available at any time point (Memory: N = 3125; Processing speed: N = 3127) was compared on key childhood and adulthood variables with the sample with missing data on all assessments of cognition and affective symptoms (Memory: N = 2237; Processing speed: N = 2235). The sample with key data available did not differ from the sample with missing data on anxiolytic medication use ($p = .08$). However, the sample with missing data had significantly more males and fewer females than the sample with complete data available ($p < .001$). The sample with missing data also had significantly lower socioeconomic position at age 15 ($p = .02$), lower cognitive scores at age 15 ($p < .001$), lower educational level ($p < .001$), higher affective symptom scores at age 36 ($p = .01$), higher affective symptom scores at age 43 ($p = .03$), and lower antidepressant usage in adulthood ($p < .001$). Due to differences between the sample with complete covariate data and the sample with missing data, a sensitivity analysis was conducted using a multiple imputation approach to impute all covariate data. Further information

about the multiple imputation process is available in Supplementary Material 1B. Table 4.6.1 shows demographic information for the samples included in the analysis.

Longitudinal measurement model for affective symptoms.

Before fitting the cross-lagged model, the second order confirmatory factor analysis of the GHQ measurements over time was fitted to ensure this was an appropriate fit to the data for subsequent analysis. The second order CFA fit the data well (χ^2 (3387) = 17138.88, $p < .001$; CFI = .915; TLI = .912; RMSEA = .036). Indicators all loaded significantly onto the factors ($p < .001$). Measurement invariance of the first order factors was assessed by constraining factor loadings to be equal across time over the first order. There was not a significant deterioration in model fit after constraining according to a chi square difference test (Supplementary Table 2). Next, factor loadings were constrained to be equal over the first and second order factors. Again, model fit did not significantly deteriorate (Supplementary Table 2). Therefore, it was concluded that the GHQ measure captured the same latent construct over the three waves for both the first and second order factors.

Cross-lagged models.

Memory.

The cross-lagged memory model showed excellent fit to the data (χ^2 (2) = 5.39, p = .07; CFI = 1.00, TLI = 1.00; RMSEA = 0.02). The unadjusted model showed that all autoregressive pathways were significant, demonstrating stability in constructs over time for both memory and affective symptoms. There were significant cross-sectional associations between memory and affective symptoms at all ages (Age 43: β = -0.09, SE = 0.05, p = .05; Age 60-64: β = -0.04, SE = 0.02, p = .03; Age 69: β = -0.03, SE = 0.01, p = .04). Poorer memory function at age 53 significantly predicted higher affective

symptoms at age 60-64 (β = -0.002, SE = 0.001, *p* = .004). Additionally, higher affective symptoms at age 60-64 was significantly associated with poorer memory function at age 69 (β = -0.60, SE = 0.25, *p* = .02) (Supplementary Figure 2).

The fully adjusted model also fit the data very well (χ^2 (2) = 7.03, *p* = .03; CFI = 1.00, TLI = 0.99; RMSEA = 0.03). The fully adjusted model showed that all autoregressive pathways were significant. Results also revealed that there was a significant association between memory and affective symptoms at age 53 (β = -0.18, SE = 0.04, *p* < .001), but this cross-sectional effect no longer persisted over time at ages 60-64 (β = -0.03, SE = 0.02, *p* = .20) and age 69 (β = -0.03, SE = 0.02, *p* = .06). Additionally, higher affective symptoms at age 53 significantly predicted lower memory performance at age 60-64 (β = -0.58, SE = 0.27, *p* = .03), and higher affective symptoms at age 60-64 were significantly associated with poorer memory at age 69 (β = -0.64, SE = 0.29, *p* = .03). There were no significant longitudinal associations between memory scores and subsequent level of affective symptoms (Figure 4.6.3).

Processing Speed.

The cross-lagged processing speed model was also an excellent fit to the data (χ^2 (2) = 0.81, *p* = 67; CFI = 1.00, TLI = 1.00; RMSEA = 0.00). The unadjusted model revealed that as with the memory model, all autoregressive pathways were statistically significant, showing stability in constructs over time. In this unadjusted model, there were no cross-sectional or longitudinal associations between affective symptoms and processing speed (Supplementary Figure 3).

The fully adjusted model was also a good fit to the data (χ^2 (2) = 1.76, *p* = .41; CFI = 1.00, TLI = 1.00; RMSEA = 0.00). In the fully adjusted model, all of the autoregressive pathways remained significant. There was a significant association

between affective symptoms and processing speed present at age 53 (β = -0.13, SE = 0.06, p = .05), but not at ages 60-64 (β = -0.02, SE = 0.03, p = .52) or 69 (β = -0.02, SE = 0.02, p = .31). Additionally, results from the fully adjusted model showed that higher level of affective symptoms at age 60-64 significantly predicted worse processing speed performance at age 69 (β = -1.27, SE = 0.41, p = .002). No other cross lagged pathways were statistically significant (Figure 4.6.4).

Sensitivity analysis.

As a sensitivity analysis, the main models were re-run after excluding participants who died by age 69 from the analysis, to ensure results were not influenced by mortality. These models fit the data well (Memory: χ^2 (2) = 6.86, p = .03; CFI = 1.00; TLI = 0.99; RMSEA = 0.04. Processing speed: χ^2 (2) = 1.76, p = .42; CFI = 1.00; TLI = 1.00; RMSEA = 0.00). Results from memory models including the sample alive by age 69 remained consistent. The fully adjusted model showed a significant cross-sectional association between affective symptoms and memory at age 53 (β = -0.16, SE = 0.05, p = .001), and significant lagged pathways between affective symptoms at age 53 and memory at age 60-64 (β = -0.65, SE = 0.28, p = .02) and between affective symptoms at age 60-64 and memory at age 69 (β = -0.64, SE = 0.29, p = .03). No other pathways reached statistical significance (Supplementary Figure 4). Results from processing speed models excluding people who died by age 69 were also similar to those from the main models. Specifically, affective symptoms at age 60-64 significantly predicted poorer processing speed at age 69 (β = -1.27, SE = 0.41, p = .002). Again, no other pathways were statistically significant (Supplementary Figure 5).

Main models were re-run excluding people taking anxiolytic or antidepressant medication. Results from this analysis were similar to main models. The models fit the

data well (Memory: χ^2 (2) = 4.82, p = .09; CFI = 1.00; TLI = 0.99; RMSEA = 0.03. Processing speed: χ^2 (2) = 1.22, p = .54; CFI = 1.00; TLI = 1.00; RMSEA = 0.00). Results from memory models show that there is a cross-sectional association between affective symptoms and memory function at age 53 (β = -0.14, SE = 0.05, p = .002), and a longitudinal association between affective symptoms at age 53 and memory function at age 60-64 (β = -0.63, SE = 0.31, p = .04). No other cross-sectional or lagged pathways reached statistical significance (Supplementary Figure 6). Results from processing speed models showed no significant cross-sectional associations between affective symptoms and processing speed function. However, affective symptoms at age 60-64 significantly predicted lower processing speed scores at age 69 (β = -1.38, SE = 0.46, p = .003). No other longitudinal pathways were significant (Supplementary Figure 7).

Finally, to check whether results were affected by missing data, a sensitivity analysis was run using multiple imputation to impute covariate data. Models fit the data well (Memory: χ^2 (2) = 2.88, p = .24; CFI = 1.00; TLI = 1.00; RMSEA = 0.01. Processing speed: χ^2 (2) = 1.29, p = .53; CFI = 1.00; TLI = 1.00; RMSEA = 0.00) and results were consistent with main models. The fully adjusted memory model showed significant cross sectional associations between affective symptoms and memory function at age 53 (β = -0.15, SE = 0.04, p < .001) and age 60-64 (β = -0.04, SE = 0.02, p = .03), but not at age 69 (β = -0.02, SE = 0.01, p = .10). Affective symptoms at age 60-64 also significantly predicted poorer memory at age 69 (β = -0.73, SE = 0.25, p = .004). No other longitudinal pathways were significant (Supplementary Figure 8). The fully adjusted processing speed model revealed a significant cross-sectional association between affective symptoms and processing speed at age 53 (β = -0.16, SE = 0.05, p = .003) but not at ages 60-64 (β = -0.01, SE = 0.02, p = .68) or age 69 (β = -0.03, SE =

0.02, p = .12). Affective symptoms at age 60-64 significantly predicted poorer processing speed at age 69 (β = -0.73, SE = 0.36, p = .04), but no other pathways reached statistical significance (Supplementary Figure 9).

4.5. Discussion

There was a cross-sectional inverse association between affective symptoms and cognitive function (both memory and processing speed) in mid-life (age 53), but not at ages 60-64 or 69. Additionally, higher affective symptoms at age 53 significantly predicted lower memory scores at age 60-64, and affective symptoms at age 60-64 also predicted lower memory at age 69. However, memory function did not predict subsequent affective symptoms at any time-point. Results for processing speed models were similar; higher affective symptoms at age 60-64 significantly predicted poorer processing speed at age 69. Processing speed did not predict later affective symptoms at any time-point assessed. Overall, these results are consistent with previous research showing that affective symptoms can predict subsequent cognitive function (James et al., 2018; John et al., 2019, 2018). Our findings extend previous evidence by demonstrating that this relationship does not operate in the opposite direction over the period of 16-years.

There are four primary hypotheses that can explain associations between affective symptoms and cognitive function over time. First, it has been proposed that affective symptoms be a risk factor for poorer cognitive outcomes (Bennett & Thomas, 2014; Butters et al., 2008). Second, it is possible that affective symptoms may be a prodromal symptom of cognitive impairment (Bennett & Thomas, 2014; Butters et al., 2008; Byers & Yaffe, 2011). Third, there may be some common cause factor which increases risk for both affective disorders and poorer cognitive function (Bennett & Thomas, 2014; Djernes, 2006; Enache et al., 2011). Finally, it has also been proposed that affective symptoms may emerge as a response to subjective awareness of memory impairment (Vinkers et al., 2004). The temporal sequencing over an extended time frame which emerges in this study does not support the fourth possibility that affective

symptoms reflect a subjective response to cognitive impairments. Instead, these results indicate that affective symptoms may precede cognitive impairments by several years and that increased affective symptoms predict later cognitive function.

Our finding that affective symptoms predicted subsequent processing speed at the later time-point only (age 69) suggests that the effects of affective symptoms on lower processing speed, may not be observed until later in the life course. This is consistent with previous research showing that adult affective symptoms can predict poorer mid-life memory function at age 50, but no effects were observed on information processing speed at this age (John et al., 2019). This finding is inconsistent with work that suggests processing speed may be an important component in memory processing (Salthouse, 1996). This can potentially be explained by the digit checking task containing a motor component, compared to the verbal component within the memory task.

Future research should focus on identifying biological and socio-behavioural pathways and mechanisms of the longitudinal association between affective disorders and cognitive function. An additional important avenue for future research is to investigate whether effective treatment of affective symptoms can reduce risk of poorer cognitive outcomes later in life.

The key strength of the study is a large, nationally representative, and prospective sample, with 16-years follow-up period. An additional strength of the study is the use of consistent measures of affective symptoms and cognitive function. However, sample attrition is a problem in all long-running cohort studies. In the present study, missing data was addressed using full information maximum likelihood (FIML) methods and an additional supplementary analysis was conducted using multiple

imputation to deal with missing data. Another limitation of the study is that single cognitive tests were used to measure memory and processing speed, rather than more comprehensive cognitive batteries. Additionally, other cognitive domains, such as attention and inhibitory processes, could not be assessed.

Results from the present study show that affective symptoms can predict poorer cognitive outcomes over a 16-year period: from middle to late adulthood. These findings have significant value for public health. Understanding longitudinal associations between affective symptoms and cognitive function offers insights into maintaining better cognitive health for longer.

4.6. Tables & figures

Figure 4.6.1: Conceptual framework of Chapter 4

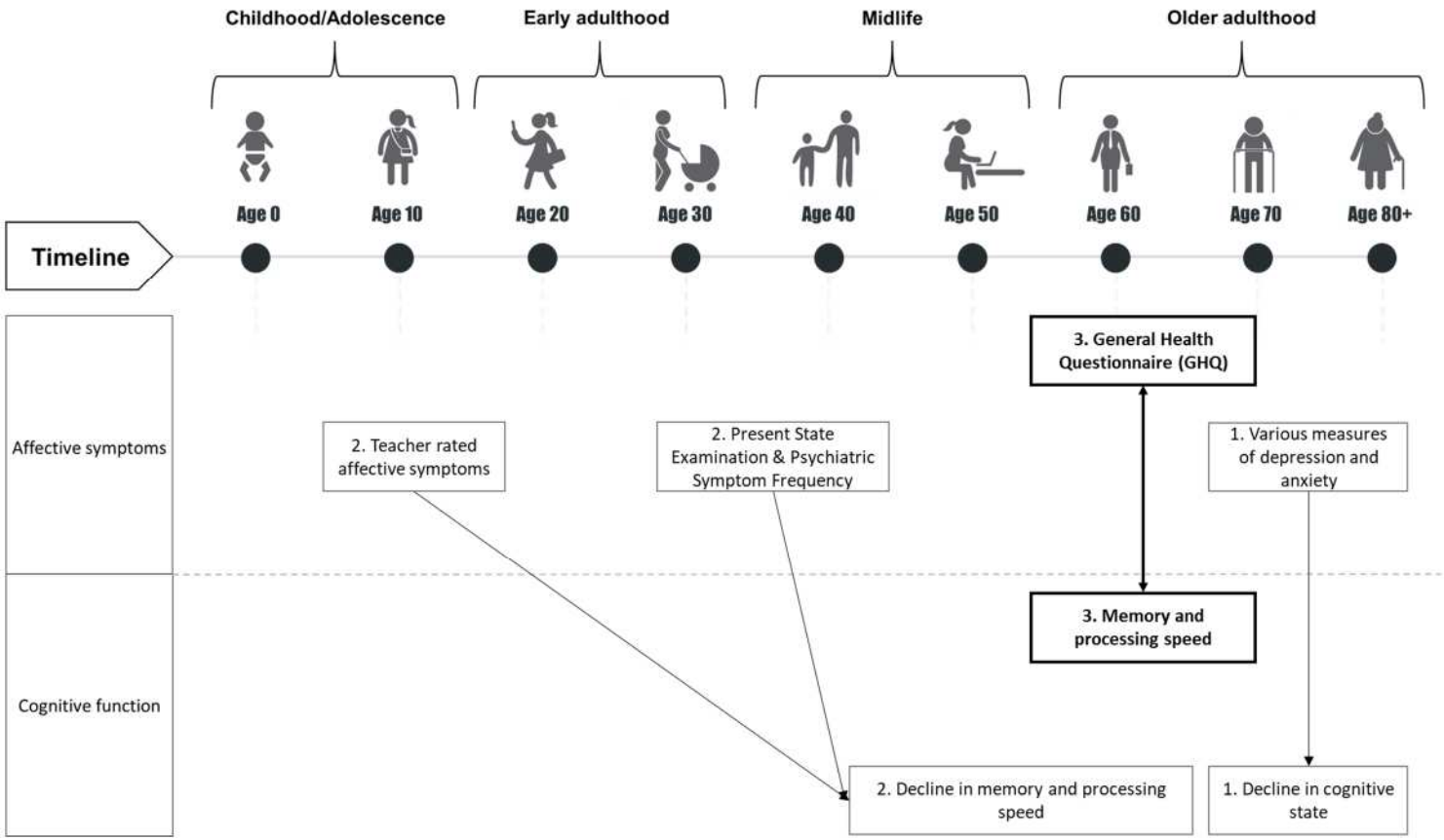


Table 4.6.1: Demographic information for analysed sample

Demographic Information		**Memory (N=3125)**	**Processing Speed (N=3127)**
Sex N (%)	Male Female	1557 (49.8) 1568 (50.2)	1559 (49.9) 1568 (50.1)
Childhood socioeconomic position N (%)	Professional Intermediate Skilled non-manual Skilled manual Partly skilled Unskilled	209 (6.7) 725 (23.2) 468 (15.0) 962 (30.8) 570 (18.2) 191 (6.1)	209 (6.7) 725 (23.2) 468 (15.0) 963 (30.8) 570 (18.2) 192 (6.1)
Educational attainment N (%)	None attempted A-Level or below Degree or above	1149 (36.8) 1670 (53.4) 306 (9.8)	1151 (36.8) 1670 (53.4) 306 (9.8)
National Adult Reading Test score Mean (SD)	NART Score	17.2 (9.8)	17.2 (9.8)
Antidepressant medication use N (%)	Yes No	292 (9.3) 2833 (90.7)	293 (9.4) 2834 (90.6)
Anxiolytic medication use N (%)	Yes No	157 (5.0) 2968 (95.0)	157 (5.0) 2970 (95.0)
Cognitive score	Age 53 Age 60-64 Age 69	23.93 (6.30) 24.26 (6.11) 22.20 (6.02)	281.07 (76.09) 266.71 (71.74) 262.30 (74.15)

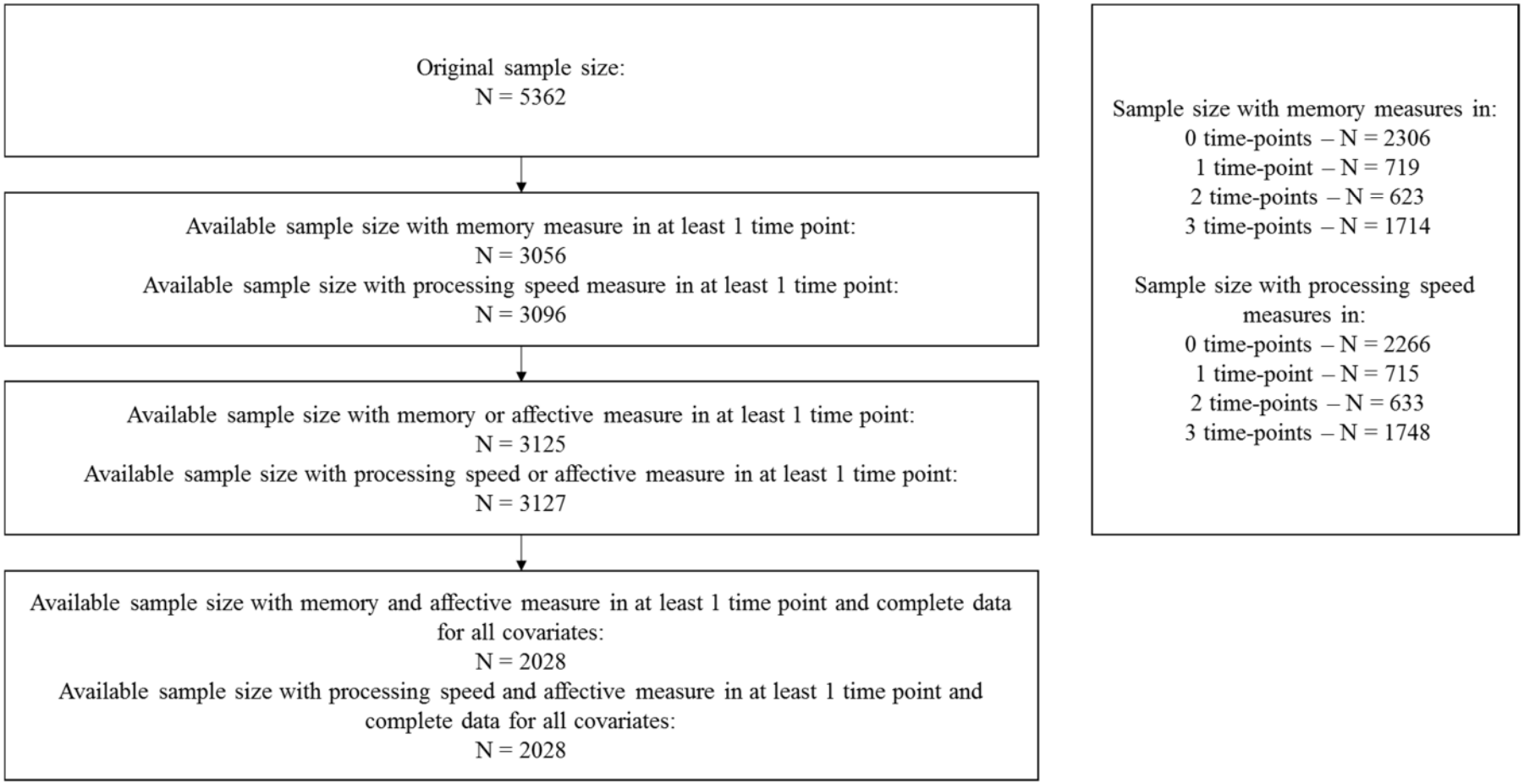


Figure 4.6.2: Flow chart showing available sample size

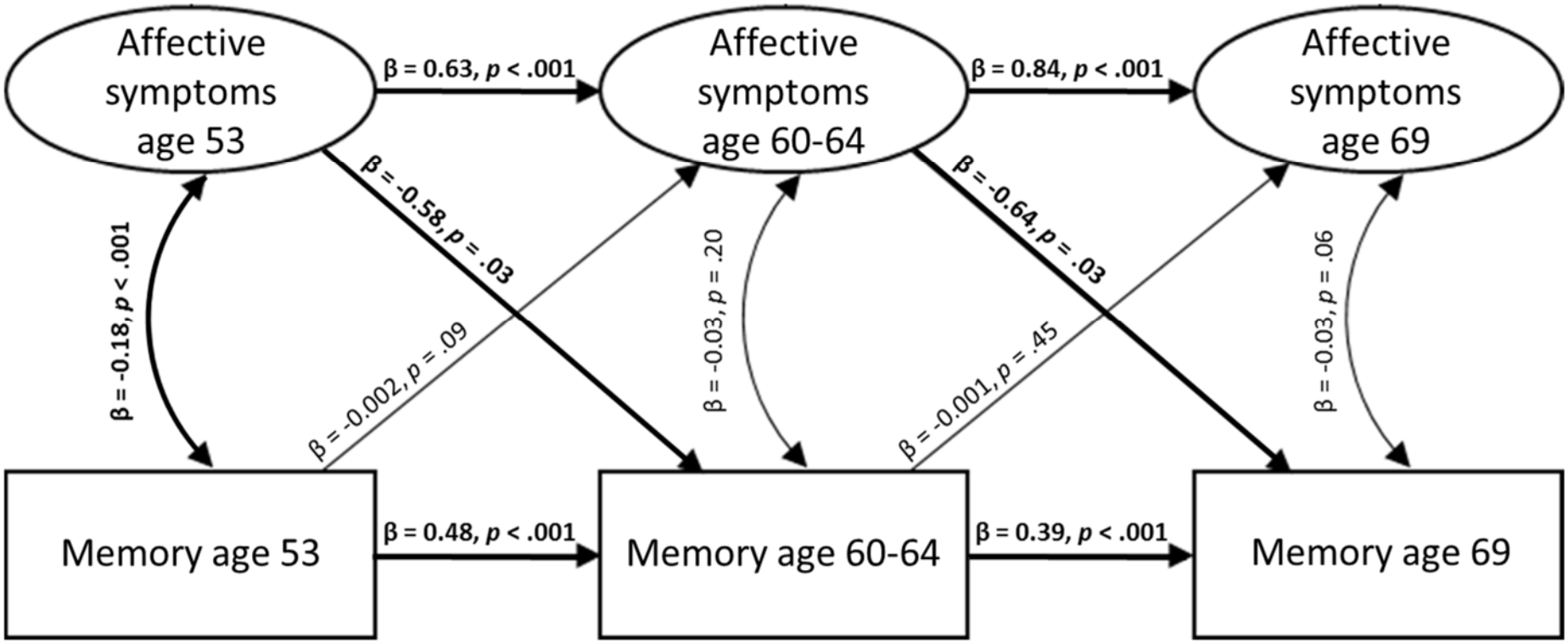


Figure 4.6.3: Cross lagged model of affective symptoms and memory from age 53 to 69. Fully adjusted model

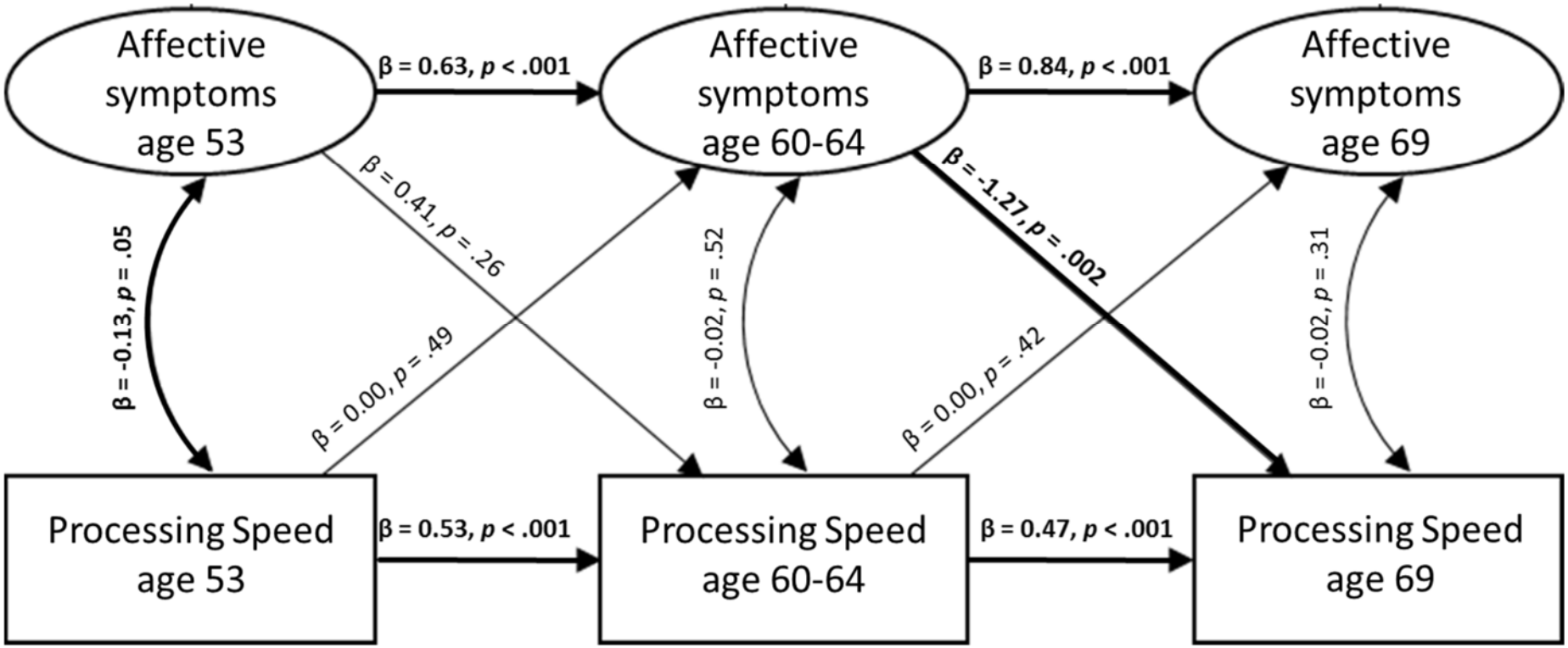


Figure 4.6.4: Cross lagged model of affective symptoms and processing speed from age 53 to 69. Fully adjusted model

4.7. Supplementary material

Supplementary Material 1A: Details about covariables

Supplementary Material 1B: Technical details for the multiple imputation process

Supplementary Table 1: Model fit for memory and processing speed data stratified by sex

Supplementary Table 2: Measurement invariance for GHQ over time

Supplementary Figure 1: Diagram of second order confirmatory factor analysis of GHQ measurements from age 53 to 69

Supplementary Figure 2: Unadjusted memory model

Supplementary Figure 3: Unadjusted processing speed model

Supplementary Figure 4: Memory model excluding participants who died by age 69

Supplementary Figure 5: Processing speed model excluding participants who died by age 69

Supplementary Figure 6: Memory model excluding participants using psychotropic medications

Supplementary Figure 7: Processing speed model excluding participants using psychotropic medications

Supplementary Figure 8: Memory model using imputed data

Supplementary Figure 9: Processing speed model using imputed data

Supplementary Material 1A: Details about covariables

Fathers' occupation was used as a measure of childhood SEP for each participant. This was coded into 6 categories based on social classes I-V in the Classification of Occupations: professional; intermediate; skilled non manual; skilled manual; partly skilled; unskilled. The highest qualification achieved by the participant at age 26 was used as a measure of education. This was coded based on the UK Burnham Scale into 9 categories: None attempted; Vocational course; Sub GCE or sub Burnham C; GCE O Level or Burnham C; GCE A Level or Burnham B; Burnham A2; 1st degree; higher degree (Masters); higher degree (doctorate).

Supplementary Material 1B: Technical details for the multiple imputation process

For this analysis, eighteen imputations were conducted over 12 sweeps. Firstly data collected at birth was imputed (birthweight, mother's age when cohort member was born, father's age when cohort member was born). Next, the measures collected at birth were used as auxiliary variables to impute socioeconomic position at age 4. As a next step, all birth and age 4 variables described above were used to impute variables at age 6 (mother's educational level and father's educational level). Next, all birth, age 4 and 6 variables were used to impute cognitive function at age 8. Cognitive function at age 11 was then imputed using the data from birth, age 4, 6, and 8. Data from birth, age 4, 6, 8, and 11 were used to impute adolescent affective symptoms at age 13. Measures from birth, age 4, 6, 8, 11, and 13 were used to impute age 15 variables (adolescent affective symptoms, cognitive function, and socioeconomic position). Educational attainment at age 26 was imputed using data from birth, age 4, 6, 8, 11, 13, and 15. Psychiatric symptoms at age 36 were imputed using the data from birth, age 4, 6, 8, 11, 13, 15, and 26. These variables at birth, age 4, 6, 8, 11, 15, 26, and 36 were next used to impute psychiatric symptoms at age 43. The data from birth, age 4, 6, 8, 11, 15, 26, 36, and 43 were then used to impute National Adult Reading Test score at age 53. Finally, lifetime use of antidepressant and anxiolytic medications was imputed using data from birth, age 4, 6, 8, 11, 13, 15, 26, 36, 43, and 53.

Supplementary Table 1: Comparison of fit statistics for memory and processing speed models stratified by sex

Model	**χ2**	**χ2 difference test**
Model 1*	$\chi2$ (2) = 5.39, p = .07	*Reference*
Model 2	$\chi2$ (4) = 7.10, p = .13	p = .43 **(Neither model is better)**
Model 3*	$\chi2$ (2) = 0.81, p = .67	*Reference*
Model 4	$\chi2$ (4) = 1.40, p = .84	p = .74 **(Neither model is better)**

*Reference models

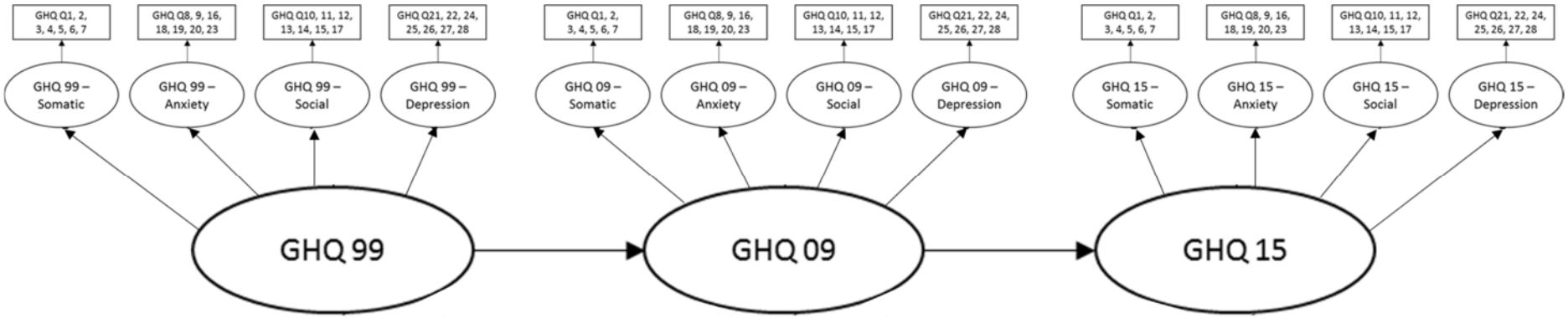
Model 1: Un-stratified memory model; Model 2: Memory model stratified by sex; Model 3: Un-stratified processing speed model; Model 4: Processing speed model stratified by sex

Supplementary Table 2: Measurement invariance for GHQ over time

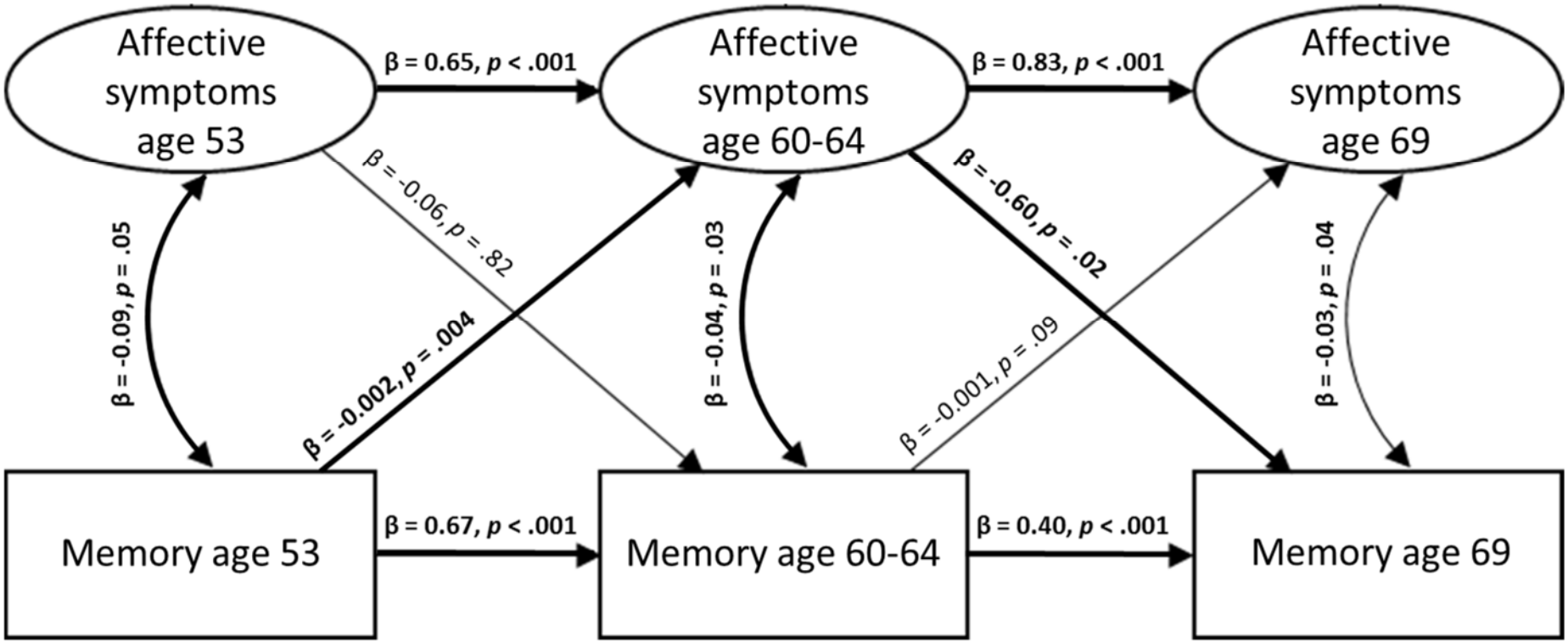
Model	χ2 Model fit	χ2 difference test
Model 1*	$\chi 2\ (3387) = 17138.88,\ p < .001$	*Reference*
Model 2	$\chi 2\ (3435) = 16208.54,\ p < .001$	$\chi 2\ (48) = 930.33,\ p = .00$ **(Model 2 is better)**
Model 3	$\chi 2\ (3441) = 15549.97,\ p < .001$	$\chi 2\ (54) = 1588.91,\ p = .00$ **(Model 3 is better)**

*Reference model

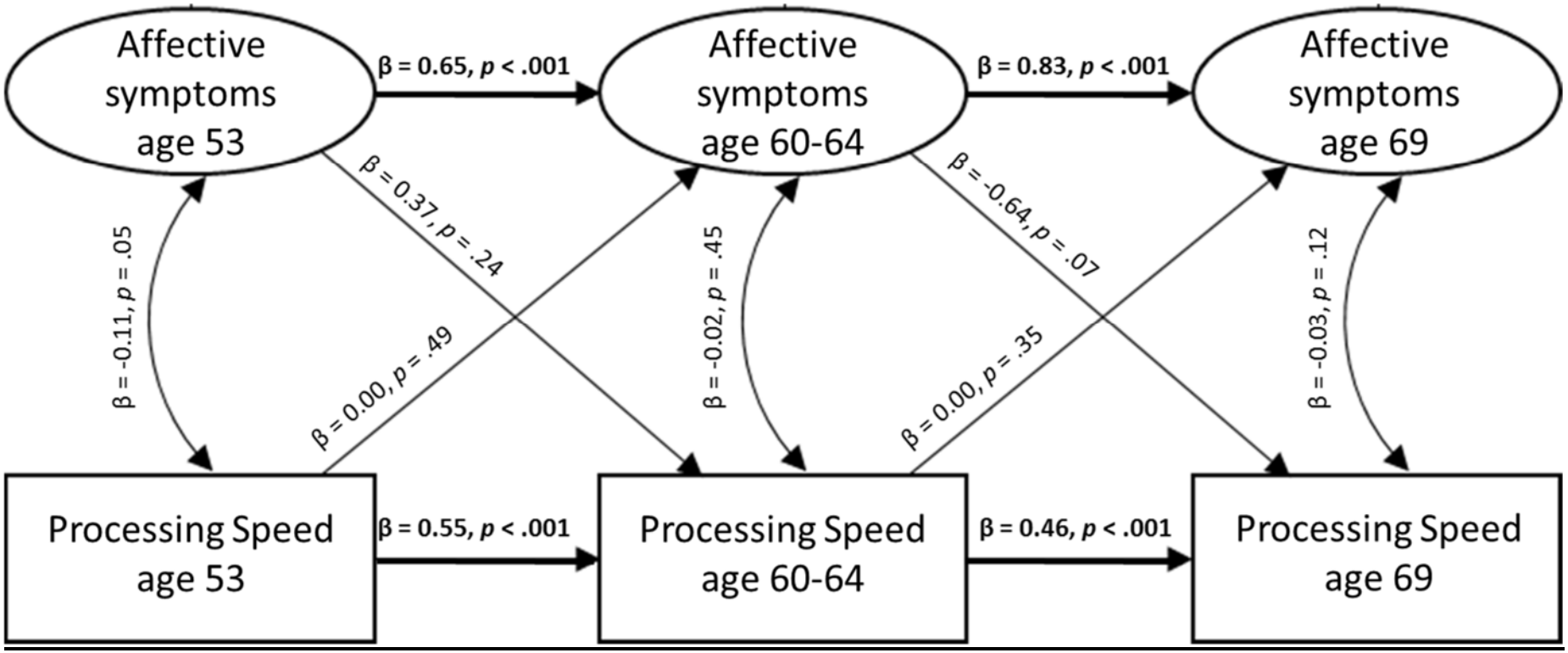
Model 1: Unconstrained model (reference); Model 2: First order factor loadings constrained to be equal; Model 3: First and second order factor loadings constrained to be equal



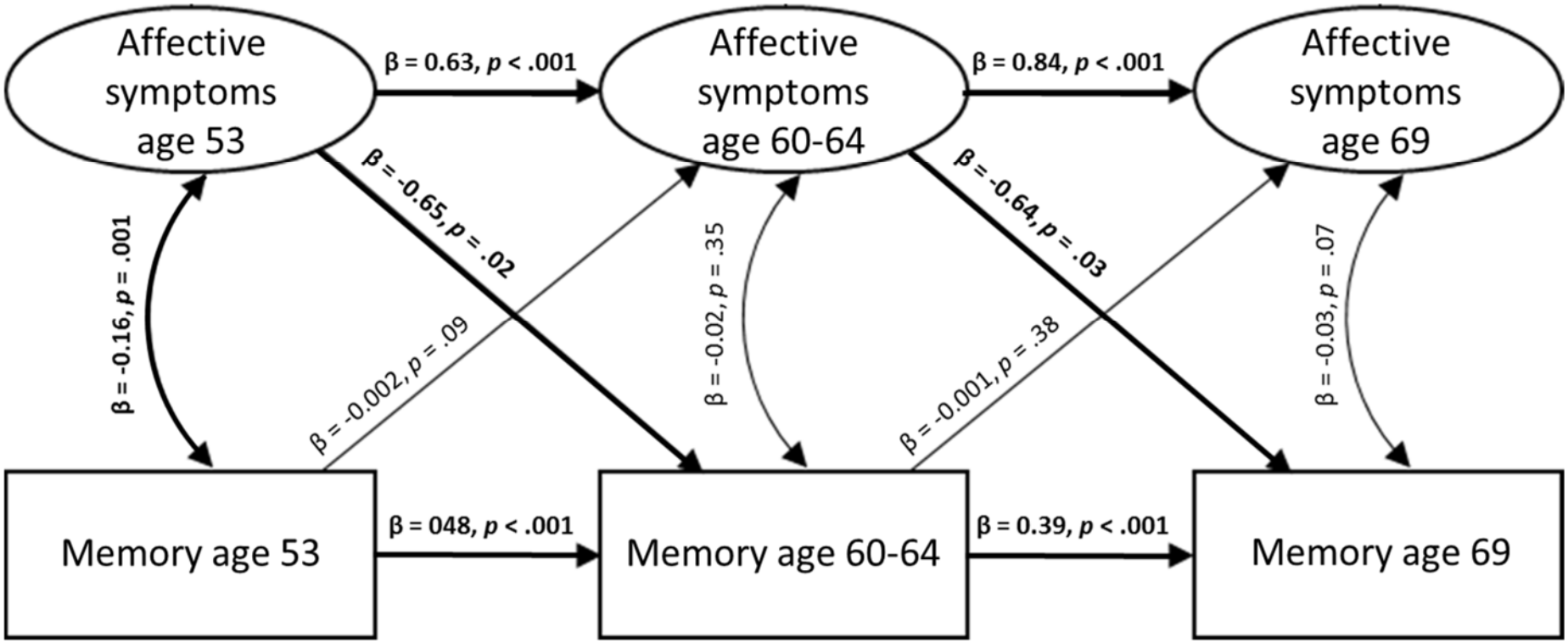
Supplementary Figure 1: Diagram of second order confirmatory factor analysis of GHQ measurements from age 53 to 69



Supplementary Figure 2: Unadjusted memory model

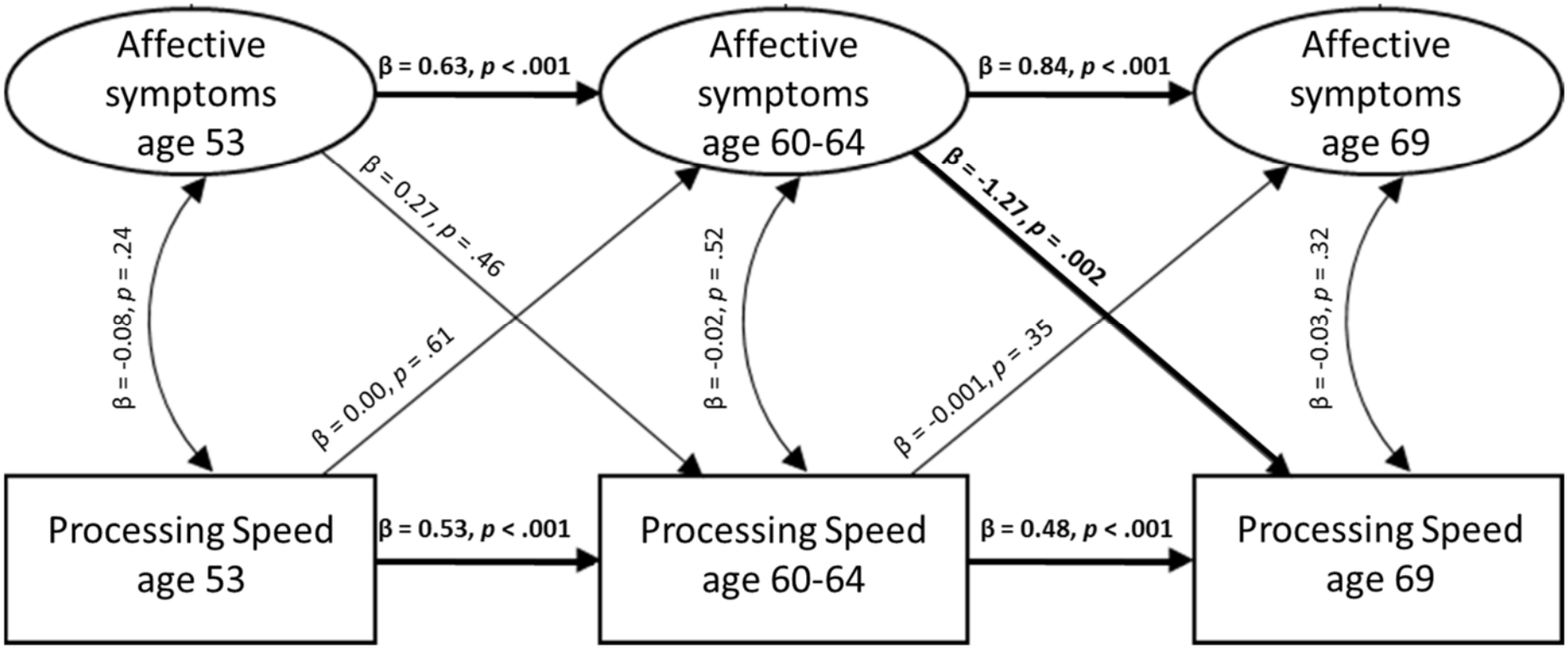


Supplementary Figure 3: Unadjusted processing speed model



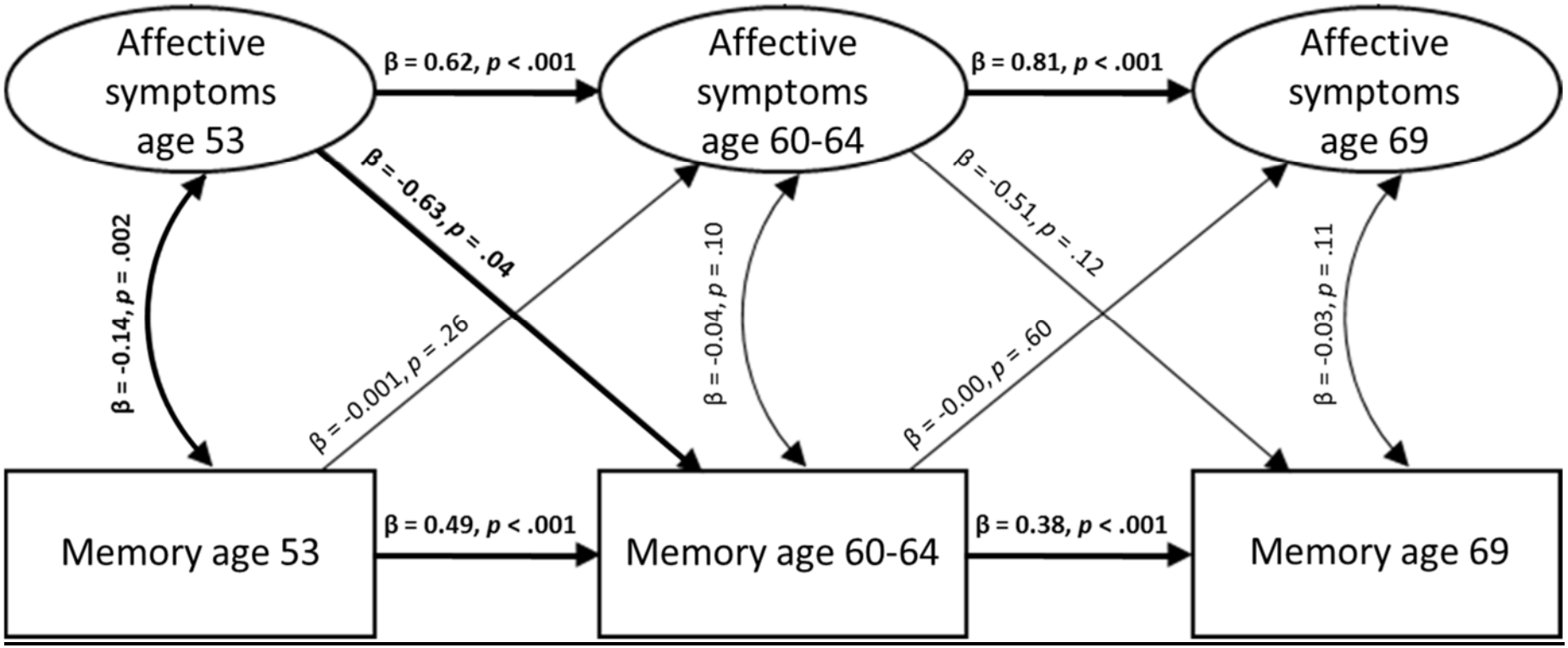
Supplementary Figure 4: Memory model excluding participants who died by age 69

* Adjusted for sex, childhood socioeconomic position, education, and National Adult Reading Test (NART) score.



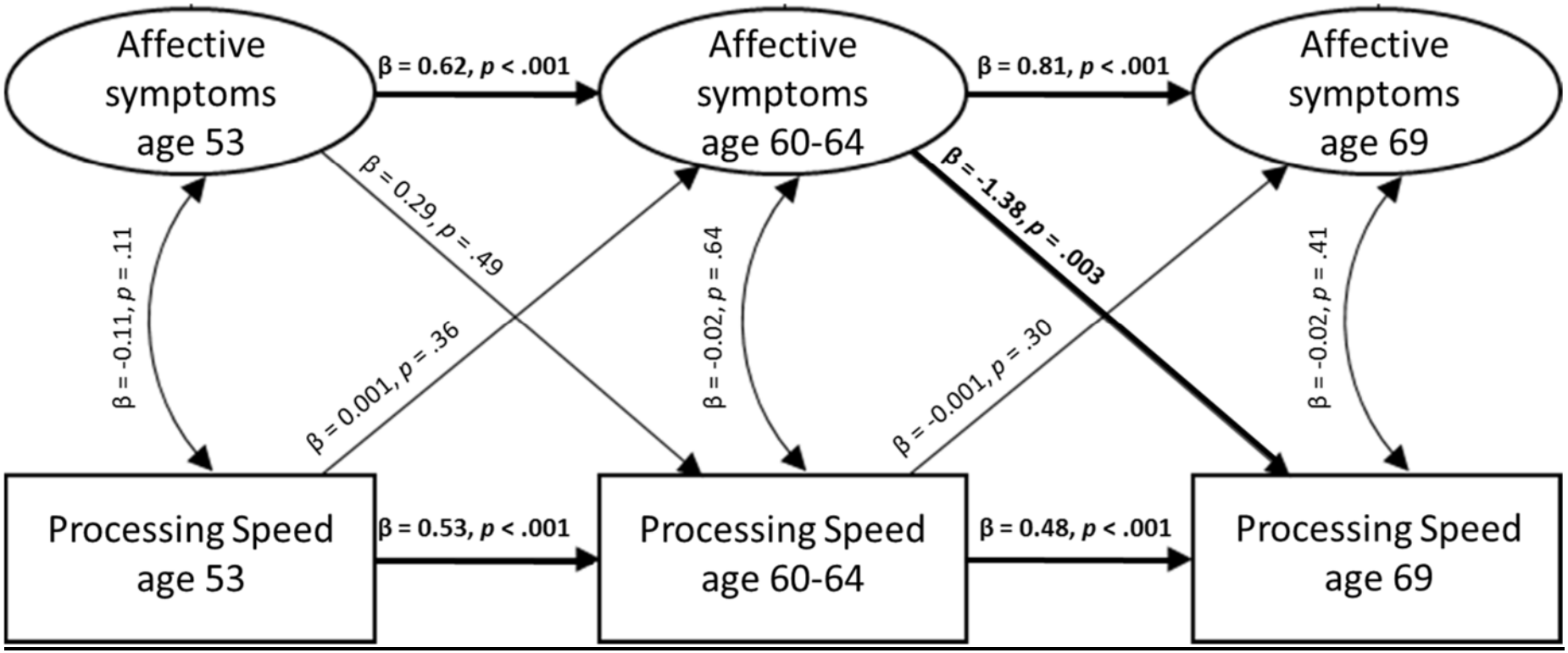
Supplementary Figure 5: Processing speed model excluding participants who died by age 69

* Adjusted for sex, childhood socioeconomic position, education, and National Adult Reading Test (NART) score.



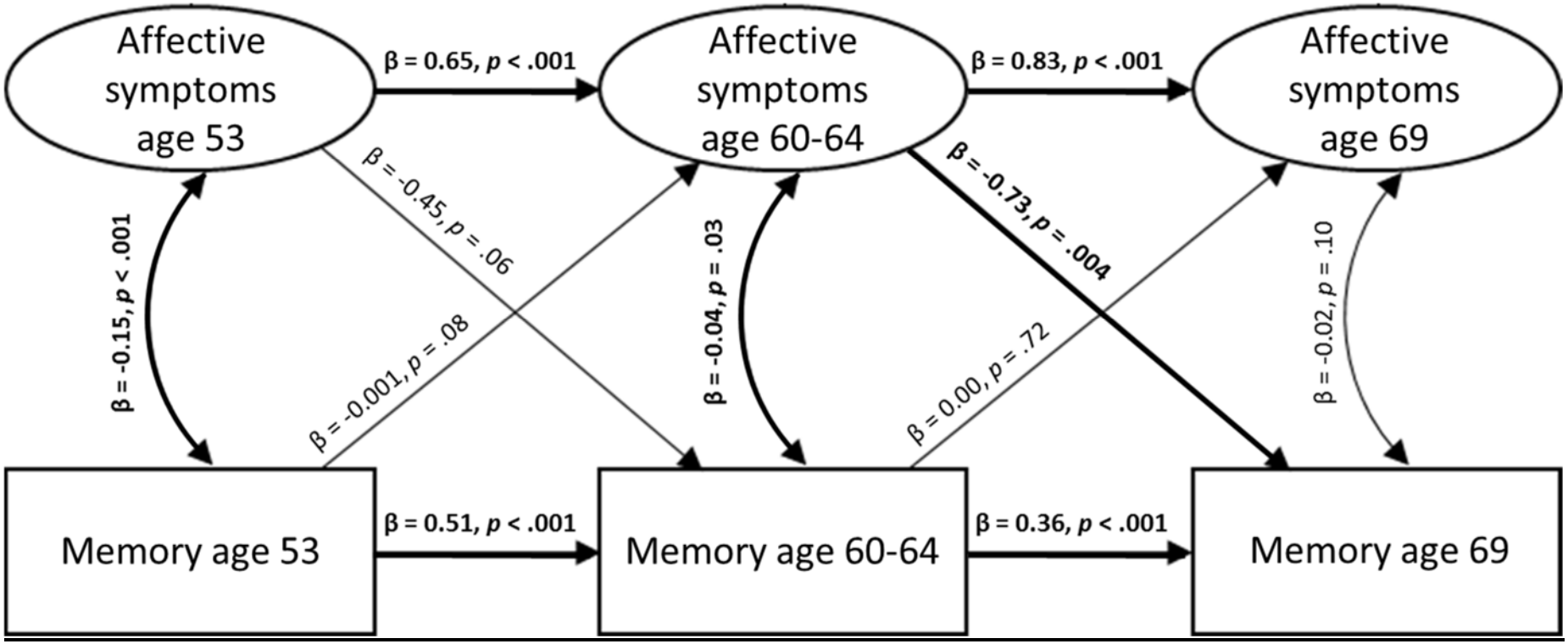
Supplementary Figure 6: Memory model excluding participants using psychotropic medications

* Adjusted for sex, childhood socioeconomic position, education, and National Adult Reading Test (NART) score.



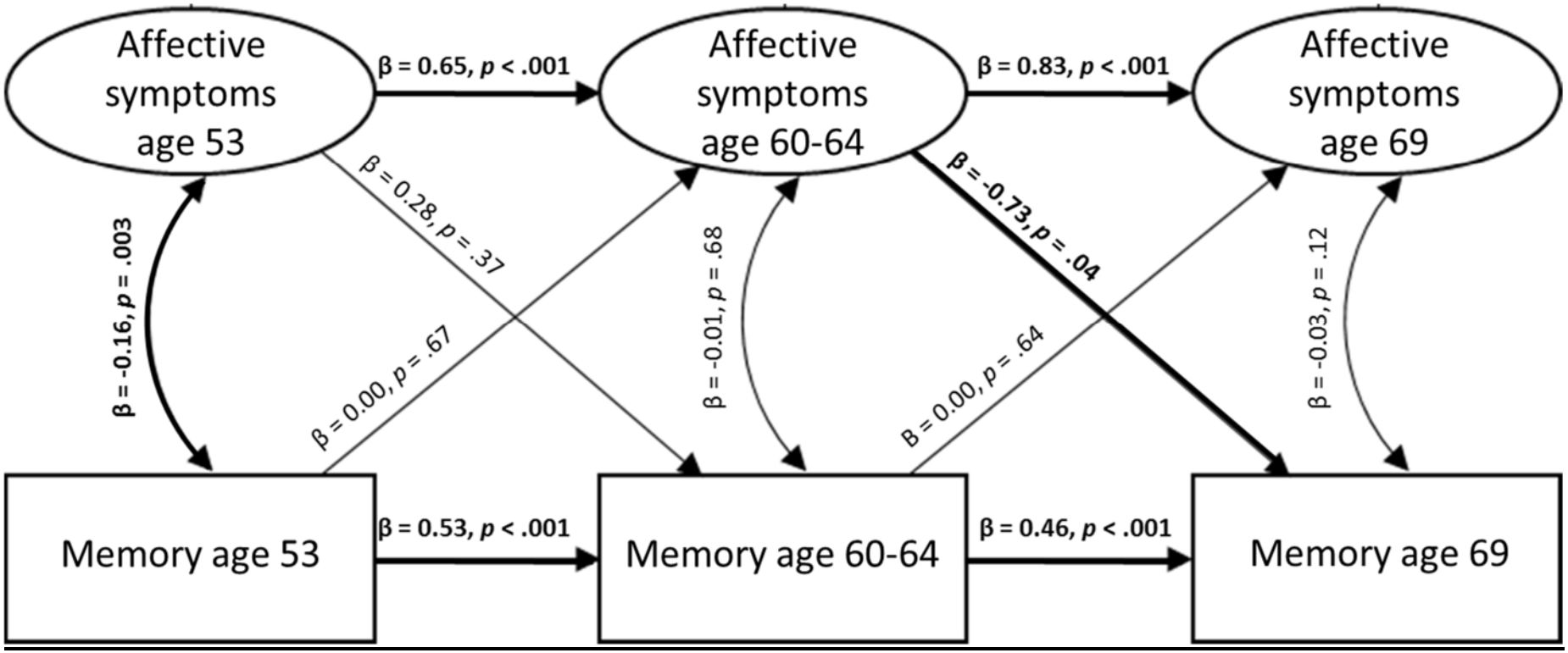
Supplementary Figure 7: Processing speed model excluding participants using psychotropic medications

* Adjusted for sex, childhood socioeconomic position, education, and National Adult Reading Test (NART) score.



Supplementary Figure 8: Memory model using imputed data

* Adjusted for sex, childhood socioeconomic position, education, and National Adult Reading Test (NART) score.



Supplementary Figure 9: Processing speed model using imputed data

* Adjusted for sex, childhood socioeconomic position, education, and National Adult Reading Test (NART) score.

CHAPTER 5

Study 4: Longitudinal associations of affective symptoms with midlife cognitive function: evidence from a British birth cohort.

Study 4 is published in *British Journal of Psychiatry* as:

John, A., James, S. N., Patel, U., Rusted, J., Richards, M., & Gaysina, D. (2019). Longitudinal associations of affective symptoms with midlife cognitive function: evidence from a British birth cohort. *British Journal of Psychiatry*.

Doi: 10.1192/bjp.2019.24.

5.1. Abstract

Affective disorders are associated with poorer cognition in older adults; however, whether this association can already be observed in midlife remains unclear. This study investigated effects of affective symptoms over a period of 30 years on midlife cognitive function. First, we explored whether timing (sensitive period) or persistence (accumulation) of affective symptoms predicted cognitive function. Second, we tested how different longitudinal trajectories of affective symptoms were associated with cognitive function. The study used data from the National Child Development Study. Memory, verbal fluency, information processing speed and accuracy were measured at age 50. Affective symptoms were measured at ages 23, 33, 42, and 50 and used to derive longitudinal trajectories. A structured modelling approach compared a set of nested models in order to test accumulation versus sensitive period hypotheses. Linear regressions and structural equation modelling were used to test for longitudinal associations of affective symptoms with cognitive function. Accumulation of affective symptoms was found to be the best fit for the data, with persistent affective symptoms being associated with poorer immediate memory (b = -0.07, SE = 0.03, p = .01), delayed memory (b = -0.13, SE = 0.04, p < .001), and information processing accuracy (b = 0.18, SE = 0.08, p = .03), but not with information processing speed (b = 3.15, SE = 1.89, p = .10). Longitudinal trajectories of repeated affective symptoms were associated with poorer memory, verbal fluency, and information processing accuracy. Persistent affective symptoms can affect cognitive function in midlife. Effective management of affective disorders to prevent recurrence may reduce risk of poor cognitive outcomes and promote healthy cognitive ageing.

5.2. Introduction

Affective disorders, such as depression and anxiety, have been associated with impaired cognition, dementia and accelerated cognitive decline in late adulthood (Da Silva et al., 2013; Gulpers et al., 2016; John et al., 2018). However, there are significant gaps in our understanding of this association. The majority of studies have been conducted in older adults, usually over the age of 60 and have only considered this association in the context of short follow-up periods (<10 years) (Singh-Manoux et al., 2010). Therefore, it is unclear how affective symptoms are associated with cognitive function over time. There is some evidence that risk of dementia increases with the number of affective episodes experienced over the life course; whereby rate of dementia is estimated to increase by around 13% with each additional depressive episode (Kessing & Andersen, 2004). Additionally, evidence shows that individuals with persistent depressive symptoms may be at greater risk for subsequent cognitive deficits than individuals with fewer episodes (Singh-Manoux et al., 2010). Another line of evidence suggests that timing, rather than frequency, of affective symptoms can be an important predictor of cognitive outcomes. For example, depressive symptoms in older age only were shown to be associated with increased risk of dementia (Singh-Manoux et al., 2017). However, there is limited inconsistent evidence for associations between affective disorders and cognitive function before old age in two studies using data from the MRC National Survey of Health and Development (NSHD). The first study (Richards et al., 2014) found no associations of affective symptoms measured between ages 13 to 53 with objectively measured cognitive outcomes at age 60-64, whereas the most recent study reported that persistent case-level affective symptoms were associated with poorer cognitive state, verbal memory, and letter search speed and accuracy at age 69 (James et al., 2018). The current study tested for associations of affective symptoms

across adulthood (ages 23, 33, 42 and 50) with aspects of cognitive function at age 50. Specifically, two complementary advanced statistical approaches were employed. First, a structured modelling approach comparing a set of nested models was used to investigate whether accumulation or timing of case-level affective symptoms can predict midlife cognition. Second, a latent growth mixture modelling approach was employed to derive longitudinal trajectories of affective symptoms and to examine how different longitudinal trajectories of affective symptoms were associated with midlife cognition.

The conceptual framework for this chapter is presented in Figure 5.6.1. The previous chapters showed that: 1.) Affective symptoms in older adulthood are associated with decline in cognitive state; 2.) Affective symptoms in adolescence are associated with cognitive intercept but not slope from midlife to early old age; 3.) Affective symptoms are associated with poorer subsequent cognitive scores from midlife to early old age, but the association did not operate in the opposite direction. This chapter extends those findings by testing whether accumulation or timing of affective symptoms are associated with midlife cognition and whether particular trajectories of affective symptoms predict midlife cognition.

5.3. Method

Participants.

Participants were from the National Child Development Study (NCDS), a population representative sample of 18,558 people born during one week of 1958 in England, Scotland and Wales (i.e., British 1958 birth cohort). This sample comprised 98.2% of total births that week. Data were subsequently collected from participants at ages 7, 11, 16, 23, 33, 42, 46, and 50 years. Further information about the study sample, respondent profiles, and data collection methods are described in depth by Power & Elliott (2006) (Power & Elliott, 2006). Data are available from the UK Data Service (University of London,. Institute of Education,. Centre for Longitudinal Studies, 2008a, 2008b, 2012, University of London, Institute of Education, & Centre for Longitudinal Studies, 2008, 2014). Cohort members gave written informed consent to participate. Ethical approval for the data collection in 2008 was provided by London MREC (REC reference: 08/H0718/29). Ethical approval for the present study was also provided by the University of Sussex (Reference number: ER/AJ316/1).

Detailed information about the sample analysed in the present study is presented in Supplementary Material 1A; Supplementary Figure 1; Supplementary Table 1. There were 9790 people who participated in 2008 data collection (at age 50). A total of 9385 people of this sample completed the cognitive tests at this time point (95.9%). Of the 9385 participants who completed the cognitive tests at age 50, 4625 had complete information for all predictors and covariates (49.3% of those with cognitive measures).

Measures.

Cognitive function.

Cognitive measures collected at age 50 were verbal memory, verbal fluency, information processing speed and accuracy (Brown & Dodgeon, 2010). Memory was assessed using a word-recall test with immediate and delayed components. Verbal fluency was assessed using an animal naming task, in which participants named as many animals as possible in a 1-minute period. Information processing was assessed using a letter cancellation task. In this task, cohort members crossed as many target letters as possible from a grid of letters in a 1 minute period. The results of this task were split into two scores. The total number of letters scanned represented information processing speed, and the number of target letters missed up to the final letter searched represented information processing accuracy. Accuracy was negatively scored, so higher scores represent poorer performance.

Affective symptoms.

Affective symptoms were assessed using the Malaise Inventory Scale, administered at ages 23, 33, 42, and 50. This is a measure of psychological distress and comprises 24 self-completion items, which are combined to assess levels of emotional disturbance and associated somatic symptoms. The total number of questions answered 'yes' was summed, creating a sum score of affective symptoms out of 24. This score was dichotomised using a standard cut-off threshold score of 7 out of 24 to represent 'case-level' affective symptoms, indicating clinically relevant affective symptoms (Hope, Power, & Rodgers, 1999; Lacey et al., 2012; Sacker & Cable, 2006). At age 50, a short form of the Malaise Inventory Scale was administered, comprising 9 items. For this time-point, a recommended cut-off score of 3 was used to categorise case-level affective symptoms (Bowling, Pikhartova, & Dodgeon, 2016).

As the short form of the Malaise Inventory Scale was used at age 50, the 9 items from this short form were extracted from the longer forms used at ages 23, 33, and 42, in order to make malaise scores over time more comparable to be used for modelling longitudinal trajectories.

Covariates.

Based on previous research, the following factors were included as potential confounders: sex, childhood cognition (McGurn et al., 2008), childhood emotional adjustment (Lupien, McEwen, Gunnar, & Heim, 2009), childhood socio-economic position (Kaplan et al., 2001), adult socio-economic position (Sattler, Toro, Schönknecht, & Schröder, 2012), and education (Brayne et al., 2010). Childhood cognition was assessed at age 11, using a general ability test administered at the child's school. Childhood emotional adjustment was assessed at age 11 using the Bristol Social Adjustment Guides (BSAG) (Mcdermott & Watkins, 2017). This questionnaire was completed by teachers and is designed to assess behaviour that may be indicative of maladjustment and emotional disturbance. A measure of household socio-economic position at age 11 was derived using guidelines from the Centre for Longitudinal Studies (CLS) (Elliott & Lawrence, 2014), based on measures of father's occupation, mother's occupation, and household tenure. Highest educational attainment was derived by combining education data from 1991, 2000, 2004, and 2008 to ascertain the highest academic qualification the cohort member had achieved by age 50. Adult socio-economic position was based on occupation, with three categories (working, intermediate and middle class). Additional information about these covariates are included in Supplementary Material 1B.

Analytical procedure.

First, a structured modelling approach was used to compare a set of nested models corresponding to accumulation and sensitive period hypotheses to a saturated model including all main effects and all possible interactions (James et al., 2018; Mishra et al., 2009; Murray et al., 2011). The sensitive period model included three measures indicating whether an individual experienced case-level affective symptoms at three time windows across the life course: early adulthood (age 23); middle adulthood (ages 33 and/or 42); midlife (age 50). The accumulation model included a measure of the number of time-points (of the three time windows described above) in which each individual experienced case-level affective symptoms. The saturated model was also compared with a 'null' model that assumed no effect of affective symptoms on midlife cognition. Partial F tests were used to compare each hypothesis to the fully saturated model. Where multiple *P* values were > .05, the model with the highest *P* value and lowest F statistic were selected as the best fit for the data. This analysis was conducted in STATA V14.2.

Four variables with case-level affective symptoms were summed up to create a variable for accumulation of adult affective symptoms (ranging from 0 to 4). Linear regression models were fitted to test for associations of accumulation of adult affective symptoms and cognitive function at age 50. For these analyses, four models were fitted: unadjusted (Model 1); adjusted for sex only (Model 2); additionally adjusted for child cognition, emotional disturbance and socio-economic position (Model 3); and additionally adjusted for highest educational attainment, and adult socio-economic position (Model 4). This analysis was conducted in R V3.5.1.

To account for missing data, multiple imputation analysis was conducted on the sample with cognitive data. All analyses described above were re-run using imputed variables for the key predictors. Multiple imputation was conducted in R using the

MICE package (Azur et al., 2011; Buuren & Groothuis-Oudshoorn, 2011). Twenty imputations were conducted using data across 7 sweeps over the life course. This multiple imputation approach includes a large number of covariates and auxiliary variables in the models, which maximises the plausibility of the missing at random (MAR) assumption, and limits possibility of missing not at random (MNAR) data (Coley et al., 2011). These multiple imputation techniques have been used extensively to address missing data in the National Child Development Study (Barboza Solís et al., 2015; Blane, Wahrendorf, Webb, & Netuveli, 2012; Kelly-irving et al., 2013). Technical details of the multiple imputation process are reported in Supplementary Material 1C.

Second, a confirmatory factor analysis was conducted to generate latent factor scores of affective symptoms at each time-point (see Supplementary Table 2 for details about model fit). Linear mixed models were then used to examine trajectories of affective symptoms over time, using factor scores from each time-point. Linear and quadratic models were fitted and compared and the model with the best fit according to the Akaike information criterion (AIC) and Bayesian information criterion (BIC) was selected for subsequent analyses. Next, growth mixture models (GMM) were fit to the data to identify trajectory classes. Models with a 2-class, 3-class, 4-class, and 5-class solution were fitted and compared using AIC, BIC, and the Lo-Mendel-Rubin Adjusted likelihood ratio test (Lo-Mendel-Rubin Adjusted LRT). Once longitudinal trajectories were identified using GMM, a structural equation model was used to investigate whether class membership predicted cognitive outcomes at age 50, after controlling for key covariates. One-step estimation approaches have been criticised in recent years on the basis that including distal outcomes into the measurement model in one step may lead to an unintended and problematic circular relationship in which the classes from

the trajectory modelling are determined in part by the distal outcome which they are meant to be predicting (Bakk & Vermunt, 2015; Vermunt, 2010; Zhu, Steele, & Moustaki, 2017). This analysis was therefore conducted in a step-wise fashion to avoid drawbacks associated with one-step estimation methods. Missing data were dealt with using full information maximum likelihood estimation (FIML). Analysis was conducted in Mplus V.8. According to Mplus defaults, variances across classes were held equal

5.4. Results

Missing data and descriptive statistics.

Of the sample who completed the cognitive tests at age 50 (n = 9,385), participants with complete information (n = 4625) were compared to the sample with missing data (n = 4,760). Results revealed that participants with missing data did not differ by sex ($p = .54$). However, participants with missing data had significantly lower childhood cognitive scores ($p < .001$), higher levels of childhood psychological maladjustment ($p < .001$), lower level of education ($p < .001$), lower SEP in childhood ($p < .001$) and adulthood ($p < .001$), and more case-level affective symptoms at ages 23 ($p < .001$), 33 ($p < .001$), 42 ($p < .001$), and 50 ($p < .001$).

The imputed dataset was created for the sample of 9385 participants. Socio-demographic information for the sample with complete information for cognitive outcomes, main predictors and covariates (n = 4,625; 50.5% women) and the imputed sample (n = 9,385; 50.8% women) is presented in Supplementary Table 3.

Accumulation of affective symptoms and midlife cognitive function.

Results from the analysis using a structured modelling approach revealed that the accumulation model was the best fit for the data. For this model, there were no significant differences observed from the saturated model for any of the cognitive outcomes (Table 5.6.1). This was particularly prominent for memory outcomes (immediate memory: F = 1.81; $p = .09$; delayed memory: F = 1.39, $p = .22$), for which none of the other models (i.e., ‘no effect’ model, or sensitive period models) fit the data well ($p < .05$ for all other models).

Fully adjusted regression models revealed significant linear associations, whereby as the number of case-level affective symptoms increased over the life course,

midlife immediate memory (b = -0.07, SE = 0.03, p = .01), delayed memory (b = -0.13, SE = 0.04, p < .001) and information processing accuracy (b = 0.18, SE = 0.08, p = .03) decreased (Table 5.6.2). No effects were apparent for verbal fluency or information processing speed in fully adjusted models. Results of the analyses using imputed data were similar (Supplementary Tables 4 & 5).

Trajectories of affective symptoms and midlife cognitive function.

Linear mixed models revealed that a linear trajectory (AIC = 9020.291; BIC = 9065.883), rather than a quadratic trajectory (AIC = 9021.989; BIC = 9075.18), fitted adult affective symptom latent variables scores better and were therefore used to identify trajectory classes. When comparing models with a 2-class, 3-class, 4-class, and 5-class solution, the 5-class solution was found to be the best fit for the data (Supplementary Table 6). Therefore, five different trajectories of adult affective symptoms were identified (Figure 5.6.2): Class 1) no affective symptoms (51.4%); Class 2) consistent mild/moderate affective symptoms (28.3%); Class 3) initially low and increasing to high affective symptoms (5.4%); Class 4) initially high and persistently increasing affective symptoms (7.3%); Class 5) initially high and decreasing to low affective symptoms (7.5%).

A fully adjusted structural equation model revealed that class membership predicted cognitive function at age 50 (Table 5.6.3). Belonging to a trajectory with initially high and increasing affective symptoms was associated with lower midlife immediate memory (b = -0.25, SE = 0.07, p < .001), delayed memory (b = -0.23, SE = 0.09, p = .006), and verbal fluency scores (b = -0.79, SE = 0.30, p = .01), as compared to the trajectory with no affective symptoms. Belonging to a trajectory with initially low and increasing affective symptoms was associated with significantly lower midlife

immediate (b = -0.16, SE = 0.07, p = .03) and delayed memory (b = -0.23, SE = 0.09, p = .007), and information processing accuracy (b = 0.50 SE = 0.21, p = .02). Belonging to a trajectory with initially high and decreasing affective symptoms was associated with poorer immediate memory (b = -0.15, SE = 0.07, p = .04). Finally, belonging to a trajectory with consistently mild/moderate affective symptoms was associated with poorer immediate memory (b = -0.09, SE = 0.04, p = .03). No associations were found for information processing speed and accuracy. Unadjusted and partially adjusted models are reported in Supplementary Table 7.

5.5. Discussion

The present study found that accumulation of affective symptoms across three decades of adulthood (from age 23 through age 50) was associated with poorer cognitive function in midlife: a greater number of case-level affective symptoms was linearly associated with poorer memory and information processing accuracy in midlife. Analysis of longitudinal trajectories of affective symptoms showed that belonging to a trajectory with high and increasing level of affective symptoms across adulthood was significantly associated with poorer verbal memory and fluency in midlife. Belonging to a trajectory with low and increasing affective symptoms was associated with lower verbal memory and information processing accuracy scores at age 50. Belonging to a trajectory with initially high and decreasing affective symptoms or a trajectory with consistently mild/moderate affective symptoms was associated with lower immediate memory scores in midlife.

These findings suggest that associations between affective symptoms and cognitive function may be evident even by midlife, an earlier stage in the life course than considered by many previous studies (Ganguli et al., 2006). It is now believed that for those experiencing dementia in later life, there is a long pre-clinical period before cognitive impairment becomes evident (Morris, 2005). It is possible that older participants may have already developed cerebral pathology by the time of baseline assessment, even if they are not yet displaying symptoms of cognitive impairment. It is plausible that associations between affective disorders and cognition in older adults may be the result of reverse causality from subtle cognitive changes short of dementia. For this reason, it is important to explore this association earlier in the life course and in a population who have not developed dementia pathology. Midlife may prove a better age to guarantee forward temporal associations between risk factors, such as affective

disorders, and subsequent cognitive impairments (Exalto et al., 2014; Lancaster, Tabet, & Rusted, 2017). Additionally, if associations between affective disorders and cognitive function are already apparent by midlife, this may be an important window for early intervention (Sperling et al., 2011). These results advance previous findings, demonstrating for the first time that effects may be apparent even many years prior to development of any substantial cognitive deficits and also may be apparent even if no dementia develops. This observation has value in clarifying the temporal order of this association and minimises the issue of reverse causality inherent in studies focussing exclusively on older adults.

These results also suggest that accumulation of multiple, repeated affective episodes can predict poorer cognitive function in midlife. While the late-life trajectory of cognitive decline in this current cohort cannot be modelled, the findings add to previous research which reports a monotonic increase in dementia risk with each additional affective episode, by demonstrating that the pattern of accumulating affective episodes is important in predicting midlife cognitive function in a general population (Kessing & Andersen, 2004). Singh-Manoux et al (2017) (Singh-Manoux et al., 2017) investigated depression trajectories over a period of 28 years for a population of individuals who developed dementia up to 2015 (participants aged 65-85 in 2015), and those who remained cognitively healthy, and found an accelerated growth in depressive symptoms during the decade before dementia diagnosis. Our results complement findings from recent studies using data from the NSHD cohort born in 1946, which reported that recurrent case-level affective symptoms were associated with poorer cognitive state (as measured with Addenbrooke's Cognitive Examination third edition), verbal memory, and search speed and accuracy in early old age (James et al., 2018), but not with objectively measured cognitive outcomes in late mid-adulthood (Richards et

al., 2014). Because prevalence of depression and psychological distress has been increasing in the UK over the past few decades (Fink et al., 2015) it is possible that the effect of mental health problems on cognitive ageing can manifest earlier (by midlife) in younger cohorts, such as NCDS born in 1958.

Taken together, these results suggest that verbal memory is affected by the number of affective episodes experienced and by longitudinal trajectories of affective symptoms. Information processing accuracy is affected by the number of affective episodes experienced and by a trajectory of initially low and increasing affective episodes. Verbal fluency scores are affected by a pattern of initially high and increasing accumulation affective episodes. Strongest effects of affective symptoms were therefore observed on midlife verbal memory, verbal fluency, and information processing accuracy, while information processing speed was consistently unaffected by affective symptoms. Several studies have found untreated depressive symptoms persistent over the entire life course may lead to cumulative hippocampal volume loss (Sheline, Gado, & Kraemer, 2003); a key structure associated with verbal memory (Bird & Burgess, 2008). This could potentially explain effects of affective problems on memory. It is possible that midlife may be too early for effects to be observed in information processing speed, and that effects of affective disorders may become apparent on this cognitive domain as individuals transition from midlife into older adulthood.

Strengths & limitations.

The key strength of the study is a large nationally-representative sample with a long follow-up period (three decades). Moreover, multiple cognitive domains were assessed in midlife, and prospective assessments of affective symptoms using the same instrument from early adulthood through midlife were available for the analyses.

However, results should be interpreted with consideration of a number of limitations. Cognitive function was only assessed at one time-point in adulthood (age 50) in the NCDS, and therefore it was not possible to investigate the effects of affective problems on cognitive change over time. Cognitive assessments at this time point were also limited in breadth; single, rather than multiple, cognitive tests were used for each domain (immediate and delayed memory, verbal fluency, information processing speed and accuracy); and functions in other cognitive domains (e.g., inhibitory processes, attention) known to be affected in people with affective disorders, were not assessed in NCDS. Additionally, although cognitive ability in childhood was controlled for, this does not completely eliminate the possibility of reverse causality, whereby the association may operate in the opposite direction with lower cognitive function leading to higher affective symptoms across adulthood (Hatch, Jones, et al., 2007). We were also unable to take the effect of medications into account, which may play an important role in this association.

Missing data are inevitable in the long-running cohorts such as NCDS, and indeed there was a lot of missing data that could potentially lead to biased estimates. We have dealt with this by imputing missing data using a multiple imputation approach. The benefits of the multiple imputation approach are that missing data can be dealt with prior to analysis (Schafer & Graham, 2002) using a large amount of additional information from other variables available in the dataset. Specifically, this allows extra information that isn't included in our main models (such as birthweight, parental education etc.) to be used as auxiliary variables to aid with imputing the missing data. This maximises plausibility of the missing at random assumption (Coley et al., 2011). Notably, the results using imputed data were substantially identical to the ones obtained

using a complete dataset and also were consistent and complementary with the analysis using FIML to account for missing data.

Plausible mechanisms.

Both biological and socio-behavioural pathways have been proposed to explain the link between affective disorders and cognitive function. Specifically, hypothalamic pituitary adrenal (HPA) axis function has been proposed as one potential mechanism linking affective problems and subsequent cognitive dysfunction (Byers & Yaffe, 2011). Affective symptoms and chronic stress may give rise to HPA axis activity and lead to increased glucocorticoid production, which in turn may lead to hippocampal atrophy and cognitive dysfunction. Animal studies exploring response to stress have proposed that conditions of high stress and exogenous glucocorticoids can lead to cognitive impairment (Park, Zoladz, Conrad, Fleshner, & Diamond, 2008).

Another potential pathway involves cardio-metabolic risk factors. Affective problems and psychological distress across the life course have been associated with higher cardio-metabolic risk (Winning, Glymour, McCormick, Gilsanz, & Kubzansky, 2015). Additionally, cardio-metabolic disorders have also been linked with Alzheimer's disease and cognitive decline (Bhat, 2010). Related to this, physical health and health behaviours (Ströhle, 2009), including physical activity and exercise may also play an important role in the association between affective problems and cognitive ageing. Beyond this, chronic inflammation plays a role in both depression and dementia, and as such may act as an important pathway between the two. Moreover, Aβ deposition is known to play an important role in the pathogenesis of dementia (Hardy & Selkoe, 2002) and has additionally been associated with major depression (Wu et al., 2014). Educational attainment (Geerlings, Schmand, Braam, & Jonker, 2000) and socio-

economic position (Sattler et al., 2012) may also play a role in the association between affective problems and cognitive ageing. It is plausible that the association between affective problems and cognitive ageing is underpinned by a complex interaction of biological and socio-behavioural mechanisms, rather than by one single aetiological determinant (Da Silva et al., 2013).

Conclusions.

In conclusion, the present study suggests that individuals with affective symptoms in adulthood are at increased risk of poorer cognitive outcomes by midlife. This finding has implications for prevention efforts, as the asymptomatic phase before development of dementia pathology may be a critical window to target for early intervention (Sperling et al., 2011). Additionally, in the absence of pathological change, one further important avenue of research is to investigate whether effective treatment and management of affective problems early in life can reduce risk of poor cognitive outcomes and promote healthy cognitive ageing. Future research should also focus on determining the biological and socio-behavioural mechanisms that underpin the association between affective and cognitive factors. All interventions to promote and sustain healthy ageing are important to health policy development in an ageing population.

5.6. Tables & figures

Figure 5.6.1: Conceptual framework of Chapter 5

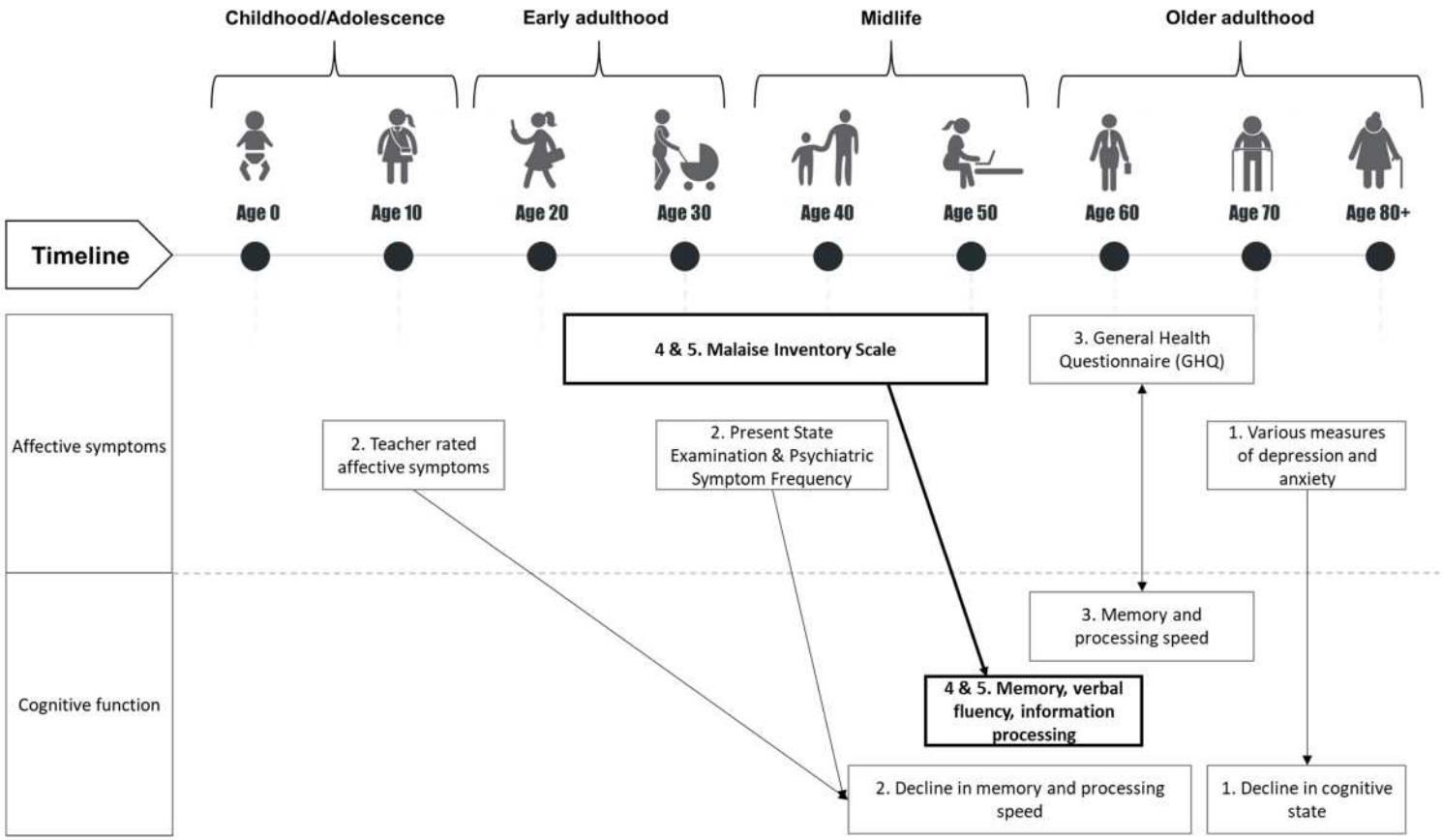


Table 5.6.1: A structured modelling approach comparing life course hypotheses of the association between lifetime affective symptoms and midlife cognitive function (no effect hypothesis, accumulation hypothesis, sensitive period hypothesis)

	Immediate Memory		**Delayed Memory**		**Verbal Fluency**		**Processing Speed**		**Processing Accuracy**	
Models	**F**	***P***	**F**	***P***	**F**	***P***	**F**	***P***	**F**	***P***
Saturated model	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
No effect	4.15	.0001	5.1	<.0001	2.97	.004	**1.24**	**.28**	2.58	.01
Accumulation	**1.81**[a]	**.09**	**1.39**	**.22**	**0.56**	**.76**	**0.88**	**.51**	**0.66**	**.68**
Sensitive period 1 (age 23)	2.97	.01	3.46	.002	1.86	.08	**1.15**	**.33**	2.19	.04
Sensitive period 2 (age 33-42)	3.51	.002	3.89	.001	**1.35**	**.23**	**1.14**	**.34**	**1.8**	**.10**
Sensitive period 3 (age 50)	3.14	.01	3.23	.004	2.46	.02	**1.12**	**.33**	**1.4**	**.21**
Best fitting model	**Accumulation**		**Accumulation**		**Accumulation**		**Accumulation**		**Accumulation**	

[a] Bold values represent estimates which are non-significant at the $p < .05$ level. Non-significant *P* values represent a good fit for the data. The hypothesis with the smallest F statistic is taken as the hypothesis with the best fit for the data.

Table 5.6.2: Life course accumulation of affective symptoms and cognitive function at age 50

Cognitive Functions	Model 1[a]			Model 2			Model 3			Model 4			Model 5		
	b	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***
Immediate Memory	**-0.14**[b]	**0.03**	**<.001**	**-0.17**	**0.03**	**<.001**	**-0.09**	**0.03**	**.003**	**-0.07**	**0.03**	**.01**	**-0.08**	**0.03**	**.01**
Delayed Memory	**-0.2**	**0.04**	**<.001**	**-0.25**	**0.04**	**<.001**	**-0.14**	**0.04**	**<.001**	**-0.13**	**0.04**	**<.001**	**-0.13**	**0.04**	**<.001**
Verbal Fluency	**-0.51**	**0.13**	**<.001**	**-0.52**	**0.13**	**<.001**	-0.13	0.13	.31	-0.06	0.12	.61	-0.07	0.12	.59
Processing Speed	**3.82**	**1.87**	**.04**	1.45	1.88	.44	2.78	1.89	.14	3.15	1.89	.10	3.25	1.89	.09
Processing Accuracy	**0.32**	**0.08**	**<.001**	**0.3**	**0.08**	**<.001**	**0.17**	**0.08**	**.04**	**0.18**	**0.08**	**.03**	**0.19**	**0.08**	**.02**

[a] Results are presented for model 1 (unadjusted estimates), model 2 (estimates adjusted for sex), model 3 (estimates adjusted for sex, childhood socio-economic status, childhood emotional adjustment, and childhood cognition), and model 4 (estimates adjusted for sex, childhood socio-economic status, childhood emotional adjustment, childhood cognition, adult socio-economic status, and highest educational attainment at age 50). Model 5 is a sensitivity analysis, using all the covariates in Model 4, but excluding childhood emotional adjustment.

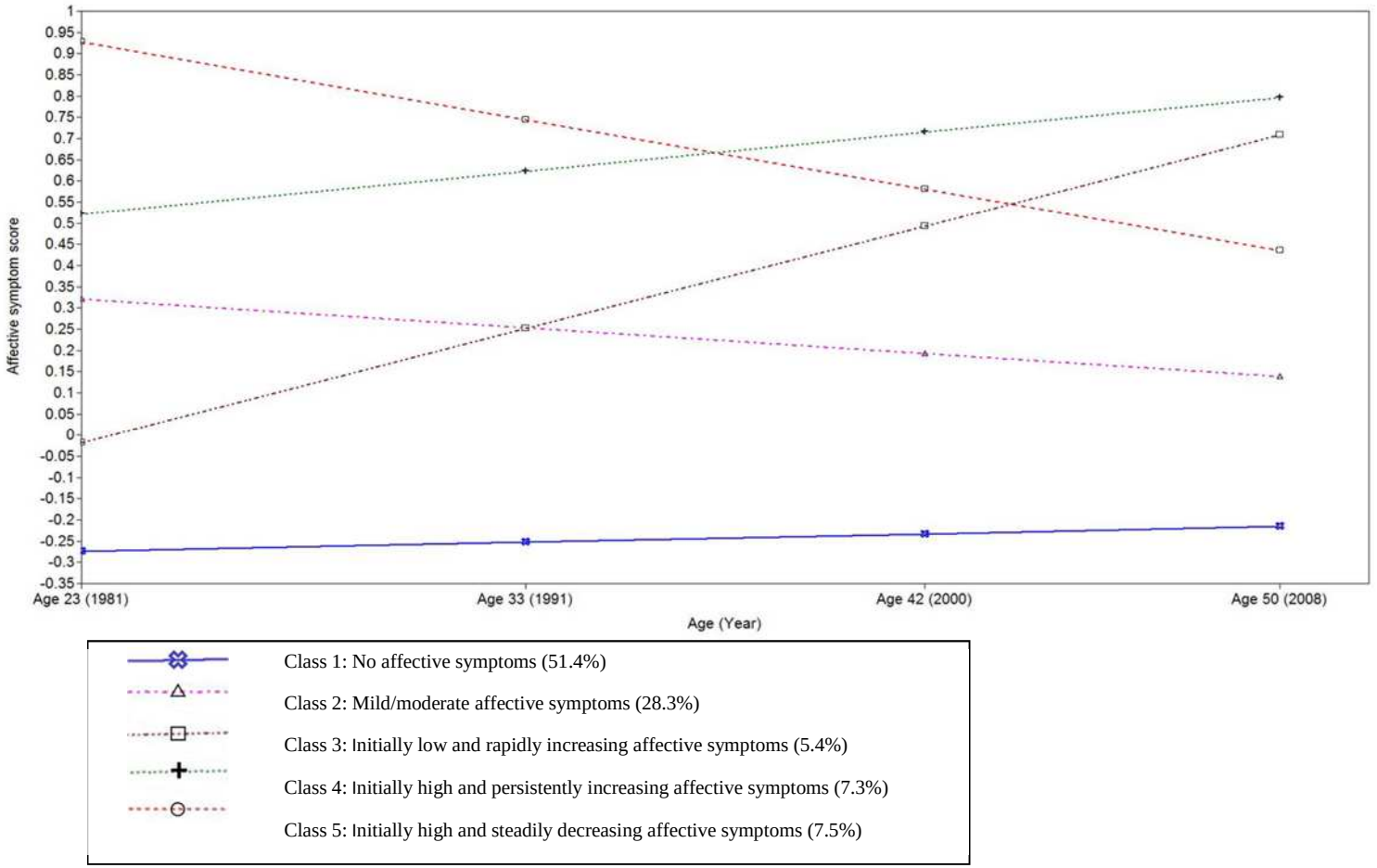
[b] Bold values represent estimates significant at the $p < .05$ level. Estimates are based on sample with complete data for all key factors and covariates (N = 4,625).

Table 5.6.3: Fully adjusted structural equation model output for class membership predicting midlife cognitive function

Predictors	Immediate memory			Delayed memory			Verbal fluency			Processing Speed			Accuracy		
	b	**SE**	**P**	**b**	**SE**	**P**	**b**	**SE**	**P**	**b**	**SE**	**P**	**b**	**SE**	**P**
Affective symptom trajectories: No affective symptoms	*Reference*			*Reference*			*Reference*			*Reference*			*Reference*		
Mild/moderate affective symptoms	**-0.09**	**0.04**	**.03**[a]	0.03	0.05	.58	-0.32	0.18	.08	0.96	2.66	.72	0.10	0.12	.41
Initially low and rapidly increasing affective symptoms	**-0.16**	**0.07**	**.03**	**-0.23**	**0.09**	**.007**	-0.23	0.30	.45	7.02	4.50	.12	**0.50**	**0.21**	**.02**
Initially high and persistently increasing affective symptoms	**-0.25**	**0.07**	**<.001**	**-0.23**	**0.09**	**.006**	**-0.79**	**0.30**	**.01**	-2.80	4.48	.53	0.17	0.21	.42
Initially high and steadily decreasing affective symptoms	**-0.15**	**0.07**	**.04**	-0.17	0.09	.05	-0.59	0.31	.06	3.95	4.69	.40	0.24	0.22	.26
Sex	**0.19**	**0.04**	**<.001**	**0.35**	**0.04**	**<.001**	**-0.33**	**0.16**	**.03**	**23.66**	**2.32**	**<.001**	**0.40**	**0.11**	**<.001**
Childhood affective problems	<.001	0.002	.87	-0.002	0.003	.50	-0.01	0.10	.55	0.05	0.15	.75	**0.02**	**0.01**	**.001**
Childhood cognition	**0.02**	**0.001**	**<.001**	**0.03**	**0.002**	**<.001**	**0.09**	**0.01**	**<.001**	**0.29**	**0.09**	**.001**	**-0.05**	**0.004**	**<.001**
Child socio-economic position	-0.01	0.02	.60	0.002	0.03	.94	**-0.40**	**0.10**	**<.001**	0.53	1.56	.73	-0.02	0.07	.82
Adult socio-economic position	**-0.08**	**0.02**	**.001**	**-0.07**	**0.03**	**.02**	**-0.23**	**0.11**	**.03**	**-5.83**	**1.57**	**<.001**	-0.09	0.07	.24
Education	**0.08**	**.009**	**<.001**	**0.11**	**0.01**	**<.001**	**0.37**	**0.04**	**<.001**	**1.96**	**0.58**	**.001**	**0.07**	**0.03**	**.007**

[a] Bold values represent estimates significant at the $p < .05$ level.

Figure 5.6.2: Life course trajectories of affective symptoms (estimated from 5-class growth mixture model)



5.7. Supplementary material

Supplementary Material 1A: Details of available study sample and sample selection process.

Supplementary Figure 1: Flow chart showing available study sample.

Supplementary Table 1: Missing data for each key variable (N=9385).

Supplementary Material 1B: Additional information on covariates.

Supplementary Material 1C: Technical details of multiple imputation process.

Supplementary Table 2: Model fit statistics for confirmatory factor analysis of items in Malaise Inventory Scale at ages 23, 33, 42, 50 (N=14,745).

Supplementary Table 3: Demographic information of the complete case and imputed sample (N = 9,385).

Supplementary Table 4: A structured modelling approach comparing life-course hypotheses of the association between lifetime affective problems and midlife cognitive function (no effect hypothesis, accumulation hypothesis, sensitive period hypothesis) using imputed data (N=9,385).

Supplementary Table 5: Linear regressions of number of time-point with case-level affective symptoms (Range 0-4) on cognitive outcomes at age 50 using imputed data (N=9,385).

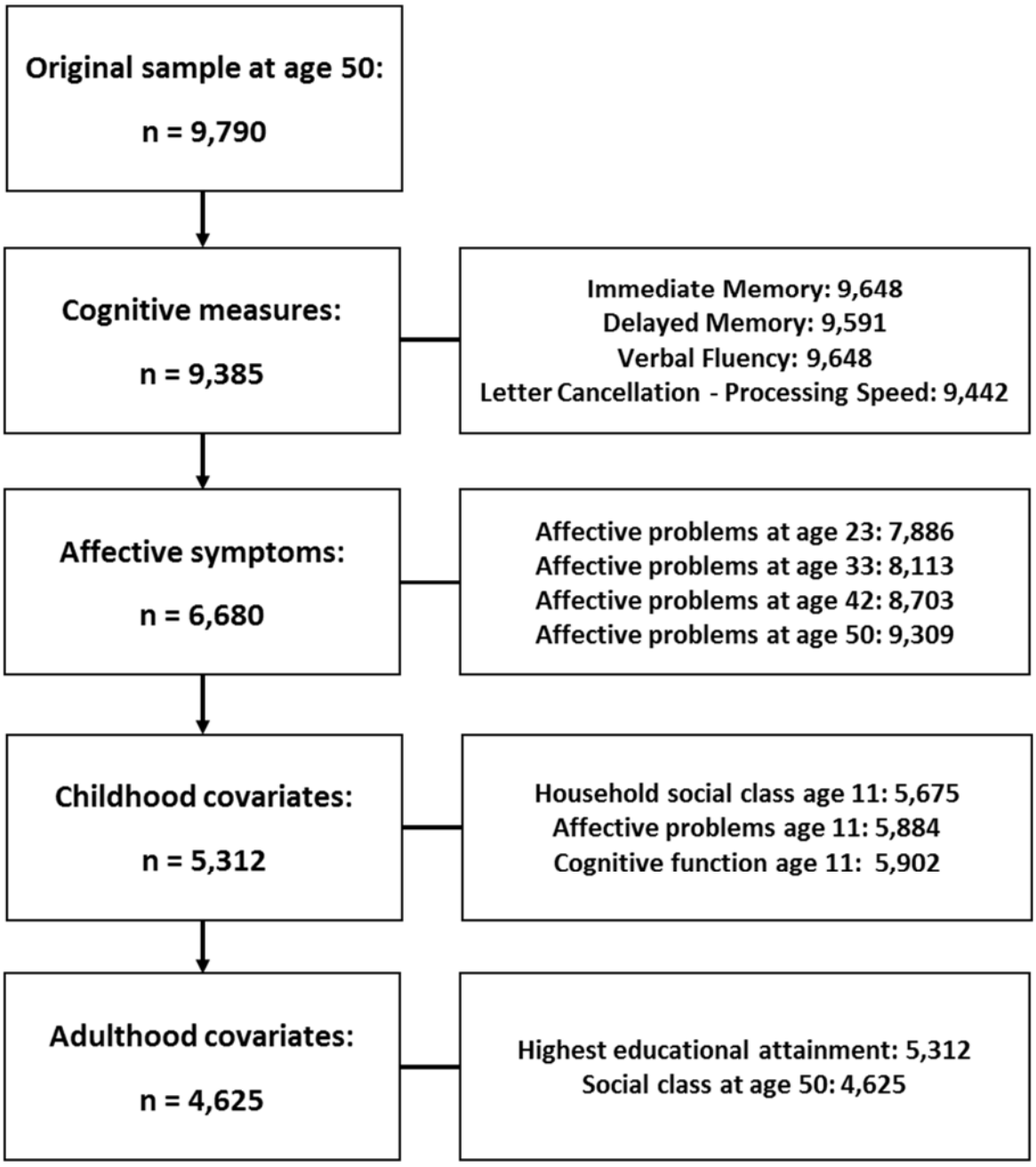
Supplementary Table 6: Comparison of 2-class, 3-class, 4-class, and 5-class growth mixture models.

Supplementary Table 7: Unadjusted and partially adjusted structural equation model output for class membership predicting midlife cognitive test scores.

Supplementary Material 1A: Details of available study sample and sample selection process

During the sweep in 2008 (cohort members aged 50), the target sample was all cohort members in Great Britain, excluding permanent refusals and participants who had been excluded for specific reasons (n = 12,369). It was possible to issue 12,316 of the original 18,558 participants to interviewers. These 12,316 participants either had participated in sweeps in 2000, 2002 or 2004 and were still alive and residing in Great Britain with a known address (n = 11,320), or had not participated in the above sweeps but had confirmed their current address since 2000 (n=387), or had not participated in any of the above but contact details had been obtained through tracing exercises (n = 609). Of the total issued sample in 2008 (n = 12,316), 11,461 (93.1%) were confirmed eligible to take part, as 37 (0.3%) had died, 101 (0.9%) had emigrated, 4 (0.0%) were issued in error (duplication), 676 (5.5%) could not be traced, and 37 (0.3%) were not reissued or traced due to lack of time. Productive interviews were completed for 9,790 cohort members (85.4% of confirmed eligible sample). Of these, 9,385 people had complete information on cognitive assessments (Supplementary Figure 1 & Supplementary Table 1).

Supplementary Figure 1: Flow chart showing available study sample.



Supplementary Table 1: Missing data for each key variable (N=9385)

	Measure	N with data available (%)	N with missing data (%)
Affective symptoms	Malaise Score Age 23	7886 (84.03)	1499 (15.97)
	Malaise Score Age 33	8113 (86.45)	1272 (13.55)
	Malaise Score Age 42	8703 (92.73)	682 (7.27)
	Malaise Score Age 50	9309 (99.19)	76 (0.81)
	Accumulation of Malaise Score	6680 (71.18)	2705 (28.82)
Covariates	Childhood Affective Symptoms	8133 (86.66)	1252 (13.34)
	Childhood Cognitive Score	8145 (86.79)	1240 (13.21)
	Childhood SEP	7767 (82.76)	1618 (17.24)
	Adulthood SEP	7972 (84.94)	1413 (15.06)
	Education	9385 (100)	0 (0)

* Sample with cognitive data (N = 9385)

Supplementary Material 1B: Additional information on covariates

Childhood cognition was assessed at age 11, using a general ability test administered at the child's school. This test (Douglas 1964) comprised verbal and non-verbal components, which combined into an overall cognitive score. Childhood mental health also assessed at age 11 using the Bristol Social Adjustment Guides (BSAG) (Mcdermott et al. 2017). This questionnaire was completed by teachers and is designed to assess behaviour which may be indicative of maladjustment and emotional disturbance. Teachers were asked to underline descriptions of the child which they felt to be most accurate. This information was then coded and summed to create a quantitative score of emotional disturbance and adjustment to school at age 11.

A measure of household socio-economic position at age 11 was derived using guidelines from the Centre for Longitudinal Studies (CLS) (Elliott & Lawrence 2014), based on measures of father's occupation, mother's occupation, and household tenure. Specifically, cohort members were categorised as being 'middle class' if their father was in Registrar General's Social Classes class I or II (professional, managerial, administrative etc.) during the sweep at age 11 (1969), they were not living in rented council accommodation, and their mother was not in a manual occupation while she was pregnant or when the cohort member was age 11. Cohort members were categorised as being 'intermediate class' if their father was in Registrar General's Social Classes I or II (professional, managerial, administrative etc.) during the sweep at age 11, but either resided in council accommodation or the mother was working in manual labour either during the pregnancy or once the child was 11 years old. Additionally, children were categorised as being 'intermediate class' if their father was in routine non-manual (Class IIIa). Finally, children were also categorised as 'intermediate class' if their father was either in manual work when the child was 11, or was in routine

service work (class IVa), but were residing in owner occupied accommodation. Finally, cohort members were categorised as ‘working class’ if their father was working in routine service (Class IVa) and at age 11 they were not residing in owner-occupied accommodation, or if their father was working in a manual occupation.

Highest educational attainment was derived by combining education data from 1991, 2000, 2004, and 2008 to ascertain the highest academic qualification the cohort member had achieved by age 50. Adult socio-economic position was derived using the same method as for the age 11 social class variable (Elliott & Lawrence 2014). This was based on occupation, creating three categories (working, intermediate and middle class).

Supplementary Material 1C: Technical details of multiple imputation process

The process of multiple imputation involves replacing missing cases with plausible values generated from analysing distributions and the relationships between the observed variables within data. Multiple imputation with this data involved 7 stages. Firstly a number of variables from birth (birthweight, mother's age at birth, husband's age in years, socioeconomic position of mother's husband, mother's father's socio-economic position, and mother's education) were imputed. Imputation method used varied depending on the nature of the variable (continuous, ordinal or binary). Next, all birth variables plus sex were used as auxiliary variables to impute variables at age 7 (father's education, whether parents had mental illness or neurosis, BSAG score, arithmetic score, and reading score). Next, all birth and age 7 variables were used to impute age 11 variables (BSAG score, cognitive score, household socioeconomic position). As a next step, birth, age 7, and age 11 variables were used to impute malaise scores at age 23. Birth, age 7, age 11 variables, plus malaise scores at age 23 were used to impute malaise scores at age 33. Malaise scores at age 42 were then imputed from birth, age 7, and age 11 variables, as well as malaise scores at age 23 and 33. Finally, birth age 7, age 11 variables, as well as malaise scores at age 23, 33, and 42 were used to impute age 50 variables (malaise score, socioeconomic position, and educational attainment).

Supplementary Table 2: Model fit statistics for confirmatory factor analysis of items in Malaise Inventory Scale at ages 23, 33, 42, 50 (N=14,745).

Fit statistic	Fit value
CFI	.963
TLI	.960
RMSEA	.025
X^2	5885.35 (588), <.001

Supplementary Table 3: Demographic information of the complete case and imputed sample (N = 9,385).

Characteristics	Complete Case Sample N = 4,625	Imputed Sample N = 9,385
Sex		
Male	2289 (49.5)	4614 (49.2)
Female	2336 (50.5)	4771 (50.8)
Highest educational attainment by age 50, N (%)[a]		
No academic qualification	501 (10.8)	1772 (18.9)
GCSE to A-Level and Scottish equivalent	2916 (63.1)	5329 (56.8)
Diploma, degree, PGCE, or higher degree	1208 (26.1)	2284 (24.3)
Childhood social class, N (%)		
Middle	1048 (22.7)	1994 (21.2)
Intermediate	1788 (38.7)	3449 (36.8)
Working	1789 (38.7)	3942 (42.0)
Adult social class, N (%)		
Middle	2274 (49.2)	4320 (46.0)
Intermediate	1429 (30.9)	2996 (31.9)
Working	921 (19.9)	2062 (22.0)
Childhood cognitive score, Mean (SD)	47.27 (14.68)	45.34 (15.39)
Mean cognitive scores, Mean (SD)		
Immediate Memory	6.67 (1.42)	6.55 (1.47)
Delayed Memory	5.55 (1.77)	5.42 (1.83)
Verbal Fluency	22.71 (6.22)	22.30 (6.26)
Letter cancellation - Processing speed	336.03 (90.00)	333.97 (88.81)
Letter cancellation - Accuracy	4.25 (4.03)	4.41 (4.12)
Case-level at each time-point, N (%)		
Age 23	235 (5.1)	593 (6.3)

Age 33[b]	208 (4.5)	560 (6.0)
Age 42	431 (9.3)	1191 (12.7)
Age 50	542 (11.7)	1374 (14.6)
Malaise scores at each time-point, Mean (SD)		
Age 23	2.35 (2.59)	2.58 (2.77)
Age 33	2.05 (2.57)	2.32 (2.86)
Age 42	3.14 (3.08)	3.54 (3.51)
Age 50	1.28 (1.74)	1.48 (1.93)
Accumulation of case-level affective symptoms, N (%)		
No time-points	3692 (79.8)	7025 (74.9)
1 time-point	597 (12.9)	1427 (15.2)
2 time-points	224 (4.8)	599 (6.4)
3 time-points	77 (1.7)	243 (2.6)
4 time-points	35 (0.8)	91 (1.0)

[a] Frequency data is presented as N (%); Continuous data is presented as Mean (SD).

[b] In the structured model to compare accumulation and sensitive period hypotheses, malaise data from ages 33 and 43 were merged to create one time-point representing middle adulthood.

Supplementary Table 4: A structured modelling approach comparing life-course hypotheses of the association between lifetime affective problems and midlife cognitive function (no effect hypothesis, accumulation hypothesis, sensitive period hypothesis) using imputed data (N=9,385)[a].

	Immediate Memory		**Delayed Memory**		**Verbal Fluency**		**Processing Speed**		**Accuracy**	
	F	***P***	**F**	***P***	**F**	***P***	**F**	***P***	**F**	***P***
Saturated model	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
No effect	16.07	<.001	15.67	<.001	20.3	<.001	**0.59**	**0.77**	6.21	<.001
Accumulation	**1.05**	**.39**[b]	**0.82**	**0.55**	**1.28**	**0.26**	**0.68**	**0.66**	**0.82**	**0.55**
Critical period 1 (age 23)	13.36	<.001	11.8	<.001	18.23	<.001	**0.58**	**0.75**	6.38	<.001
Critical period 2 (age 33-42)	8.81	<.001	9.73	<.001	5.67	<.001	**0.55**	**0.77**	3	0.01
Critical period 3 (age 50)	6.34	<.001	5.72	<.001	11.81	<.001	**0.68**	**0.67**	**2.01**	**0.06**
Best fitting model	**Accumulation**		**Accumulation**		**Accumulation**		**Critical Period 2**		**Accumulation**	

[a] Estimates are based on the imputed sample (N = 9,385).

[b] Bold values represent estimates which are non-significant at the $p < .05$ level. Non-significant *P* values represent a good fit of the data. The hypothesis with the smallest F statistic is taken as the hypothesis with the best fit of the data.

Supplementary Table 5: Linear regressions of number of time-point with case-level affective symptoms (Range 0-4) on cognitive outcomes at age 50 using imputed data (N=9,385)[a].

	Model 1[b]			Model 2			Model 3			Model 4			Model 5		
	b	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***
Immediate memory	**-0.2**[c]	**0.02**	**<.001**	**-0.23**	**0.02**	**<.001**	**-0.12**	**0.02**	**<.001**	**-0.1**	**0.02**	**<.001**	**-0.11**	**0.02**	**<.001**
Delayed memory	**-0.24**	**0.02**	**<.001**	**-0.29**	**0.02**	**<.001**	**-0.15**	**0.02**	**<.001**	**-0.13**	**0.02**	**<.001**	**-0.13**	**0.02**	**<.001**
Verbal fluency	**-0.92**	**0.08**	**<.001**	**-0.93**	**0.08**	**<.001**	**-0.45**	**0.08**	**<.001**	**-0.36**	**0.08**	**<.001**	**-0.37**	**0.08**	**<.001**
Information processing speed	-0.04	1.15	.97	**-2.41**	**1.15**	**.04**	-0.53	1.17	.65	0.14	1.17	.90	0.07	1.17	.95
Letter cancellation accuracy	**0.34**	**0.05**	**<.001**	**0.32**	**0.05**	**<.001**	**0.17**	**0.05**	**.002**	**0.17**	**0.05**	**.002**	**0.18**	**0.05**	**.001**

[a] Estimates are based on the imputed sample (N = 9,385).

[b] Results are presented for model 1 (unadjusted estimates), model 2 (estimates adjusted for sex), model 3 (estimates adjusted for sex, childhood socioeconomic status, childhood emotional adjustment, and childhood cognition), and model 4 (estimates adjusted for sex, childhood socioeconomic status, childhood emotional adjustment, childhood cognition, adult socioeconomic status, and highest educational attainment at age 50). Model 5 is a sensitivity analysis, using all the covariates in Model 4, but excluding childhood emotional adjustment.

[c] Bold values represent estimates significant at the $p < .05$ level.

Supplementary Table 6: Comparison of 2-class, 3-class, 4-class, and 5-class growth mixture models.

	2-class	**3-class**	**4-class**	**5-class[a]**
AIC	7354.32	6101.344	4899.587	4665.861
BIC	7445.504	6215.324	5036.362	4825.433
Entropy	.815	.776	.865	.764
Sample Proportion	13; 87	16; 75; 10	43; 5; 18; 34	7; 51; 8; 28; 5
Classification Accuracy	.738 - .98	.746 - .951	.875 - .966	.622 - .911
Lo-Mendel-Rubin Adjusted LRT	<.001	<.001	.038	<.001

[a] 5-class model was selected for subsequent analysis, due to lower AIC, BIC, and significant Lo-Mendel-Rubin Adjusted LRT.

Supplementary Table 7: Unadjusted and partially adjusted structural equation model output for class membership predicting midlife cognitive test scores.

	Model 1[a]			**Model 2**			**Model 3**			**Model 4**		
	b	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***	**b**	**SE**	***P***
Immediate Memory												
No affective symptoms	*Reference*			*Reference*			*Reference*			*Reference*		
Mild/moderate affective symptoms	**-0.15**	**0.04**	**<.001[b]**	**-0.21**	**0.04**	**<.001**	**-0.10**	**0.04**	**.01**	**-0.09**	**0.04**	**.02**
Initially low and rapidly increasing affective symptoms	**-0.27**	**0.06**	**<.001**	**-0.30**	**0.06**	**<.001**	**-0.21**	**0.06**	**.001**	**-0.15**	**0.07**	**.03**
Initially high and persistently increasing affective symptoms	**-0.47**	**0.06**	**<.001**	**-0.55**	**0.06**	**<.001**	**-0.29**	**0.06**	**<.001**	**-0.25**	**0.07**	**<.001**
Initially high and steadily decreasing affective symptoms	**-0.32**	**0.06**	**<.001**	**-0.42**	**0.06**	**<.001**	**-0.16**	**0.07**	**.02**	**-0.14**	**0.07**	**.05**
Delayed Memory												
No affective symptoms	*Reference*			*Reference*			*Reference*			*Reference*		
Mild/moderate affective symptoms	**-0.05**	**0.04**	**.27**	**-0.15**	**0.05**	**.001**	<.001	0.05	1.00	0.02	0.05	.65
Initially low and rapidly increasing affective symptoms	**-0.35**	**0.07**	**<.001**	**-0.39**	**0.07**	**<.001**	**-0.26**	**0.08**	**<.001**	**-0.23**	**0.09**	**.006**
Initially high and persistently increasing affective symptoms	**-0.47**	**0.07**	**<.001**	**-0.60**	**0.07**	**<.001**	**-0.29**	**0.08**	**<.001**	**-0.23**	**0.09**	**.006**
Initially high and steadily decreasing affective symptoms	**-0.35**	**0.08**	**<.001**	**-0.51**	**0.08**	**<.001**	**-0.21**	**0.08**	**.01**	-0.17	0.09	.05

Verbal Fluency												
No affective symptoms	*Reference*			*Reference*			*Reference*			*Reference*		
Mild/moderate affective symptoms	**-0.91**	**0.15**	**<.001**	**-0.96**	**0.15**	**<.001**	**-0.41**	**0.17**	**.01**	-0.34	0.18	.05
Initially low and rapidly increasing affective symptoms	**-0.98**	**0.25**	**<.001**	**-1.00**	**0.25**	**<.001**	-0.49	0.27	.06	-0.26	0.30	.39
Initially high and persistently increasing affective symptoms	**-2.09**	**0.24**	**<.001**	**-2.15**	**0.24**	**<.001**	**-0.92**	**0.26**	**<.001**	**-0.82**	**0.30**	**.006**
Initially high and steadily decreasing affective symptoms	**-1.82**	**0.26**	**<.001**	**-1.90**	**0.26**	**<.001**	**-0.72**	**0.29**	**.01**	-0.60	0.31	.06
Information Processing Speed												
No affective symptoms	*Reference*			*Reference*			*Reference*			*Reference*		
Mild/moderate affective symptoms	2.16	2.19	.32	-2.99	2.19	.17	0.12	2.50	.96	0.81	2.65	.76
Initially low and rapidly increasing affective symptoms	-0.37	3.58	.92	-2.47	3.54	.49	1.44	3.96	.72	6.40	4.46	.15
Initially high and persistently increasing affective symptoms	-2.58	3.39	.45	**-9.16**	**3.39**	**.007**	**-8.03**	**3.85**	**.04**	-2.24	4.47	.62
Initially high and steadily decreasing affective symptoms	**8.78**	**3.75**	**.02**	-1.90	3.75	.93	7.56	4.26	.08	4.11	4.68	.38
Letter Cancellation Accuracy												
No affective symptoms	*Reference*			*Reference*			*Reference*			*Reference*		
Mild/moderate affective symptoms	**0.26**	**0.10**	**.01**	**0.23**	**0.10**	**.02**	0.08	0.12	.49	0.13	0.12	.30

Initially low and rapidly increasing affective symptoms	**0.38**	**0.17**	**.02**	**0.36**	**0.17**	**.03**	0.31	0.18	.09	**0.51**	**0.21**	**.01**
Initially high and persistently increasing affective symptoms	**0.74**	**0.16**	**<.001**	**0.70**	**0.16**	**<.001**	0.21	0.18	.24	0.22	0.21	.29
Initially high and steadily decreasing affective symptoms	**0.78**	**0.17**	**<.001**	**0.74**	**0.18**	**<.001**	**0.51**	**0.20**	**.009**	0.28	0.22	.20
N	9,643			9,643			7,423			6,359		
Model Fit	X2(2)=102.46 *p*<.001, CFI=.991, TLI=.867, RMSEA=.072			X2(2)=73.53, *p*<.001, CFI=.994, TLI=.893, RMSEA=.061			X2(2)=8.35, *p*=.02, CFI=.999, TLI=985, RMSEA=.021			X2(2)=1.64, *p*=.44, CFI=1.000, TLI=1.001, RMSEA=.000		

[a] Results are presented for model 1 (unadjusted estimates), model 2 (estimates adjusted for sex), and model 3 (estimates adjusted for sex, childhood socioeconomic status, childhood emotional adjustment, and childhood cognition). Model 4 is a sensitivity analysis, adjusted for sex, childhood socioeconomic status, childhood cognition, adult socioeconomic status, and highest educational attainment, but excluding childhood emotional adjustment.

[b] Bold values represent estimates significant at the $p < .05$ level.

CHAPTER 6

Study 5: Accumulation of affective symptoms and midlife cognitive function: the role of inflammation.

Study 5 is under review in *Brain, Behavior and Immunity*.

6.1. Abstract

The aim of the present study was to test whether C-Reactive Protein (CRP), a proxy measure of inflammation, can mediate associations between affective symptoms in childhood and adulthood and midlife cognitive function. Data were used from the National Child Development Study (n = 6276). Measures of memory, verbal fluency, information processing speed and accuracy were available in midlife (age 50). Affective symptoms were assessed in childhood (ages 7, 11, 16) and in adulthood (ages 23, 33, 42, 50). The level of plasma CRP was measured at age 44. Pathway models, unadjusted and fully adjusted for sex, education, childhood SEP, childhood cognitive ability and affective symptoms at age 50, were fitted to test direct associations between affective symptoms and midlife cognitive function, and indirect associations mediated by the inflammatory pathway (CRP level). In a fully adjusted model, there were significant indirect associations between adult affective symptoms and immediate memory (β = -0.01, SE = 0.003, p = .03) and delayed memory (β = -0.01, SE = 0.004, p = .03) mediated by CRP. In addition, there were significant indirect associations between affective symptoms in childhood and immediate memory (β = -0.001, SE = 0.00, p = .03) and delayed memory (β = -0.001, SE = 0.001, p = .03), mediated by adult affective symptoms and associated CRP. Independent of CRP, there was a significant direct association between adult affective symptoms and information processing errors (β = 0.47, SE = 0.21, p = .02). There were no direct or indirect associations between affective symptoms and verbal fluency or information processing speed. CRP can mediate associations between affective symptoms and midlife cognitive function.

6.2. Introduction

Systematic reviews have shown that affective symptoms (depression and anxiety) are associated with faster cognitive decline and an increased risk of dementia in older adulthood (Da Silva et al., 2013; Gulpers et al., 2016; John et al., 2018; Jorm, 2001; Livingston et al., 2017; Ownby et al., 2006) More recent studies using longitudinal data from British birth cohorts suggest that persistent affective symptoms are associated with poorer cognitive function, specifically verbal memory in early old age (age 69) (James et al., 2018) and midlife (age 50) (John et al., 2019). Taken together, these findings suggest that persistent affective episodes can affect cognitive function as early as midlife.

There is a growing body of research, investigating possible biological mechanisms that may contribute to observed associations between affective symptoms and subsequent cognitive function. One plausible hypothesis is that inflammation plays an important role in the association between affective symptoms and cognition (Byers & Yaffe, 2011; Leonard, 2007; Leonard & Myint, 2006). Inflammation refers to the immune system's response to threat, such as infection or injury. C-Reactive Protein (CRP) is an acute phase reactant, produced in the liver and released into the bloodstream in response to inflammation. High concentrations of CRP are indicative of elevated levels of inflammation and can therefore be used as an inflammatory marker. There is evidence that peripheral measures correlate with inflammatory markers in the brain (Schmidt et al., 2002).

Research has shown a cross-sectional association between depressive symptoms and plasma levels of inflammatory markers, including CRP (Dantzer et al., 2008; Raison et al., 2006). A growing body of research has also focussed on the association

between depression and CRP over time, showing elevated CRP levels in people with cumulative depressive symptoms across adolescence and early adulthood (Copeland et al., 2012).

In addition to this, research has proposed that inflammatory changes may be an important pathological feature of dementia (Leonard & Myint, 2006). Specifically, evidence from longitudinal studies have shown that peripheral inflammatory markers measured during midlife are associated with risk of dementia after 25 years, and that these processes are operating long before emergence of clinical symptoms of dementia (Schmidt et al., 2002). Systematic reviews have also shown that high concentrations of peripheral inflammatory markers are associated with increased risk of cognitive impairment and dementia (Koyama et al., 2013; Kuo et al., 2005). In addition to dementia, markers of inflammation including CRP can also prospectively predict poorer cognitive function after follow up and faster cognitive decline over time (Yaffe et al., 2003). These converging lines of evidence suggest that inflammation may play an important mediating role within the association between affective symptoms and midlife cognitive function. However, to the best of our knowledge this hypothesis has never been directly tested in a prospective population-based birth cohort.

The aim of the present study was therefore to test whether inflammation, measured with CRP, can mediate associations between affective symptoms over the life course and midlife cognitive outcomes. In order to address this aim, direct associations of affective symptoms in childhood and adulthood, as well as their indirect associations with midlife cognitive function, mediated by the inflammatory pathway were estimated.

The conceptual framework for this chapter is presented in Figure 6.6.1. The previous chapters showed that: 1.) Affective symptoms in older adulthood are

associated with decline in cognitive state; 2.) Affective symptoms in adolescence are associated with cognitive intercept but not slope from midlife to early old age; 3.) Affective symptoms are associated with poorer subsequent cognitive scores from midlife to early old age, but the association did not operate in the opposite direction; 4.) Accumulation of affective symptoms, rather than timing, are associated with poorer midlife cognition and trajectories with greater experience of affective symptoms predict poorer midlife cognition. This chapter extends those findings by testing whether inflammation can mediate observed associations between affective symptoms from early to mid adulthood and cognitive outcomes in midlife.

6.3. Method

Participants.

Data were used from the National Child Development Study (NCDS), a national representative sample of 18,558 people born in England, Scotland and Wales during one week of 1958. Data have been collected at ages 0, 7, 11, 16, 23, 33, 42, 44, 46, 50, and 55 (Power & Elliott, 2006). At age 44, biomedical data were collected from a subset of cohort members (N=9377), and blood samples were drawn. Ethical approval for the biomedical sweep at age 44 was provided by the South-East Multi-centre Research Ethics Committee. Additional ethical approval for the present study was obtained from the University of Sussex (Reference number: ER/AJ316/1).

Measures.

Cognitive function.

Cognitive data were available at age 50. Short-term and delayed memory were assessed using a word recall task consisting of a list of 10 common words recalled immediately after presentation and again after a 5-minute delay. Verbal fluency was captured by naming as many animals as possible in one minute ((Roth et al., 1986). Information processing was measured using a letter cancellation task, in which participants are required to cross out as many target letters (Ps and Ws) as possible within a grid of random letters in one minute. Information processing speed is based on the total number of letters searched, and information processing accuracy is based on the number of target letters missed up to the last letter searched (higher scores represent more errors). These cognitive tasks are described in detail elsewhere (Brown & Dodgeon, 2010).

Affective symptoms.

Affective symptoms were assessed repeatedly in childhood and adolescence using the Rutter Behaviour Child Scale A at ages 7, 11 and 16. These questionnaires were completed by cohort members' parents, usually the mother. At ages 7 and 11, the Rutter Behaviour scale comprised 14 items, and at age 16 this comprised 18 items, encompassing both internalising and externalising symptoms. Consistent with previous research (Clark, Rodgers, Caldwell, Power, & Stansfeld, 2007; Winning et al., 2015), at age 16 five items from this scale were used to create a measure of internalising (worries, solitary, miserable, fearful, fussy). Four of these items were also available at ages 7 and 11 (worries, solitary, miserable, fearful) and these were used to create a measure of internalising at these time-points. Confirmatory factor analysis (CFA) was used to derive latent scores of affective symptoms at each time-point. This was a good fit to the data (Supplementary Table 1). Mean latent score was also calculated across ages 7, 11 and 16 to derive an overall measure of affective symptoms in childhood.

Affective symptoms were assessed repeatedly in adulthood at ages 23, 33, 42, and 50 using the Malaise Inventory Scale (Rodgers, Pickles, Power, Collishaw, & Maughan, 1999). At ages 23, 33, and 42, this was a 24-item self-completion questionnaire designed to capture psychological distress. At age 50, the short-form questionnaire (9 items) was used. These 9 items were selected from all four time-points to make scores more comparable over time. CFA was conducted on these 9 items at each available time-point to derive latent scores of affective symptoms at ages 23, 33, 42, and 50. This fitted the data well (Supplementary Table 1). Mean latent score was calculated for ages 23, 33, and 42 and this was used to predict CRP at age 44. The latent affective symptom score at age 50 was used as a covariable.

Inflammation.

For the purposes of this paper, inflammation status was assessed by recorded level of C-Reactive Protein (CRP) in citrated plasma (mg/L), acquired from blood samples collected during the biomedical sweep at age 44 by trained nurses and analysed by partnered laboratories (Elliott, Johnson, & Shepherd, 2008). CRP values of >10mg/L (N = 230) are indicative of recent infection (Pepys & Hirschfield, 2003) and as such these cases were excluded from the analysis to be consistent with previous research (Lacey, Kumari, & Bartley, 2014; Lacey, Kumari, & McMunn, 2013).

Covariables.

Covariables selected for the study were based on previous research and comprised measures of sex, educational attainment (Brayne et al., 2010; Richards et al., 2019; Richards & Sacker, 2003), childhood cognition (Hatch, Jones, et al., 2007; McGurn et al., 2008; Richards et al., 2019; Richards & Sacker, 2003), and childhood socio-economic position (Kaplan et al., 2001; Richards et al., 2019). Affective symptoms at age 50 were also included in the model to account for concurrent affective symptoms. Education was captured by cohort member's highest educational qualification achieved by age 50. This was categorised into 1) Low education (up to GCSE level); 2) middle education (up to A Level); and 2) high education (Degree). Two measures of childhood cognitive ability (reading and mathematics) at age 7 were included. Reading ability was captured using the Southgate Group Reading Test, a task designed to assess word recognition and comprehension, producing a score ranging from 0-30. Mathematical ability was measured using the Problem Arithmetic Test, requiring completion of 10 problem questions, producing a score ranging from 0-10.

Socio-economic position at age 11 was based on parental occupation and household tenure, categorised into working, intermediate and middle (Elliott & Lawrence, 2014).

Analytical procedure.

A series of pathway mediation models were run, estimating the direct associations between childhood and adult affective symptoms and cognitive function at age 50. Indirect pathways between symptoms and cognitive function through CRP were also estimated. All measures of cognitive function were included in the same model to account for covariances between different cognitive domains; non-significant covariances were removed from the model. Pathway analysis was conducted in Mplus Version 8 (Muthén & Muthén, 2017).

The initial pathway model was unadjusted, and subsequent models were adjusted for sex, education, childhood cognitive ability, childhood socioeconomic position, and affective symptoms at age 50. Including sex as a stratifying variable did not significantly improve model fit, and as such this was used in all analyses as a covariable (Supplementary Table 2). Model fit was assessed using chi-square goodness of fit, CFI, TLI and RMSEA statistics. All missing data were addressed using full information maximum likelihood (FIML) (Enders, 2001b, 2001a; Enders & Bandalos, 2001).

To check whether missing data for covariables affected the results, a sensitivity analysis was run using multiple imputation technique to impute data for all the covariables, using the MICE package in R (Azur et al., 2011; Buuren & Groothuis-Oudshoorn, 2011). Sixteen imputations were conducted across 5 sweeps, resulting in imputed data for the sample of 9377 participants (John et al., 2019).

6.4. Results

Missing data and demographic information.

The initial sample was comprised of 9377 participants who took part in the biomedical sweep at age 44. Of these 9377 people, 7928 (84.5%) had complete information on all cognitive domains. Within the sample with complete cognitive data, 7859 (99.1%) also had complete information on affective symptoms. There were 6325 (80.5%) people who also had a CRP measure. Finally, there were 4908 (77.6%) people who also had complete covariable data (Figure 6.6.2). This final sample did not differ significantly from the sample with missing data on sex (p = .94), childhood affective symptoms (p = .08), education (p = .09), or childhood socioeconomic position (p = .27). However, the sample with complete information showed significantly lower adult affective symptoms (p < .001). Additionally, the sample with complete information also had significantly lower CRP levels (p = .02), and had significantly higher childhood cognitive scores, based on maths (p = .002) and reading (p < .001). The full information maximum likelihood (FIML) method resulted in the analytical sample of 6276 participants (see Table 6.6.1).

Direct associations with midlife cognitive function.

After adjustment for all key covariables, *adult affective symptoms* (age 23 to 42*)* were directly associated with information processing accuracy (β = 0.47, SE = 0.21, p = .02) at age 50, but no other cognitive domains. In this fully adjusted model, there were no significant direct associations between *childhood affective symptoms* and any cognitive domain. There were, however, significant direct associations between *CRP* and immediate memory (β = -0.04, SE = 0.01, p < .001) and delayed memory (β = -0.05, SE = 0.01, p < .001) at age 50 (Table 6.6.2; Figure 6.6.3).

Indirect associations with midlife cognitive function

After adjustment for the covariables, there were significant indirect associations between *adult affective symptoms* on immediate (β = -0.01, SE = 0.003, p = .03) and delayed memory (β = -0.01, SE = 0.004, p = .03) at age 50, mediated by CRP level. In this fully adjusted model, there were significant indirect associations between *childhood affective symptoms* and information processing accuracy (β = 0.07, SE = 0.03, p = .03) mediated by adult affective symptoms. Finally, there were significant indirect associations between *childhood affective symptoms* and immediate memory (β = -0.001, SE = 0.00, p = .03) and delayed memory (β = -0.001, SE = 0.001, p = .03) mediated by an indirect pathway through adult affective symptoms and subsequent CRP level (Table 6.6.2; Figure 6.6.3).

Total associations with midlife cognitive function.

The fully adjusted model showed a significant total association between *adult affective symptoms* and immediate memory (β = -0.22, SE = 0.04, p < .001), delayed memory, (β = -0.24, SE = 0.05, p < .001), verbal fluency (β = -0.92, SE = 0.18, p < .001), and information processing accuracy (β = 0.55, SE = 0.12, p < .001), but not information processing speed (β = -1.32, SE = 2.58, p = .61). There were no significant total associations between *childhood affective symptoms* and any cognitive domains (Table 6.6.2).

Sensitivity analysis.

The results using imputed data were similar to the models using non-imputed data (Supplementary table 3). However, in fully adjusted models using imputed data, there were also direct associations between adult affective symptoms and verbal fluency as well as indirect associations mediated by CRP level.

6.5. Discussion

Summary of findings & comparison to previous research.

This study suggests that inflammation may contribute to the link between adult affective symptoms and midlife memory. Specifically, there were significant indirect associations between adult affective symptoms and immediate memory and delayed memory, mediated by CRP level at age 44. Similarly, there were significant indirect associations between childhood affective symptoms and immediate and delayed memory, mediated by an indirect pathway through adult affective symptoms and subsequent CRP level. There was also a direct association between adult affective symptoms and information processing accuracy, independent of CRP level. There were no significant direct or indirect associations between affective symptoms and verbal fluency or information processing speed.

These results support previous research, showing elevated levels of CRP in chronic depression (Copeland et al., 2012). Additionally, findings from the current study also support previous research, showing that peripheral inflammation levels can be associated with poorer verbal memory function in healthy older adults, and that participants with detectable CRP levels had reduced medial temporal lobe volume (Bettcher et al., 2012). Indeed, other studies have also shown that chronically high levels of inflammation in healthy older adults may lead to changes in brain morphology, including reduced total grey matter volume (Satizabal, Zhu, Mazoyer, Dufouil, & Tzourio, 2012), white matter integrity (Wersching et al., 2010), and hippocampal volume (Satizabal et al., 2012). There is also evidence that the effects of inflammation on brain structure can be observed during midlife (Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2013; Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008;

Marsland et al., 2015; Verstynen et al., 2013). Therefore, impaired midlife memory function can be a consequence of structural brain changes accompanying chronically elevated inflammation levels. In the current study, the absence of brain imaging data limits interrogation of the precise biological mechanism behind the observed associations noted here.

In contrast to the association between affective symptoms and memory, there were only significant direct associations between adult affective symptoms and information processing accuracy. This may be related to the differences in brain structures that the information processing accuracy measure draws on compared to memory measures. The inflammation hypothesis is closely linked with hippocampal volume change, so this could potentially explain why CRP level selectively contributed to the association between affective symptoms and memory measures, but not for other cognitive outcomes.

Strengths and limitations.

Key strengths include the use of data from a large prospective birth cohort followed up until age 50. Multiple measures of affective symptoms were available from age 7 through age 50, testing the effects of persistent affective symptoms on cognitive function, with a follow up period of more than 40 years.

However, there was only one time point in which measurements of CRP were available in this dataset (age 44), meaning that CRP levels from earlier in the life course could not be explored. Additionally, only one single peripheral marker of inflammation (CRP) was used, meaning that caution should be used when interpreting these findings, and that results should be confirmed using other large longitudinal and prospective cohorts. There was also no brain imaging data available in this study and as such the

neural mechanisms behind observed associations could not be tested. In addition, measures of cognitive function were only available at one time point in this dataset (age 50), so cognitive trajectories and rate of decline over time could not be modelled in this analysis. An additional limitation is the presence of missing data in the study. Attrition is common in long running cohorts; however, in this study it was addressed using full information maximum likelihood (FIML) in main analyses and multiple imputation as an additional sensitivity analysis.

Future research & conclusions.

These findings show that inflammation may contribute to the observed associations between accumulation of affective symptoms and memory function as early as in midlife, a period when differences in ageing related cognitive trajectories can first be observed prior to the presence of clinical cognitive impairment (Salthouse, 2004). Results revealed that observed associations between adult affective symptoms and information processing accuracy were independent of CRP level. Further research is needed to identify the particular biological mechanisms which may underlie this association.

6.6. Tables & figures

Figure 6.6.1: Conceptual framework of Chapter 6

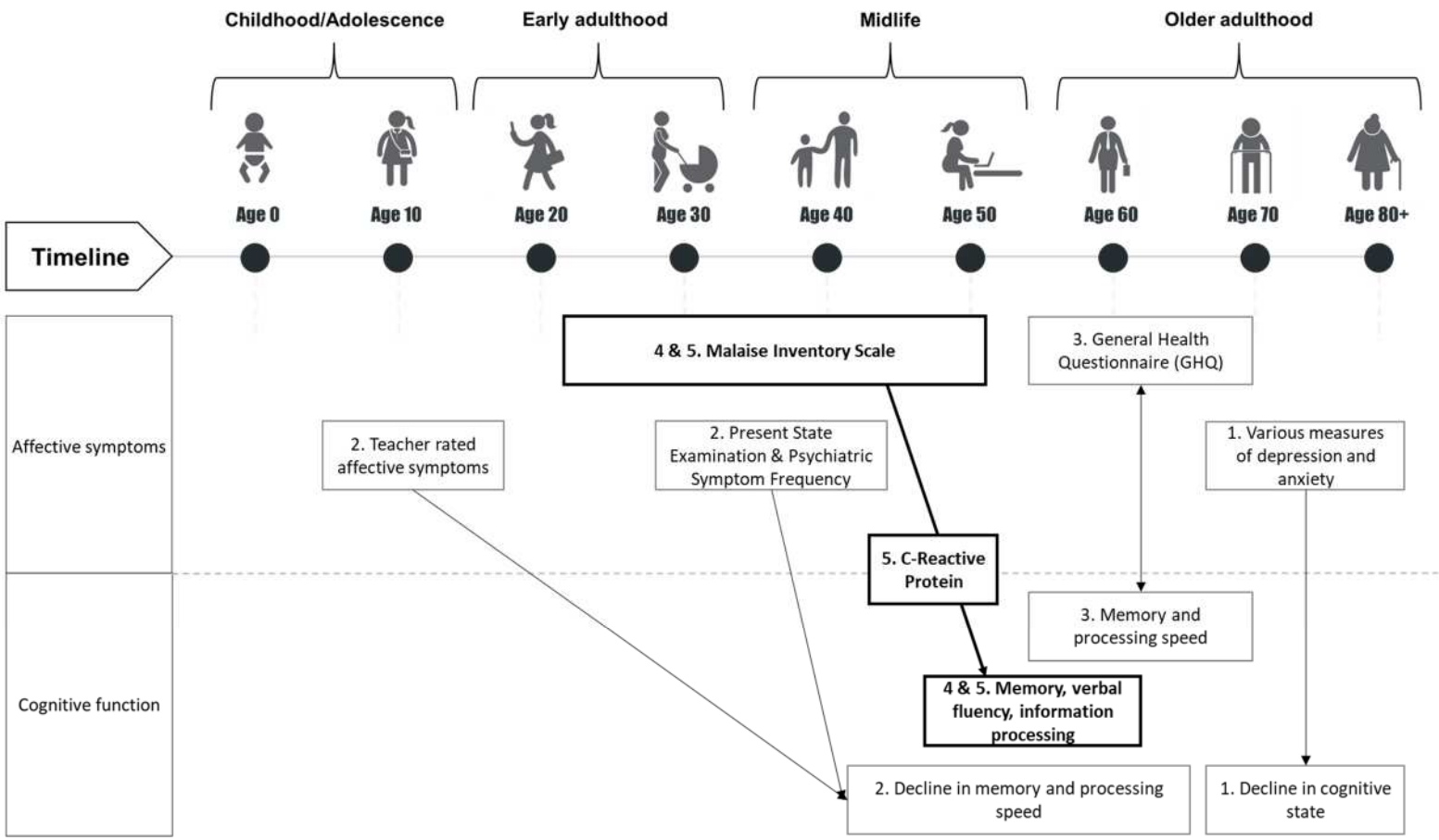


Table 6.6.1: Demographic information about sample included in fully adjusted model (n = 6276)

Measures		**Mean (SD) (unless specified otherwise)**
Immediate memory		6.60 (1.47)
Delayed memory		5.49 (1.82)
Verbal fluency		22.54 (6.25)
Information processing speed		333.21 (87.78)
Information processing accuracy		4.26 (3.89)
Child affective symptoms		0.03 (0.53)
Adult affective symptoms		0.05 (0.46)
Age 50 affective symptoms		0.07 (0.54)
CRP level		1.61 (1.82)
Sex N (%)	Male Female	3067 (48.9) 3209 (51.1)
Child SEP N (%)	Middle Intermediate Working	1356 (21.6) 2326 (37.1) 2594 (41.3)
Childhood cognition	Reading Arithmetic	24.49 (6.32) 5.39 (2.43)
Education N (%)	Degree level Up to A Level Up to GCSE Level	1626 (25.9) 565 (9.0) 4085 (65.1)

Table 6.6.2: Unadjusted and adjusted mediation models showing direct, indirect and total associations between child and adult affective symptoms and mid-life cognitive outcomes

		Immediate memory	Delayed memory	Verbal fluency	Information processing speed	Information processing accuracy
Model 1: Unadjusted (N = 9292) (X2 (1) = 10.42, *p* = .001; CFI =1.00; TLI = 0.97; RMSEA = 0.03)						
Childhood/ adolescence affective symptoms	Direct	0.01 (0.03), .83	-0.02 (0.04), .59	-0.02 (0.14), .91	-2.02 (1.98), .31	0.06 (0.09), .53
	Indirect (child AS -> CRP -> cognition)	0.00 (0.002), .90	0.00 (0.003), .90	0.001 (0.01), .90	0.00 (0.01), .93	0.00 (0.001), .90
	Indirect (child AS -> adult AS -> CRP -> cognition)	**-0.003, (0.001), <.001**	**-0.004 (0.001), <.001**	**-0.01 (0.003), <.001**	-0.004 (0.04), .91	0.001 (0.002), .40
	Indirect (child AS -> adult AS -> cognition)	**-0.05 (0.01), <.001**	**-0.04, (0.01), <.001**	**-0.29 (0.03), <.001**	0.64 (0.40), .11	**0.11 (0.02), <.001**
	Total direct and indirect	-0.04 (0.03), .19	-0.07 (0.04), .09	**-0.32 (0.14), .02**	-1.39 (1.94), .47	0.17 (0.09), .06
Adulthood affective symptoms	Direct	**-0.26 (0.04), <.001**	**-0.24 (0.05), <.001**	**-1.61 (0.16), <.001**	3.56 (2.22), .11	**0.61 (0.10), <.001**
	Indirect (adult AS -> CRP -> cognition)	**-0.02 (0.004), <.001**	**-0.02 (0.01), <.001**	**-0.06 (0.02), <.001**	-0.02 (0.19), .91	0.01 (0.01), .40
	Total	**-0.28, (0.04), <.001**	**-0.26 (0.05), <.001**	**-1.67 (0.16), <.001**	3.53 (2.21), .11	**0.62 (0.10), <.001**
Model 2: Fully adjusted (N = 6276) (X2 (3) = 1.41, *p* = 70; CFI =1.00; TLI = 1.00; RMSEA = 0.00)						
Childhood affective symptoms	Direct	-0.02 (0.03), .59	-0.04 (0.04), .39	-0.03 (0.15), .86	-3.78 (2.14), .08	-0.05 (0.10), .61
	Indirect (child AS -> CRP -> cognition)	0.00 (0.002), .85	0.001 (0.002), .85	0.001 (0.004), .85	-0.01 (0.03), .85	0.00 (0.00), .94
	Indirect (child AS -> adult AS -> cognition)	-0.02 (0.01), .16	-0.003 (0.01), .82	-0.06 (0.05), .21	0.63 (0.73), .39	**0.07 (0.03), .03**

		Immediate memory	Delayed memory	Verbal fluency	Information processing speed	Information processing accuracy
	Indirect (child AS -> adult AS -> CRP -> cognition)	**-0.001 (0.00), .03**	**-0.001 (0.001), .03**	-0.002 (0.001), .17	0.01 (0.02), .49	0.00 (0.001), .94
	Total	-0.05 (0.03), .12	-0.07 (0.04), .09	-0.17 (0.14), .24	-3.99 (2.10), .06	0.04 (0.10), .69
Adulthood affective symptoms	Direct	-0.10 (0.07), .16	-0.02 (0.09), .82	-0.39 (0.31), .21	4.03 (4.63), .39	**0.47 (0.21), .02**
	Indirect (adult AS -> CRP -> cognition)	**-0.01 (0.003), .03**	**-0.01 (0.004), .03**	-0.01 (0.01), .17	0.08 (0.11), .49	0.00 (0.01), .94
	Total	**-0.22 (0.04), <.001**	**-0.24 (0.05), <.001**	**-0.92 (0.18), <.001**	-1.32 (2.58), .61	**0.55 (0.12), <.001**
Sex		**0.28 (0.04), <.001**	**0.47 (0.05), <.001**	-0.05 (0.16), .74	**25.09 (2.34), <.001**	**0.24 (0.11), .02**
Education		**0.25 (0.02), <.001**	**0.35 (0.03), <.001**	**1.26 (0.09), <.001**	**8.13 (1.39), <.001**	0.11 (0.06), .08
Childhood cognition (maths)		**0.06 (0.01), <.001**	**0.06 (0.01), <.001**	**0.27 (0.04), <.001**	**1.12 (0.54), .04**	-0.05 (0.02), .05
Childhood cognition (reading)		**0.03 (0.003), <.001**	**0.04 (0.004), <.001**	**0.08 (0.01), <.001**	**0.51 (0.21), .02**	**-0.04 (0.01), <.001**
Childhood socioeconomic position		**-0.07 (0.03), <.001**	-0.06 (0.03), .06	**-0.67 (0.11), <.001**	-2.68 (1.55), .08	0.02 (0.07), .83
Affective symptoms at age 50		-0.11 (0.06), .07	**-0.20 (0.08), .01**	**-0.51 (0.26), .05**	-5.34 (3.78), .16	0.08 (0.17), .64

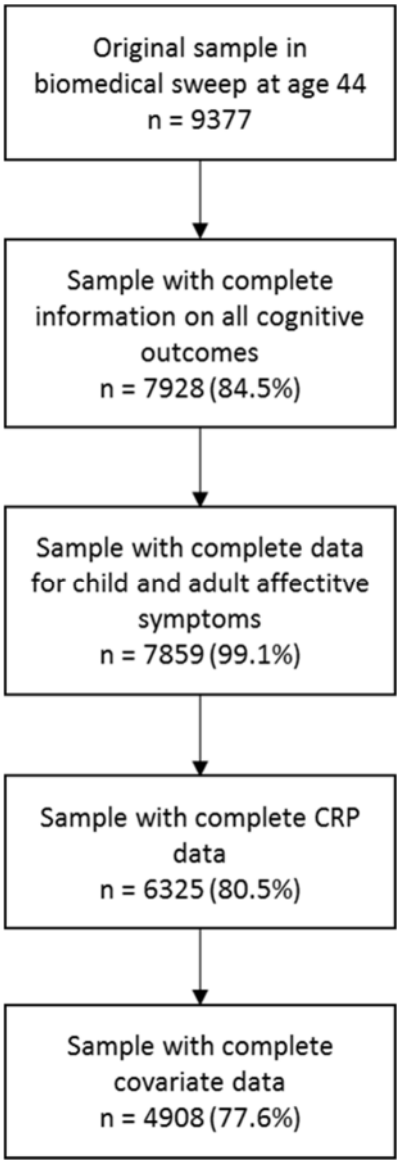


Figure 6.6.2: Flow chart to show missing data patterns

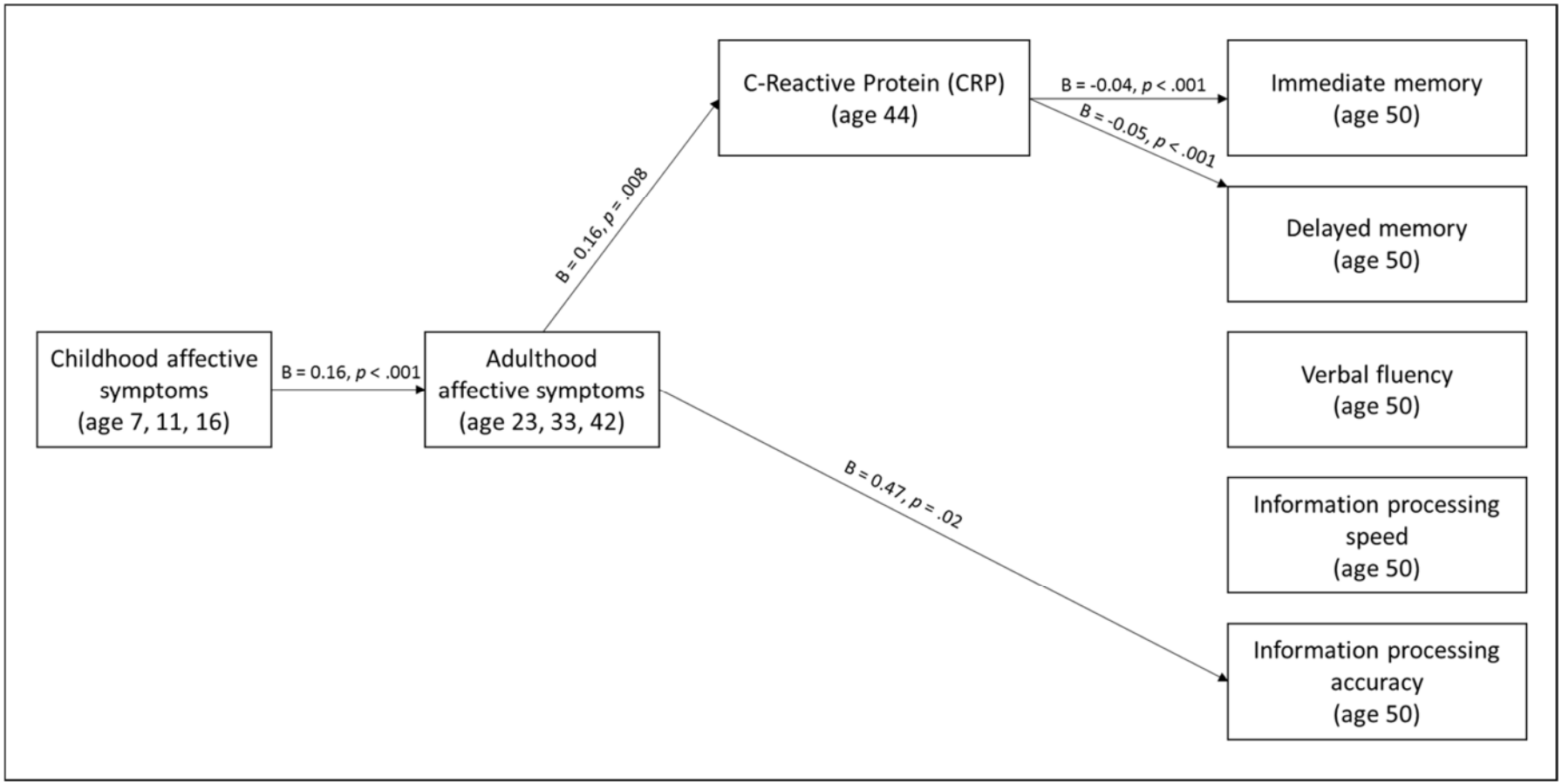


Figure 6.6.3: Significant pathways in fully adjusted mediation model

6.7. Supplementary material

Supplementary Table 1: Model fit for CFAs of childhood and adulthood affective symptoms

Supplementary Table 2: Fit statistics for model stratified by sex and model which was not stratified

Supplementary Table 3: Unadjusted and adjusted mediation models showing direct, indirect and total associations between child and adult affective symptoms and mid-life cognitive outcomes using imputed data

Supplementary Table 1: Model fit for CFAs of childhood and adulthood affective symptoms.

	Childhood affective symptoms	**Adulthood affective symptoms**
X2	X2 (129) = 2167.92, $p < .001$	X2 (588) = 4907.10, $p < .001$
CFI	0.90	0.96
TLI	0.89	0.96
RMSEA	0.04	0.03

Supplementary Table 2: Fit statistics for model stratified by sex and model which was not stratified.

	X2	**CFI**	**TLI**	**RMSEA**
Model 1: Not stratified by sex	X2 (1) = 10.421, *p* = .001	0.999	0.972	0.032
Model 2: Stratified by sex	X2 (2) = 10.994, *p* = .004	0.999	0.973	0.031

Supplementary Table 3: Unadjusted and adjusted mediation models showing direct, indirect and total associations between child and adult affective symptoms and mid-life cognitive outcomes using imputed data.

		Immediate memory	Delayed memory	Verbal fluency	Information processing speed	Information processing accuracy
Model 1: Unadjusted (N = 9377) (X2 (1) = 9.98, *p* = .002; CFI = 1.00; TLI = 0.97; RMSEA = 0.03)						
Childhood affective symptoms	Direct	0.01 (0.03), .82	-0.02 (0.04), .65	-0.02 (0.14), .90	-2.15 (1.97), .27	0.04 (0.09), .63
	Indirect (child AS -> CRP -> cognition)	0.001 (0.002), .56	0.002 (0.003), .56	0.01 (0.01), .56	0.01 (0.02), .69	-0.001 (0.001), .61
	Indirect (child AS -> adult AS -> cognition)	**-0.05 (0.01), <.001**	**-0.04 (0.01), <.001**	**-0.28 (0.03), <.001**	0.72 (0.40), .07	**0.11 (0.02), <.001**
	Indirect (child AS -> adult AS -> CRP -> cognition)	**-0.003 (0.001), <.001**	**-0.004 (0.001), <.001**	**-0.01 (0.003), <.001**	-0.02 (0.03), .59	0.001 (0.001), .32
	Total direct and indirect	-0.04 (0.03), .22	-0.06 (0.04), .11	**-0.31 (0.14), .02**	-1.45 (1.93), .45	0.15 (0.09), .08
Adulthood affective symptoms	Direct	**-0.26 (0.04), <.001**	**-0.24 (0.05), <.001**	**-1.58 (0.15), <.001**	4.00 (2.21), .07	**0.61 (0.10), <.001**
	Indirect (adult AS -> CRP -> cognition)	**-0.02 (0.004), <.001**	**-0.02 (0.01), <.001**	**-0.07 (0.02), <.001**	-0.09 (0.17), .59	0.01 (0.01), .32
	Total	**-0.27 (0.04), <.001**	**-0.26 (0.05), <.001**	**-1.64 (0.15), <.001**	3.90 (2.20), .08	**0.62 (0.10), <.001**
Model 3: Fully adjusted (N = 9377) (X2 (3) = 5.48, *p* = .14; CFI = 1.00; TLI = 1.00; RMSEA = 0.01)						
Childhood affective symptoms	Direct	0.01 (0.03), .72	-0.02 (0.04), .60	0.02 (0.13), .90	-2.79 (1.94), .15	0.01 (0.09), .87
	Indirect (child AS -> CRP -> cognition)	0.001 (0.001), .46	0.001 (0.002), .46	0.003 (0.004), .47	0.001 (0.02), .93	0.00 (0.001), .73
	Indirect (child AS -> adult AS -> cognition)	-0.02 (0.01), .08	-0.00 (0.01), .98	**-0.14 (0.04), .002**	0.34 (0.63), .59	0.05 (0.03), .08

	Indirect (child AS -> adult AS -> CRP -> cognition)	**-0.001 (0.00), .01**	**-0.001 (0.00), .002**	**-0.003 (0.001), .02**	-0.001 (0.02), .93	0.00 (0.001), .70
	Total	-0.03 (0.03), .42	-0.06 (0.04), .13	-0.16 (0.13), .22	-2.83 (1.91), .14	0.10 (0.09), .28
Adulthood affective symptoms	Direct	-0.11 (0.07), .08	-0.002 (0.08), .98	**-0.89 (0.28), .001**	2.18 (4.08), .59	0.33 (0.19), .08
	Indirect (adult AS -> CRP -> cognition)	**-0.01 (0.002), .01**	**-0.01 (0.003), .002**	**-0.02 (0.01), .02**	-0.01 (0.10), .93	0.002 (0.01), .70
	Total	**-0.24 (0.04), <.001**	**-0.25 (0.05), <.001**	**-1.16 (0.15), <.001**	-0.25 (2.25), .91	**0.52 (0.10), <.001**
Sex		**0.30 (0.03), <.001**	**0.47 (0.04), <.001**	0.19 (0.14), .18	**24.80 (2.05), <.001**	0.16 (0.09), .08
Education		**0.28 (0.02), <.001**	**0.37 (0.02), <.001**	**1.32 (0.08), <.001**	**7.41 (1.22), <.001**	0.01 (0.06), .83
Childhood cognition (maths)		**0.05 (0.01), <.001**	**0.05 (0.01), <.001**	**0.24 (0.03), <.001**	0.77 (0.47), .10	-0.04 (0.02), .08
Childhood cognition (reading)		**0.03 (0.003), <.001**	**0.03 (0.004), <.001**	**0.07 (0.01), <.001**	**0.47 (0.18), .01**	**-0.04 (0.01), <.001**
Childhood socioeconomic position		**-0.09 (0.02), <.001**	**-0.08 (0.03), .002**	**-0.64 (0.09), <.001**	-2.03 (1.36), .14	-0.01 (0.06), .94
Affective symptoms at age 50		**-0.12 (0.05), .03**	**-0.24 (0.07), <.001**	**-0.26 (0.23), .26**	-2.43 (3.35), .47	0.19 (0.15), .21

CHAPTER 7

General Discussion

This thesis uses a life course approach to test associations between affective symptoms from childhood through to later adulthood and cognitive function from middle to later adulthood. Additionally, this thesis tests inflammation as a plausible biological mechanism which may contribute to associations between affective symptoms and cognitive function. The general discussion reviews the evidence from the empirical studies included in this thesis, with consideration of key strengths and limitations of the work, directions for future research and the potential implications of these findings for research, public health, policy, and clinical practice.

7.1. Integrated summary of the research findings

All the results of the empirical chapters are included in Figure 7.6.1. Study 1, using a meta-analytical approach for a combined sample of 68,793 people without dementia, suggested that depression in older adulthood is significantly associated with faster cognitive decline. At the same time, there was limited and mixed evidence regarding associations between anxiety and cognitive decline. Study 2 used data from the National Survey of Health and Development (NSHD), and results from linear mixed modelling showed that affective symptoms in adolescence were associated with poorer memory and information processing speed in midlife, but not with the rate of decline from mid to later life. Next, results from cross lagged models in Study 3, also using NSHD data, showed that affective symptoms predicted poorer memory and information processing speed over a period of 16 years from middle to late adulthood. However, this association was not operated in the opposite direction and cognitive function at ages 53 and 60-64 did not predict subsequent level of affective symptoms. Study 4 used data from the National Child Development Study (NCDS) and results from a structured modelling approach revealed that persistent affective symptoms accumulating across adulthood were a better predictor of midlife memory function than particular sensitive

periods at ages 23, 33-42, and 50. Moreover, growth mixture modelling showed that there were five key longitudinal trajectories of adult affective symptoms, with the trajectories with more experience of affective symptoms showing worse memory, but not information processing speed, at age 50. Finally, Study 5 employed a mediation modelling technique using data from NCDS, and revealed that C-Reactive Protein (CRP), a marker of inflammation, mediated associations between affective symptoms and midlife memory function. This suggested that inflammatory pathways could be an important biological mechanism underlying observed associations.

Studies 2-5 focused on four different cognitive domains: verbal memory, verbal fluency, information processing speed, and information processing accuracy. The strongest effects of affective symptoms were observed on memory function, with inconsistent evidence for other cognitive domains, including verbal fluency, information processing speed and information processing accuracy. It is possible that associations between affective symptoms and information processing speed may not emerge until later in the life course. This is supported by Studies 4 and 5 using data from NCDS, which showed no associations between affective symptoms from early to midlife and information processing speed in midlife. This is consistent with evidence from Study 3 using data from NSHD, which showed that affective symptoms predicted subsequent information processing speed in early old age (in this cohort, age 69), but not in midlife (in this cohort, age 53). Taken together, this suggests that effects of affective symptoms can be observed on memory function as early as in midlife, but that effects on information processing speed cannot be observed until early old age.

Taken together, these findings suggest that chronic and persistent affective symptoms across the life course play an important but complex role in contributing to cognitive function across mid to later life, with particularly strong effects observed on memory

function. In addition, inflammation may be one important explanatory mediator of the association between affective symptoms and midlife memory function.

7.2. Methodological considerations

The studies included in the present thesis are subject to several key strengths and limitations which must be acknowledged and taken into account when interpreting and generalising the findings.

Key strengths of the empirical studies included in this thesis are the use of rich longitudinal data available from the British birth cohorts. Specifically, data were prospectively measured with long periods of follow up from birth through to midlife (most recent data used at age 50) in the National Child Development Study (NCDS) and through to older adulthood (most recent data used at age 69) in the National Survey of Health and Development (NSHD). These long follow up periods meant that a life course approach could be used to explore associations between affective symptoms and cognitive ageing, taking earlier life influences from childhood, adolescence and adulthood into account.

Additionally, the empirical work of this study benefits from the use of two different cohort studies with different complementary strengths. Specifically, four repeated measures of affective symptoms were available across early adulthood to midlife in NCDS. This allowed for effective modelling of adult affective symptoms across this period of life. Strengths of NSHD are the long period of follow up, from birth through to age 69. Measures of affective symptoms were available across adolescence to later life, with consistent assessment used across three time-points in midlife to later age. NSHD also includes measures of cognitive function in childhood, as well as repeated assessments of cognitive function across mid to later life. In addition to this, both

NSHD and NCDS also included a wealth of information about other factors which may play an important role in the association between affective symptoms and cognitive ageing, including sex, socioeconomic position, educational attainment, and emotional adjustment in childhood, meaning that these factors could be taken into account in statistical analyses.

However, there are also important limitations of this empirical work, which should be noted and considered when interpreting conclusions. In particular, issues of attrition are very common in long running birth cohort resources. Indeed, missing data is present in both NCDS and NSHD, which may have an important influence on findings. In this thesis, missing data has been explored in depth to test how participants with missing data differ from those with complete data on key variables. Next, missing data was dealt with using various statistical techniques, including full information maximum likelihood (FIML) (Enders, 2001b, 2001a; Enders & Bandalos, 2001) and multiple imputation (Azur et al., 2011; Buuren & Groothuis-Oudshoorn, 2011).

Findings from the two cohorts used in this thesis cannot necessarily be directly compared to one another. Specifically, differences in study design, measures used, and ages of assessment may render results from these two cohorts incomparable with each other. Careful harmonisation of data in these cohorts is necessary in order to test whether differences observed in results across cohorts are a consequence of real cohort effects or simply measurement differences. In addition, due to the observational nature of this data, causality between variables cannot be determined, and only associations can be inferred. In order to establish causality between affective symptoms and cognitive ageing, more complex causal inference statistical techniques are needed.

Moreover, these studies are also limited, albeit necessarily so, by the cognitive data available in the datasets. For example, in NCDS there is only one time point available in adulthood with cognitive data (age 50), meaning that cognitive trajectories across adulthood could not be modelled. In addition to this, both NCDS and NSHD have cognitive data for select cognitive domains (memory and information processing speed in NSHD and memory, information processing, and verbal fluency in NCDS), meaning associations between affective symptoms and other cognitive domains, such as attention or executive function, could not be estimated. However, memory and information processing are both clinically relevant cognitive domains, and as such associations between affective symptoms and these cognitive functions hold particular importance.

Beyond being limited in breadth, these cognitive assessments may also be limited in depth, as single tests are used to capture these functions (word recall test for memory, letter cancellation for information processing, and animal naming task for verbal fluency), rather than a more comprehensive cognitive battery. Reliance on these limited neuropsychological measures available in the data may have had an important influence on the results. For example, people with affective symptoms may have less motivation to perform well in these cognitive tests, and as such may show lower scores than people without affective symptoms, even if underlying cognitive processes are normal. The results across this thesis attempt to partially deal with this issue by taking into account history of affective symptoms across the life course from childhood through to early old age, instead of considering cross-sectional associations between cognitive function and contemporaneous affective symptoms.

Finally, although childhood cognitive function was included in the statistical analyses in this thesis, this does not completely eliminate the possibility of reverse causality. These limitations of the data for cognitive function are addressed in part by

the use of two different complementary cohorts with different strengths and weaknesses, using the cohort which is the best match for the particular research questions.

In addition to this, limitations of the available data for affective symptoms should also be acknowledged. In NCDS, the measures used to capture affective symptoms in childhood were not consistent with those in adulthood, and in some cases relied on parent or teacher report rather than direct reports from the cohort member. The Malaise Inventory Scale was used across early to mid-adulthood to measure affective symptoms. However, this is a generic instrument designed to assess overall psychological distress, and as such individual effects of depression and anxiety could not be disentangled. In NSHD, the measures used to assess affective symptoms varied over time, with consistent measures available only across mid to later life. Evidence suggests that there is low content overlap between different measures of affective symptoms, and that scales capture largely different symptoms (Fried, 2017). For this reason, different types of symptoms may be captured across the life course in NSHD, due to the different scales used, limiting the continuity of how the construct of affective symptoms over the time is measured.

Additionally, limitations of the biomedical data used for this thesis from NCDS must also be noted. Specifically, in the final study, a measure of C-reactive protein (CRP) provided a proxy measure of inflammation, however this was a single biomarker of inflammation measured at one time point during midlife. As such, these preliminary results should be interpreted with all due caution, and results should be replicated in other long running cohort studies. Beyond this, neuroimaging data were not used to explore the neurological mechanisms which may underlie potential associations between affective symptoms, cognitive ageing and inflammatory processes. Finally,

only inflammation was considered as a potential explanatory pathway in this study, meaning that other possible biological and socio-behavioural mechanisms, such as cortisol, vascular factors, education, socioeconomic position, and many others, were not considered.

7.3. Competing explanatory hypotheses and plausible mechanisms

7.3.1. Competing explanatory hypotheses.

There are several competing hypotheses to explain associations between affective symptoms and cognitive ageing. These possibilities are not mutually exclusive, and it is possible, even likely, that more than one may be operating simultaneously (Bennett & Thomas, 2014).

One possibility is that affective symptoms can emerge as a consequence of subjective awareness of cognitive decline or as a psychological reaction to cognitive deficits (Bennett & Thomas, 2014; Vinkers et al., 2004). Results from study 3 in the present thesis do not support this hypothesis, as findings showed that this association was not bidirectional in nature and that affective symptoms can predict subsequent cognitive performance, but not vice versa.

Another possibility is that affective symptoms can be a prodromal symptom of oncoming cognitive impairment (Bennett & Thomas, 2014). Results from study 2 and 4 suggest that it is unlikely that the prodromal hypothesis is acting in isolation. Specifically, both of these studies highlight the importance of affective symptoms present early in the life course across adolescence and early adulthood in predicting later cognitive function, in the absence of dementia or cognitive impairment. Although there is a long preclinical period of dementia, it is unlikely that prodromal symptoms could be apparent this early in the life course. This does not necessarily rule out the

prodromal hypothesis, but suggests that this is not the sole explanation of observed associations between affective symptoms and cognitive ageing.

The next possibility is that affective symptoms can act as a causal risk factor for poorer cognitive outcomes. Alternatively, affective symptoms and cognitive decline may both be caused by some other common cause mechanism (Bennett & Thomas, 2014). The studies in this thesis cannot adequately distinguish between these two possibilities. Findings from all the empirical studies show that there is an association between affective symptoms over the life course and cognitive outcomes, but it is not clear whether this link is causal in nature or whether another factor may be causing both. Causal inference statistical methods are needed in order to differentiate between these hypotheses. For example, causality could potentially be tested using techniques like Mendelian randomisation (Davey Smith & Ebrahim, 2003, 2004; Davey Smith & Hemani, 2014; Lawlor, Harbord, Sterne, Timpson, & Davey Smith, 2008), using genetic variants that have been associated with affective symptoms as a proxy variable to predict cognitive outcomes. This is beyond the scope of the present thesis.

7.3.2. Plausible socio-behavioural and biological mechanisms.

To date, there has been relatively limited evidence surrounding the particular mechanisms which may underlie associations between affective symptoms over the life course and cognitive ageing. It is likely that multiple biological and socio-behavioural processes may be operating simultaneously and interacting with one another in a complex and multifaceted way, resulting in observed associations between affective symptoms and cognitive outcomes.

It is possible that socioeconomic position may influence and contribute to associations between affective symptoms and cognitive ageing. Evidence suggests that

socioeconomic position can act as an important predictor of depression, whereby individuals with a lower socioeconomic position have a higher risk of depression (Lorant et al., 2003). In addition, socioeconomic position can have an influence on the rate of late-life cognitive decline as well as transition to cognitive conditions, such as dementia (Cerhan et al., 1998; Kaplan et al., 2001; Stern et al., 1994; Zeki Al Hazzouri et al., 2011). For example, according to Turrell et al (2002) cognitive function during later life is also likely sensitive to changes in socioeconomic position throughout the life course (social mobility) as well as cumulative disadvantage over time. Due to the association of socioeconomic position with both affective problems and with late-life cognitive health, it is plausible that socioeconomic position may act as an important common cause mechanism between the two. It was beyond the scope of the current thesis to thoroughly investigate how socioeconomic position might influence observed associations between affective symptoms and cognitive ageing. Therefore, this is an important question to be addressed in future research.

It has also been suggested that educational attainment can play an important role in the association between affective symptoms and cognitive ageing. Specifically, some research has shown that depression is associated with increased risk of Alzheimer's disease, but only in individuals with higher levels of education, suggesting that education may be an important moderator in this association (Geerlings et al., 2000). Unfortunately, this study only looked at late-onset depression, so it remains unclear whether education can underlie associations between affective symptoms present earlier in the life course and cognitive ageing.

Health behaviours may also play an important role in the association between affective symptoms and cognitive ageing. For example, research shows a bidirectional association whereby limited physical activity may increase affective symptoms and

affective symptoms may lead to greater levels of inactivity (Strawbridge, Deleger, Roberts, & Kaplan, 2002). In addition to this, Richards et al (2003) reported a protective effect of regular physical activity from earlier in life on memory performance in mid-life. Due to its association with both affective symptoms and cognitive ageing, physical activity may act as a protective pathway in the relationship between the two.

Biological mechanisms which may underlie associations between affective symptoms and cognitive ageing are also of interest. One primary pathway between affective symptoms and cognitive function which has been hypothesised is elevated cortisol and subsequent hippocampal atrophy. Specifically, affective symptoms disrupt functionality of the hypothalamic pituitary adrenal (HPA) axis and lead to increased secretion of glucocorticoids, impaired negative feedback, and changes in homeostatic regulation. Ultimately, chronically elevated levels of glucocorticoids (hypercortisolemia) can contribute to hippocampal atrophy, which is an early neuropathological feature of Alzheimer's disease and cognitive impairment (Butters et al., 2008; Byers & Yaffe, 2011). This possibility is supported by studies showing smaller hippocampal volumes in participants with later life depression (Videbech & Ravnkilde, 2004), as well as other studies demonstrating an association between lifetime depression and hippocampal atrophy (Bell-McGinty et al., 2002; Janssen et al., 2007; Sheline, 1996; Sheline et al., 2003; Sheline, Sanghavi, Mintun, & Gado, 1999). If affective symptoms contribute to higher cortisol levels, leading to disruption of structure and function of the hippocampus, this can ultimately result in observable cognitive impairments, particularly in memory function (Butters et al., 2008).

Chronic inflammation may also play an important role in the association between affective symptoms and cognitive ageing. Byers & Yaffe (2011) propose that inflammatory changes in the central nervous system may be involved in the depression-

dementia association in two different ways. Firstly, depression is associated with an increase in cytokines, which are important in brain development and in promoting healthy brain function (Yirmiya & Goshen, 2011). This increase may then subsequently result in reduced anti-inflammatory and immunosuppressant regulation and increased CNS pro-inflammatory changes, both of which predict transition to dementia (Sorrells & Sapolsky, 2007; Yaffe et al., 2003). The second possible pathway is that pro-inflammatory cytokines may disrupt metabolism of serotonin, decreasing hippocampus neurogenesis and synaptic plasticity, and as a result leading to subsequent dementia and late-life cognitive impairment (Caraci et al., 2010; Maes et al., 2009).

There is also evidence that vascular function may be involved in the association between affective problems and cognitive ageing. The vascular depression hypothesis states that cerebrovascular disease can work to predispose, trigger and maintain depressive symptoms in later life (Alexopoulos, 2003, 2005). There has been some suggestion that a reciprocal relationship between vascular disease and depression may exist, whereby each condition is related to a higher risk of subsequently developing the other (Alexopoulos, 2006; Alexopoulos et al., 1997; Newberg et al., 2006), through biological and behavioural pathways. In addition to this, vascular disease may also be involved in the presentation of late-life cognitive conditions, such as dementia (Snyder et al., 2015; Zlokovic, 2002). This may occur through ischemic damage in frontostriatal brain areas, resulting in impaired delivery of nutrients and elimination of toxins, and impairments in cognitive function. It is therefore reasonable to propose vascular disease and associated ischemic structural brain changes as potential mechanisms underlying the association between depression and dementia (Byers & Yaffe, 2011).

One particular area of interest is the interaction between affective problems and specific genes in relation to cognitive ageing. The strongest and most extensively

studied genetic risk factor for dementia is the apolipoprotein ε4 allele (*APOE4*) (Huang, 2010). Several studies have considered the association between affective problems and late-life cognitive health with reference to the *APOE4* genotype. Two studies reported a significant interaction between *APOE4* allele and late-onset depression, whereby only participants with both risk exposures (*APOE4* and depression) had an increased risk of the subsequent development of dementia (Irie et al., 2008; Kim et al., 2010). This finding has not been consistently replicated, however, with two studies reporting no significant interaction (Meng & D'arcy, 2013; Steffens et al., 1997). It is worth noting however, that although not significant, the pattern of results in these two studies was similar. It is also possible that the temporal relationship between affective problems and dementia may be important for interaction with the *APOE4* allele. Karlsson et al (2015), for example, reported that age of onset of depression influences its interaction between *APOE4* allele and risk of subsequent dementia. Specifically, late-life depression increased risk of dementia irrespective of *APOE4*, whereas remote early-onset depression (more than 10 years interval between depression and dementia) predicted risk for subsequent dementia in *APOE4* carriers only. These findings demonstrate the multifaceted and complex nature of the temporal relationship between depression and cognitive ageing, especially with consideration of the role of genetic risk in this association.

7.4. Future research and implications

7.4.1. Directions for future research.

Future research should focus on testing the biological and socio-behavioural mechanisms and pathways which can potentially underlie associations between affective symptoms and cognitive ageing. Specifically, future research could extend our

findings on the role of inflammation in the association between affective symptoms and cognitive function by replicating these findings using multiple biomarkers for inflammation across different stages of the life course. Beyond this, future research should investigate other important potential mechanisms, including the role of glucocorticoids, vascular factors, nerve growth factors, in associations between affective symptoms and cognitive ageing. Research should make use of the rich genetic, biomedical, and neuroimaging data available in long running longitudinal cohort studies in order to clarify these longitudinal life course associations.

The findings reported in this thesis suggest that accumulation of affective symptoms over the life course are associated with subsequent cognitive ageing outcomes. An important avenue for future research is therefore to investigate whether effective management and treatment of affective disorders to prevent recurrence can contribute to a reduced risk of poorer cognitive outcomes in later life. Additionally, results from this thesis show that affective symptoms present during adolescence may have particular importance in predicting later cognitive health. Future research could test whether early intervention to manage affective symptoms during this adolescent period to prevent continuation of affective disorders into adulthood can have long lasting effects on cognitive health into older adulthood. Beyond this, it is unclear whether different methods of treating affective disorders (i.e. medication, talking therapies, or combination treatment) can have differential effects on risk reduction for subsequently poorer cognitive function. Future research should therefore focus on testing how different treatment approaches affect later cognitive health.

Additionally, future research could test how particular features of affective symptoms are associated with cognitive outcomes. For example, it is possible that different types of symptoms (mood symptoms, somatic symptoms, social symptoms

etc.) may be differentially associated with cognitive function. Future research should test whether certain categories of symptoms are closely linked with cognitive health. In addition, Evidence has shown that comorbid depression and anxiety is associated with higher symptom burden, increased persistence, and poorer functional outcomes than either of these disorders in isolation (Kaufman & Charney, 2000; Roy-Byrne et al., 2000). As such, it is important for future research to test how comorbidity between depression and anxiety over the life course can affect cognitive health.

7.4.2. Implications.

Findings from the thesis improve our knowledge of associations of affective symptoms over the life course with cognitive ageing. These findings have important implications for research, public health, policy, and clinical practice, specifically through potential for identifying individuals who may be at a greater risk of cognitive deficits later in life. Understanding life course associations between affective symptoms and cognitive function can help in the development of better predictive models for dementia and cognitive ageing outcomes. Effective predictive models are critical for the development of preventative intervention efforts.

In addition, results also showed that cognitive differences in individuals with persistent affective problems can already be observed as early as midlife. This may have important implications, as this period in which cognitive differences can be observed in the absence of dementia pathology represents an important window to target for prevention and early intervention efforts. Findings also highlight that affective symptoms during adolescence may play a particularly important role in later cognitive function. Given the high and rapidly increasing prevalence of mental health disorders during adolescence (Fink et al., 2015; Patalay & Fitzsimons, 2017), these findings

suggest that early intervention to tackle mental health problems which emerge early in the life course may be key in protecting future cognitive health.

Overall, results from this thesis show that affective symptoms over the life course are associated with cognitive ageing outcomes. This therefore raises the possibility that early intervention to prevent and manage affective disorders may have important implications for reducing risk of poorer cognitive outcomes, though further research is needed to formally test this possibility. Specifically, based on these findings it is possible that effective management of affective symptoms may help to maintain better cognitive health for longer. In addition, results suggest that individuals who present with affective disorders, particularly in older age, may benefit from careful monitoring of cognitive status, because these individuals may be at greater risk of poorer cognitive outcomes. Given the expected increases in average life expectancy increases in the UK and the negative individual, social, and economic costs associated with poorer cognitive ageing, all research into potentially modifiable risk factors, such as affective symptoms, is increasingly important for the health policy development and for promotion of healthy cognitive ageing.

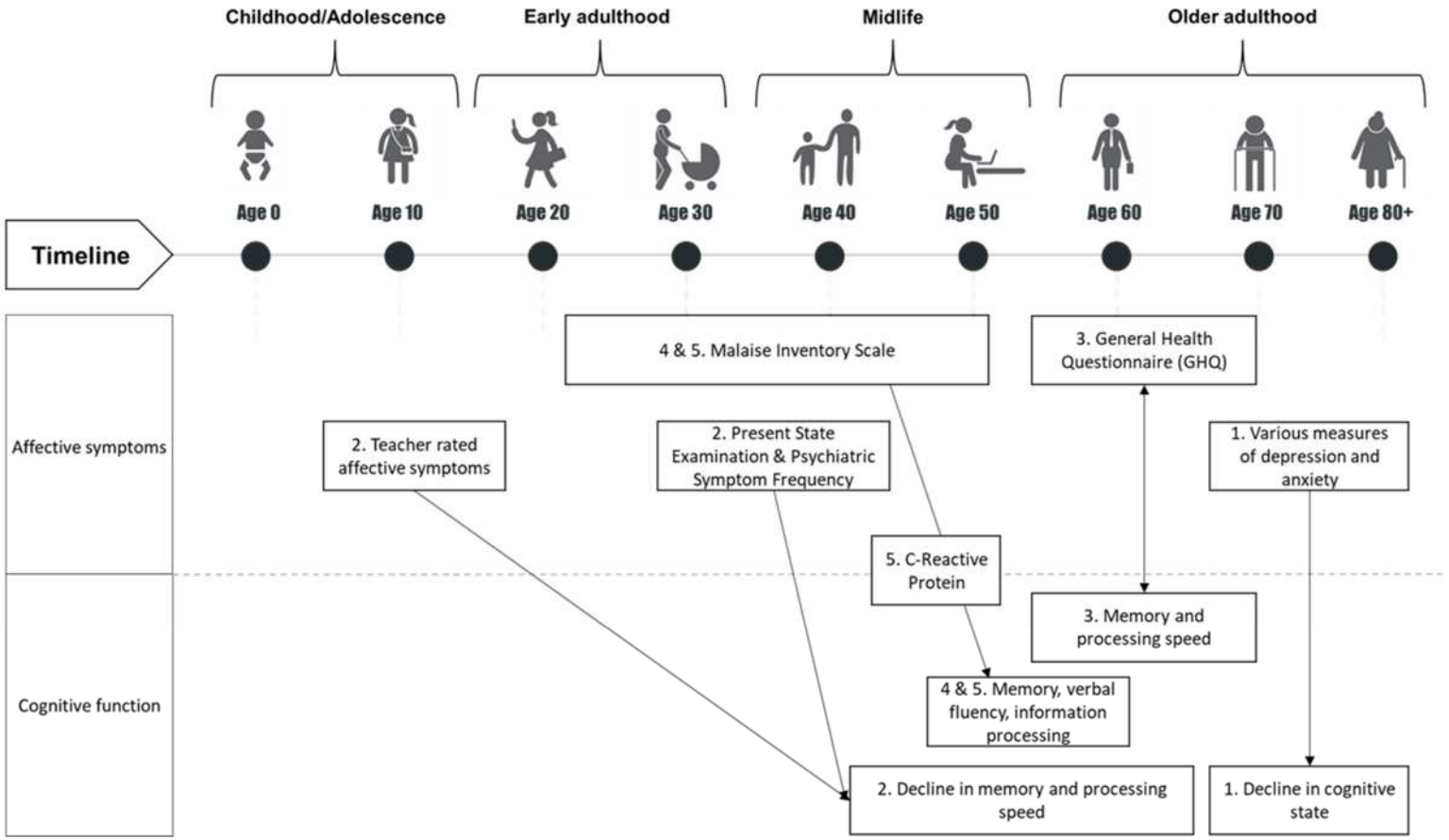
7.5. Conclusions

In conclusion, five studies included in the thesis provide strong evidence that affective symptoms across the life course are associated with poorer cognitive ageing outcomes from middle to later adulthood, particularly on memory functions. Specifically, affective symptoms in older adulthood are associated with a faster subsequent cognitive decline, whereas affective disorders in adolescence are associated with poorer cognitive function in midlife, but not rate of decline over time. Affective symptoms can predict later cognitive function across mid to later adulthood, but the

association does not operate in the opposite direction. Persistent and accumulating affective symptoms across early to mid-adulthood are associated with poorer memory function in midlife, but associations with information processing speed may not emerge until later in the life course. Finally, associations between affective symptoms and memory function may be mediated by inflammatory pathways, as measured by CRP in citrated plasma. These results highlight the importance of life course affective symptoms in the context of cognitive ageing. Given the rapidly ageing population, this research area is increasingly important for the development of better predictive models and to design better preventative intervention strategies. Future research should focus on the particular biological and socio-behavioural mechanisms which underlie associations between affective symptoms and cognitive function, and importantly whether effective treatment of affective disorders at key points during the life course can affect cognitive ageing outcomes.

7.6. Tables and figures

Figure 7.6.1: Results of all empirical studies



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