

# **Cognitive Function in Depression: Longitudinal Perspectives**

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## Abstract

*Background:* Cognitive deficits are observed after recovery from depressive episodes. It is not known whether these deficits arise at the time of the depressive episode or were already present before them. It is also unknown whether the association is explained by prodromal symptoms of dementia or residual subclinical depressive symptoms after the episode.

*Methods:* Data were obtained from a longitudinal cohort study of US residents aged over 50 and their partners, observed every two years for up to 22 years. Periods of elevated depressive symptoms (PEDS) were defined based on an abbreviated version of the Center for Epidemiological Studies Depression scale. A multidomain cognitive composite was derived from measures of episodic memory, working memory, object naming and orientation. Changes in cognitive function were modelled in the same individuals before, during and after PEDS and in individuals who did not experience PEDS, using multilevel linear regression adjusted for potential confounders and the nonlinear effect of ageing. Sensitivity analyses were used to exclude prodromal symptoms of dementia and residual subclinical symptoms.

*Findings:* Amongst 16,486 participants aged 45 to 94 free of depression and dementia at baseline, including 3,475 with incident PEDS, cognitive function was not significantly poorer before PEDS than amongst participants with no observed depression. In most age groups, after adjustment for the nonlinear effects of age and ageing, as well as sex, education and other covariates, cognitive function was poorer, and declined more rapidly, after recovery from PEDS than before PEDS. The result persisted after exclusion of subclinical symptoms and observations twelve or fewer years prior to an observed onset of dementia.

*Interpretation:* In older people, periods of depression coincide with an accelerated rate of cognitive decline which continues after the depressive symptoms are resolved.

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## Chapter 1: Introduction and Literature Review

Depressive disorders are both common and disabling (Bromet et al., 2011). It is estimated that one in seven people will experience an episode of depression during their lifetime (Bromet et al., 2011). Alongside the risk of earlier death, either by suicide (Cai et al., 2021) or through association with physical health comorbidities (Cuijpers et al., 2014), the disorder is associated with a range of chronic physical health conditions (Kessler & Bromet, 2013) and with difficulties in interpersonal relationships, education and employment (Judd et al., 2008; Lerner & Henke, 2008; Kessler & Bromet, 2013).

The combination of high prevalence and functional impact renders depression a leading global cause of disability (Ferrari et al., 2013; GBD [Global Burden of Disease] 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Unipolar affective disorder has been estimated to account for 10% of all disability-adjusted life years that are lost to non-communicable diseases worldwide (Prince et al., 2007).

The two major diagnostic systems, the *Diagnostic and Statistical Manual of Mental disorders* (DSM-5: American Psychiatric Association [APA], 2013) and the *International Classification of Diseases* (ICD-11: World Health Organization [WHO], 2019), construe depression as an episodic condition, with criteria for depressive episodes which individuals may meet at some times and not others. Cognitive deficits are common during depressive episodes (Hammar & Årdal, 2009; Lee et al., 2012; Roca et al., 2015; Trivedi & Greer, 2014) and contribute to its functional impact (McCall & Dunn, 2003; McIntyre et al., 2013; Lam et al., 2014). Deficits may persist after the episode has ended (Kessing, 1998; Hasselbalch, Knorr & Kessing, 2011; Bora et al., 2013; Ahern, White & Slattery, 2025; Semkovska et al., 2019), and these persisting cognitive deficits may continue to predict psychosocial functioning after remission from depression (Knight, Air & Baune, 2018). Individuals with a history of depression are at increased risk of developing dementia in later life (Speck et al., 1995; Geerlings et al., 2008; Barnes et al. 2012; Yang et al., 2021).

The possibility of preventing cognitive decline, by management of risk factors or preventative treatment in high-risk groups, is an issue of major public health significance (Livingston et al., 2017, 2024; Kivipelto et al., 2020). It has been suggested that treatment of depression could reduce individual risk and population incidence of dementia (Livingston et al., 2024). In this context, the temporal relationship between depressive episodes and their associated cognitive deficits is an important consideration. If cognition declines at or after the onset of depressive episodes, then depressive episodes could represent an important time to initiate interventions aimed at preventing cognitive decline. Depending on the nature and direction of causal relationships between depression and cognitive decline, these interventions could include treatment of the depressive episodes. On the other hand, if the cognitive deficits were already present before the depressive episode and not acquired during or after the episode, then interventions at this time could be too late to prevent cognitive decline. The current project aimed to use longitudinal cohort study data to investigate temporal associations between depression and cognitive function.

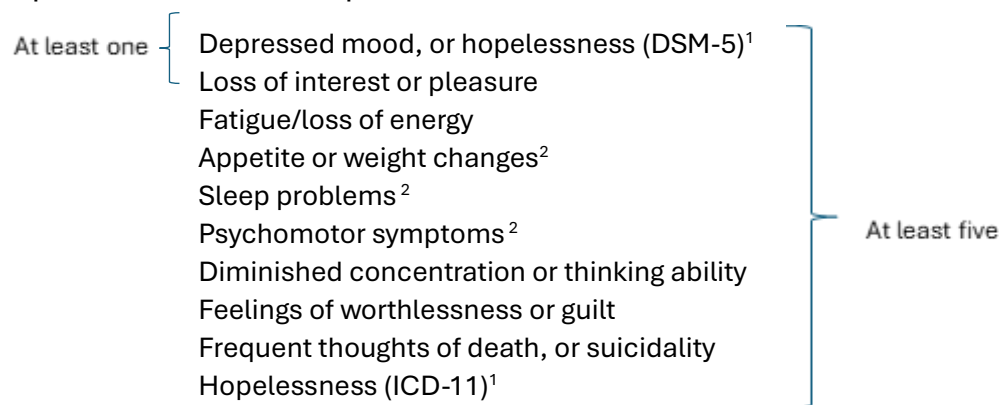
## 1.1 Depression

The concept of depressive disorder has its roots in the ancient notion of melancholia articulated by Hippocrates (Davison, 2006), but lacked a consensus definition until the emergence, in the 20th century, of agreed diagnostic criteria codified in the *Diagnostic and Statistical Manual of Mental Disorders* (now in its fifth edition, DSM-5: APA, 2013) and the *International Classification of Diseases* (now in its 11<sup>th</sup> revision, ICD-11: WHO, 2019). Terms used in diagnostic criteria for depressive disorders include ‘(major) depressive disorder’, ‘depressive episode’, descriptors of more specific subtypes of depression, and terms applicable when depressive symptoms are present but do not fulfil the diagnostic criteria for ‘major depressive disorder’. The adjective ‘major’, used in DSM-5 but not ICD-11, does not denote severity. Cases of major depressive disorder may be classified as mild, moderate or severe. The term ‘depressive episode’ (or ‘major depressive episode’ in the fourth (DSM-IV: APA, 1994) and earlier editions of the DSM) denotes a period of time during which diagnostic criteria are met. The course of depressive disorder is typically episodic,

with most patients experiencing remission within six months of onset, but many going on to experience a recurrence, i.e. a new episode after a period of remission (Ramana et al., 1995; O'Leary et al., 2000). ICD-11 (WHO, 2019) classifies depressive disorders as either 'single-episode' or (from the second episode onwards) 'recurrent'. Some differences existed between earlier versions of the two diagnostic systems, but DSM-5 (APA, 2013) and ICD-11 criteria are almost identical (Figure 1.1).

### 1.1.1 Depressive disorders

**Figure 1.1:** Diagnostic criteria for DSM-5 major depressive disorder and ICD-11 single episode or recurrent depressive disorder



Symptoms must be present over a two-week period, causing significant distress or impairment, and not attributable to a substance, medical condition, psychotic or bipolar disorder, or bereavement.

<sup>1</sup>Hopelessness is treated as equivalent to depressed mood in DSM-5 and as a separate symptom in ICD-11.

<sup>2</sup> Appetite and sleep may be increased or decreased; psychomotor symptoms may be agitation or retardation.

In some cases, depressive symptoms may persist for considerably longer than the duration of typical episodes. Where a patient continuously fulfils criteria for a major depressive disorder or depressive episode for an extended or indefinite period without remission, this chronic presentation may still be diagnostically described as a depressive episode, but may also fulfil criteria for a DSM-5 diagnosis of persistent depressive disorder which is characterised by the persistence of depressed mood for two years or longer. The diagnostic criteria for the latter overlap with the criteria for an episode of major depressive disorder, but are not identical (Uher et al., 2014). It

is possible for a two-year (or longer) episode to fail to meet criteria for persistent depressive disorder; and conversely, symptoms which fall short of the diagnostic criteria for major depressive disorder may nevertheless fulfil those for persistent depressive disorder if they persist for long enough. The nearest ICD-11 equivalent to persistent depressive disorder is dysthymic disorder, but this diagnosis is restricted to those whose chronic depressive symptoms do not meet the full criteria for a depressive episode.

Diagnoses of depressive episodes and disorders are most commonly based on the clinical judgement of non-specialist primary care clinicians (Mitchell, Vaze & Rao, 2009). Diagnostic accuracy may be improved by use of a structured clinical interview such as the Structured Clinical Interview for DSM-5 Disorders (SCID-5: First et al., 2015). Rating scales are also available for assessing depression. These may consist of self-report questionnaires completed by the individual (e.g. Beck Depression Inventory (BDI), Beck et al., 1961; Patient Health Questionnaire-9 (PHQ-9) Spitzer, Kroenke & Williams, 1999; Center for Epidemiological Studies Depression scale (CES-D), Radloff, 1977), or scales completed by a clinician or researcher who has interviewed and observed the individual (e.g. Hamilton Depression Rating Scale (HAM-D), Hamilton, 1967; Montgomery-Åsberg Depression Rating Scale (MADRS), Montgomery & Åsberg, 1979). Rating scales yield numerical scores, which may be used for classification (whereby individuals scoring higher than a recognised threshold are classified as depressed) or as a continuous measure of the extent or severity of depressive symptoms. In most cases, the content of rating scales does not correspond directly to diagnostic criteria for depressive disorder, hence the use of scales to identify cases of depressive disorder is subject to error, the extent of which may be evaluated via validation studies. For example, reported estimates of the sensitivity and specificity (respectively) of rating scales in identifying true cases of major depressive disorder include 0.77 and 0.85 for the PHQ-9 using a threshold score of  $\geq 10$  points (Manea, Gilbody & McMillan, 2015), and 0.76 and 0.91 for the HAM-D. For the purposes of the current thesis, I will adopt the term “period(s) of elevated depressive symptoms” (PEDS) to denote episodes of depression classified on the basis of questionnaire scores rather than diagnostic criteria. Prevalence estimates of depressive disorders and episodes vary widely, presumably due to a combination of substantive differences between populations, differences in

measurement and ascertainment methods (or in their validity across different groups), and differences in study design (Bromet et al., 2011). The World Health Organisation's World Mental Health Survey (Kessler et al., 2006) used a common protocol and instrument across 18 different countries. National lifetime prevalence estimates for DSM-IV (APA, 1994) major depressive episode ranged from below 6.5% to 21%, and 12-month prevalence estimates ranged from 2.2% to 10.4%, with an average 12-month prevalence of 5.5% in high-income countries (Bromet et al., 2011).

The aetiology of depression is complex and heterogeneous. Depressive disorders are approximately twice as prevalent amongst females as amongst males, due to a combination of biological and social factors (Maier et al., 1999). Most (though not all) onsets of depression are preceded by a recent stressful life event such as divorce, job loss or the development of a serious illness (Paykel, 2003; Bjørndal et al., 2024). Genetic predisposition (Flint & Kendler, 2014) increases the likelihood of a depressive reaction to such events (Nugent et al., 2011), as does a history of childhood adversity (Patten, 2013; Desch et al., 2023), the effect of the latter perhaps mediated by the development of maladaptive belief systems (Aafjes-van Doorn, Kamsteeg & Silberschatz, 2020) or of persistent hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis (Pariante & Lightman, 2008). Depression is also associated with chronic stress such as poverty or disability (Hammen, 2005). Inflammatory biomarkers are found to be elevated in some depressed patients, perhaps indicating an 'inflammatory subtype' of depression (Raison & Miller, 2011; Milaneschi et al., 2021). Depression is common amongst patients with neurological conditions, suggesting that some depressive syndromes may be at least partly understood as a consequence of primary neuropathology (Benedetti, Bernasconi & Pontiggia, 2006). High rates of depression are found in patients with vascular disease and *vice versa* (Thomas, Kalaria & O'Brien, 2004), suggesting a bidirectional relationship between depressive and vascular diseases.

Risk factors for first episodes may differ from those for recurrences. For example, although recent life events are strongly associated with first episodes of depression, they are less common prior to subsequent recurrences (Monroe & Harkness, 2005; Kendler & Gardner, 2016); and experimental depletion of monoamine availability has

been found to provoke depressive symptoms in recovered depressed patients but not in healthy volunteers (Ruhé, Mason & Schene, 2007).

### **1.1.2 Subclinical depressive symptoms**

Diagnostic criteria for depressive disorder include a list of several symptoms. Individuals may present with a subset of these symptoms, whilst falling short of the threshold for diagnosis (Rodríguez et al., 2012). Similarly, individuals who are not classified as depressed may nevertheless endorse some items on depression rating scales and, in some cases, score higher than the average level for the nondepressed population. Descriptors which have been used to denote syndromes consisting of some, but not all, of the symptoms of major depressive disorder include ‘minor depression’, ‘subclinical depression’, and ‘subthreshold depression’ (Rodríguez et al., 2012). Alongside these, the terms ‘subsyndromal symptomatic depression’ (Judd et al., 1994) and ‘nonspecific depressive symptoms’ (Backenstrass et al., 2006) have been proposed to denote presentations in which the cardinal features required for a major depressive disorder (depressed mood or anhedonia) are absent but other depressive symptoms are present.

Patients who have recovered from an episode of major depressive disorder often continue to experience persistent subclinical symptoms after the episode has remitted, with some symptoms present for over 40% of the time during a subsequent three-year follow-up (Conradi, Ormel & de Jonge, 2011). Persistence of subclinical symptoms is associated with more rapid relapse or recurrence (Judd et al., 1998).

### **1.1.3 Depression and ageing**

Prevalence of depressive disorder has been reported to peak in middle adulthood, and to fall monotonically with increasing age thereafter with no subsequent upturn (Jorm, 2000; Kessler et al., 2010; de la Torre et al., 2021). When considering symptoms rather than disorders, cross-sectional analyses have replicated this pattern (Garcia-Velázquez, Jokela & Rosenström, 2019) whereas longitudinal studies with repeated measures report a falling trajectory before the age of 60 to 70, followed by an upturn later in life (Sutin et al., 2013; Luo et al., 2023). In cross-sectional studies this late-life upturn may be obscured by cohort effects, as later-born cohorts have been reported to exhibit higher levels of depressive symptoms than

earlier-born cohorts (Luo et al., 2023). Thus it appears that, in later life, depressive symptoms appear to become more common at subclinical levels but less likely to reach the diagnostic threshold for major depressive disorder. Amongst older adults, subthreshold depression is two to three times more prevalent than major depression (Meeks et al., 2011).

Specific attention has been paid to the aetiology of late-life depression (LLD) or late-onset depression (LOD, i.e. onset, in late life, of depression in an individual without prior history), with 'late' commonly defined as over the age of 60 (Disabato & Sheline, 2012). The 'vascular depression' hypothesis (Taylor, Aizenstein & Alexopoulos, 2013) proposes that cerebrovascular disease contributes to the onset and/or persistence of some late-life depressive syndromes. This hypothesis is based on findings that LOD has been reported to be associated with cerebral MRI white-matter hyperintensities (WMHs: Disabato & Sheline, 2012), and both LOD and WMHs are associated with vascular risk factors (Taylor et al., 2013). It has been proposed that WMHs and vascular risk factors may be associated with cognitive dysfunction in LLD (see section 1.3 below), and that the associated cognitive dysfunction is associated with poorer response to treatment (Taylor et al., 2013).

Furthermore, amongst individuals who go on to develop dementia, depressive symptoms may arise during the preclinical or prodromal phase of the dementia process (Singh-Manoux et al., 2017), raising the possibility that LOD could be a symptom of underlying brain pathology. This phenomenon is discussed in sections 1.3.1 and 1.4.3.

Despite the possibility that LLD or LOD may differ from depression earlier in life in terms of aetiology, a systematic review of comparisons between late-onset and early-onset depression (Grayson & Thomas, 2013) found clear evidence of only one difference in their clinical features, namely that LOD was associated with a lower likelihood of family history of depression, whereas in other respects the phenomenology, treatment outcomes and prognosis did not differ identifiably.

#### 1.1.4 The burden of depression

Depressive disorder is associated with an increased risk of mortality (Cuijpers & Smit, 2002). As well as risk of suicide (Ribeiro et al., 2018; Cai et al., 2021), risk of death by more common causes, including cardiovascular diseases and neoplasms, is also elevated in depressive disorder (Zheng et al., 1997), as is risk of accidental death (Crump et al., 2013). Physical health status, socioeconomic status and unhealthy behaviours such as smoking and physical inactivity have been reported to account for only part of the excess mortality, and it has been hypothesised that direct physiological effects of depression may also be a contributory factor (Penninx et al., 1999).

Depressive disorder is associated with physical ill health. Prevalence of depression is high amongst patients with a wide range of conditions including neurological disorders (Rickards, 2006), cancer (Massie, 2004), diabetes (Moulton, Pickup and Ismail, 2015) and cardiovascular disease (Whooley, 2006; Thombs et al., 2006). Alongside the possibility of developing depression due to the challenges of developing and living with a medical condition, other potential mechanisms of association include physiological consequences of psychological stress (Leonard & Myint, 2009), associations with obesity (Milaneschi et al., 2019), and behavioural mechanisms including the association of depression with behaviours detrimental to health (Rozanski, Blumenthal & Kaplan, 1999; Chang et al., 2016) and with noncompliance with medical treatment (Wang et al., 2002).

Levels of disability associated with depressive disorder have been reported to be more severe than those associated with chronic medical conditions (Druss et al., 2009). Depressive disorder is associated with disrupted education, marital dissatisfaction, poorer parenting behaviours, and impaired work performance (Kessler & Bromet 2013; Judd et al., 2008; Lerner & Henke, 2008; Stewart et al., 2003), and is a leading cause of disability worldwide (Prince et al., 2007; Ferrari et al., 2013).

Subclinical depressive symptoms are also associated with disability, including greater self-reported impairments in activities of daily living (Rucci et al., 2003) and social activities (Jaffe, Froom & Galambos, 1994), and increased use of healthcare services (Goldney et al., 2004; Cuijpers, de Graaf & Van Dorsselaer, 2004)

compared with nondepressed individuals. Because subclinical depressive symptoms are more common, the aggregate cost and burden of subclinical presentations may be greater than that of major depressive disorder (Broadhead et al., 1990; Rucci et al., 2003).

Subclinical depressive symptoms have been found to be associated with poorer ratings of instrumental activities of daily living amongst over-60s (Lyness et al., 2006), and because prevalence of major depressive disorder appears to fall in later life whilst subclinical depressive symptomatology increases (as discussed in section 1.1.3), the proportion of disability attributable to subclinical depression may be greater in older age groups (Meeks et al., 2011).

A particularly disabling feature of depression is its cognitive symptoms (McIntyre et al. 2013, Lam et al. 2014). Cognitive symptoms and cognitive function are discussed and defined in section 1.2, and their associations with depression are considered in sections 1.3 and 1.4.

## **1.2 Cognitive function and dysfunction**

### **1.2.1 Definitions of ‘cognition’**

The terms ‘cognition’ and ‘cognitive’ have different meanings in different contexts. In educational, developmental and neuroscientific contexts, the term ‘cognitive function’ is commonly used to refer to mental abilities such as general intelligence, language, memory, reasoning, and perception (Carroll, 1993). Taxonomies of cognitive function are derived in part from clinical observations of patients with impairments (for example, attempts to describe the range of functions which may be impaired as a result of damage to the frontal lobes of the brain gave rise to the term ‘executive function’: Bilder, 2012), in part from developmental psychology (Binet’s observations of the development of mental abilities over the course of childhood were the basis for the construct of IQ: Anderson, 2017), and in part from factor analysis of measurements of mental task performance amongst healthy individuals (Carroll, 1993).

Although individuals vary in their profile of cognitive strengths and weaknesses, a positive correlation is consistently found between measures of all types of mental

activity (the 'positive manifold': Borg, 2018). Consequently, factor analysis yields a common factor (often described as 'general intelligence' or *g*), which contributes to all measures of cognitive function (Jensen, 1998, p.114). Subtypes of cognitive function may be classified and described on the basis of ordinary language usage (for example memory, language, attention) or in technical terms derived from psychological theory. Examples of the latter include executive function (Bilder, 2012), and specific subtypes of memory such as episodic memory (de Brigard, Umanath & Irish, 2022).

Cognitive function may be measured objectively by evaluating performance on a mental task. The interpretation of a particular test result will be determined by the user's theoretical premise and intention. Specifically, an assessment may be used either to describe the observed behaviour directly, or as an indirect measure of an underlying construct (Foster & Cone, 1995). An individual's performance may vary, either between different tests intended to measure the same purported cognitive function, or on the same test administered on different occasions. If the test is construed as an indirect measure of underlying cognitive ability, then the interpretation of the variability will depend on whether the underlying ability is hypothesised to be stable over time (in which case the variability is treated entirely as measurement error) or variable (in which case the variability is a combination of measurement error and true change). Some types of variability in performance, such as the changes associated with ageing (see section 1.2.2), are commonly accepted to reflect true, substantive changes in underlying ability, whilst others, such as the practice effect (Calamia, Markon & Tranel, 2012), are not. Consequently, in some circumstances (including in the context of depression: see section 1.3) the question of whether to interpret variability in performance as measurement error or as a true change in cognitive ability may be a matter of theoretical or conceptual stance.

Alongside objective approaches to the evaluation of cognitive function, individuals may subjectively report or complain of cognitive difficulties. In the case of depression, the DSM-5 symptom of 'diminished ability to think or concentrate, or indecisiveness' (sometimes referred to as 'cognitive symptoms') is typically ascertained on the basis of patient self-report rather than via objective observation and measurement. In other contexts, such as memory clinics providing

assessments for the possibility of dementia, cognitive problems ascertained via self-report rather than by objective measurement are referred to as 'subjective cognitive impairment' (Stewart, 2012). Subjective cognitive impairment may correspond more closely to measures of mood than to objective measures of cognitive function (Cooper et al., 2011).

In the context of depression, the terms 'cognition' and 'cognitive' are also used with an entirely different meaning. Beck's Cognitive Therapy of Depression (Beck et al., 1979) uses the term 'cognitions' to refer to depressogenic thoughts or beliefs such as 'I am worthless'. Cognitions, in this sense, are not the topic of the current thesis.

Cognitive theories of depression also propose that low mood is maintained by biases in the processing of emotionally salient information, such as reduced attention to positive stimuli (Peckham, McHugh & Otto, 2010), or memory biases in the recall of negative vs positive information (Everaert et al., 2022). Roiser & Sahakian (2013) refer to the cognitive processing of emotionally salient information as 'hot cognition'. The presence of 'hot' cognitive phenomena is a well-established feature of depression and is not the focus of this thesis.

Alongside this, depression is associated with deficits or impairments in 'cold cognition' (the processing of emotionally neutral information: Roiser & Sahakian, 2013). This association is open to various potential interpretations, and the current thesis aims to differentiate between potential contributors to the association. Specifically, the thesis investigates associations between depression and objective measures of cold cognition.

For the purposes of this thesis I define terms as follows:

- The term 'cognitive performance' refers to objectively-measured performance on emotionally neutral mental tasks.
- 'cognitive deficit' refers to cognitive performance which is measurably poorer than that of a matched or normative comparison group.
- I use the term 'cognitive decline' to indicate a change over time, whereby an individual's or group's cognitive performance is found to be measurably poorer than that same individual's or group's performance at an earlier point in time.

- The term 'cognitive impairment' will be used as defined in section 1.2.3 to denote a cognitive deficit which is considered clinically or functionally significant. (This term is used inconsistently in the literature, in some instances corresponding to the definition used here but, in other instances, encompassing lesser effects which are, in this thesis, referred to as deficits rather than impairments.)
- Self-reported experiences of difficulties with mental task performance will be described as 'subjective cognitive symptoms'. The term 'subjective cognitive impairment' will not be used in this thesis.
- The term 'cognitive function' is treated as intrinsically imprecise, and used as a general term which may encompass any of the above.

### **1.2.2 Cognitive function and ageing**

Amongst healthy individuals, the observed effects of age on cognitive performance are usually modelled as gradual and, from midlife onwards, monotonically declining (Hedden & Gabrieli, 2004).

Due to cohort effects (whereby later-born cohorts are found to perform better on cognitive tests than earlier-born cohorts assessed at the same age), cross-sectional studies tend to overestimate cognitive decline and underestimate the age at which it begins (Nyberg et al., 2012). This problem may be avoided by use of longitudinal study designs with repeated measures. However, the use of repeated measures introduces the possibility of practice effects, which may inflate performance at follow-up assessments and thus underestimate the rate of cognitive decline. A meta-analysis of studies of practice effects (Calamia et al., 2012) concluded that practice effects may persist at test-retest intervals of up to five years. The analysis also found that a number of factors may reduce the effect. These included the use of alternate forms of cognitive tests (for example, in a list learning test, using a different set of words at follow-up from those used at initial assessment), age (with the practice effect tending to decrease with increasing age) and clinical status (with lower practice effects amongst cognitively impaired groups than amongst cognitively healthy samples). Variation across different test paradigms was reported (e.g. in list learning tests, the practice effect was attenuated more quickly per intervening year

for first-trial recall than for total recall across repeated trials). Whilst these factors could reduce the average contribution of practice effects, they could also introduce confounding or misinterpretation (for example, an apparent observation of age-related decline in cognitive function might in reality be attributable to the age-related decline in practice effect).

Two specific types of cognitive changes associated with normal ageing are mental slowing (Salthouse, 1996) and declining ability to inhibit irrelevant information (Gazzaley et al., 2005). In addition, models of cognitive ageing commonly posit compensatory mechanisms (as described in the cognitive reserve hypothesis: Stern, 2002), involving increased prefrontal cortex activity to offset age-related deficits (Davis et al., 2008; Reuter-Lorenz & Cappell, 2008; Park & Reuter-Lorenz, 2009). Compensation may be more readily achieved with simpler tasks than with more difficult tasks, resulting in age-related declines which are increasingly evident with increasing task difficulty. Age-related decline in cognitive performance may therefore appear across a range of cognitive domains to a varying extent depending on task characteristics, namely the extent to which they are timed, involve distractors, and/or are difficult.

Alongside this, within the domain of episodic memory, an age-related decline in recall of context (such as the location of an item: Chalfonte & Johnson, 1996) has been observed, and has been hypothesised (by extrapolation from animal models) to be related to age-related structural changes in the medial temporal lobe, in particular the hippocampus (Wilson et al., 2006).

Hedden and Gabrieli (2004) note that some cognitive functions begin to decline at an earlier age than others (beginning with processing speed, which declines consistently from early adulthood), but that beyond the age of 55, decline is observed across most cognitive functions other than overlearned or automatic processes. Acceleration of cognitive decline is evident three to six years before death, whereas at times less proximal to death, cognition may exhibit a linear relationship with age (Hedden & Gabrieli, 2004).

### 1.2.3 Cognitive impairment

Cognitive impairments (i.e. cognitive deficits whose severity or functional impact is judged to be clinically significant) may be developmental in origin (Harris, 2014) or may arise as a consequence of any of a wide range of insults to the brain, including traumatic brain injury (Arciniegas, Held & Wagner, 2002), stroke (Sun, Tan & Yu, 2014), drug and alcohol use (Ramey & Regier, 2019) and neurological disorders (Mitchell et al., 2010).

Cognitive impairments which are both widespread (affecting multiple cognitive functions) and disabling are classified as major neurocognitive disorder (DSM-5) or dementia (ICD-11). The term 'dementia' was the common term prior to the introduction of DSM-5 (American Psychiatric Association, 2013) and is the more widely used term in the scientific literature to date. The prevalence of dementia increases with age. The condition is rare below the age of 60 but its prevalence increases exponentially thereafter, more rapidly amongst women than amongst men, and approaches or exceeds 40% amongst those over the age of 90 in many parts of the world (Prince et al., 2015).

Dementia is a life-shortening condition: the life expectancy of 70-year-olds with dementia is around ten years shorter than that of the general population (Strand et al., 2018). It is also a source of years lived with disability. Median survival time after a diagnosis of dementia has been reported to be around three to four years (Wolfson et al., 2001; Mayeda et al., 2017), extending to over ten years in some groups (Xie, Brayne & Matthews, 2008), and living with dementia is associated with disability and high costs of care (Prince et al., 2015).

Dementia (or major neurocognitive disorder) is a clinical syndrome defined by symptoms, not aetiology, and may arise due to a variety of pathologies. Historically, presumed or suspected underlying pathology has been inferred from clinical features of the dementia and specified within the dementia diagnosis (for example, 'dementia due to Alzheimer's disease', 'frontotemporal dementia'). The recent development of methods for assessing pathological biomarkers *in vivo* (including the amyloid-binding PET imaging ligand Pittsburgh Compound B: Klunk et al., 2004) has enabled not only the more accurate differential diagnosis of types of dementia, but also the detection of these pathologies in individuals without dementia. Diagnostic

classification systems diverge with respect to their treatment of asymptomatic cases. The DSM system (APA, 2013) pertains specifically to mental and behavioural disorders and, consequently, individuals without mental or behavioural symptoms do not fall within its remit. By contrast, the ICD system (WHO, 2019) is a comprehensive catalogue of diseases of all types including not only mental, behavioural or neurodevelopmental disorders (where dementia diagnoses are specified) but also diseases of the nervous system, where pathologies such as Alzheimer disease and frontotemporal lobar degeneration may be specified in the absence of dementia.

The pathology most commonly associated with dementia is Alzheimer's disease, whose signature neuropathologies are the accumulation in the brain of the proteins beta amyloid (in extracellular cerebral plaques) and tau (in neurofibrillary tangles) in combination with neurodegeneration (Trejo-Lopez, Yachnis & Prokop, 2022). Alzheimer's disease has a long preclinical period, spanning more than a decade, during which the neuropathology accumulates before the emergence and recognition of symptoms (Rafii & Aisen, 2023). Other progressive neurodegenerative conditions (for example Lewy Body disease, Huntington's disease or prion disease) may also cause dementia. Dementia may also arise due to cerebrovascular pathology, or to other causes of damage to the brain such as head injury or alcohol abuse.

A minority of cases of dementia are due to potentially reversible causes (Clarfield, 2003), for example dementia due to normal-pressure hydrocephalus (Zacharzewska-Gondek et al., 2017). However, for the most common causes of dementia, including Alzheimer's disease, the development of disease-modifying treatments is at early stages, with very limited clinical benefits and availability in clinical practice. Consequently, prevention of dementia is a significant public health priority (Livingston et al., 2017). Prevention requires the identification of risk factors which are potentially modifiable and thus represent opportunities for intervention to prevent dementia. Livingston et al. (2024) identify fourteen such factors across the life course, including education in early life, midlife factors such as hearing loss, and later-life factors such as smoking. One of the factors identified is depression. The status of depression as a risk factor for dementia will be discussed in section 1.4.3.

Where cognitive decline is detectable both subjectively (by the individual) and objectively (by quantified cognitive assessment), but does not meet the diagnostic criteria for dementia, it may be described as mild cognitive impairment (MCI: Winblad et al., 2004; Petersen et al., 2014) or, in more recent diagnostic terminology, diagnosed as mild neurocognitive disorder (Sachdev et al., 2014; Reed et al., 2019). Some individuals with MCI progress to dementia, but most do not (Mitchell & Shiri-Feshki, 2009). Amongst individuals with MCI, those with depressive symptoms may be at increased risk of progression to dementia (Mourao et al., 2016).

Not all cases of cognitive decline fulfil the criteria for MCI or mild neurocognitive disorder. Normal age-related decline is objectively detectable (Hedden & Gabrieli, 2004) but is not symptomatic of a disorder. Some researchers' operational definitions of MCI have required a cognitive test score to fall short of the expected performance for the individual's age by specified margin, for example 1.5 standard deviations (Petersen, 2004), whilst the DSM-5 (APA, 2013) diagnostic criteria for mild neurocognitive disorder require that the individual is engaging in compensatory strategies in order to maintain independence (Sachs-Ericsson & Blazer, 2015). More subtle cognitive declines or deficits may nevertheless be epidemiologically informative or predictive, even if they fall short of the threshold for diagnosis. For example, Gustavson et al. (2021) found that, amongst men in their 50s without MCI, performance on memory tests predicted progression to MCI over a subsequent six-year follow-up period; and Insel et al. (2020) found that amongst cognitively unimpaired individuals aged over 65, those with high levels of cerebral beta amyloid performed more poorly on cognitive tests.

### **1.3 Concurrent associations between depression and cognitive function**

#### **1.3.1 Cognitive function during a major depressive episode**

Patients with depression often present with subjective and/or objective cognitive difficulties. Subjective cognitive symptoms are not essential to the diagnosis of major depressive disorder, but they are the most frequently endorsed nonessential symptom. In a sample of 2,541 patients, Gaynes et al. (2007) found that over 90% reported decreased concentration or decision-making abilities.

Subjective cognitive symptoms account for a significant proportion of the disability associated with major depressive disorder. Buist-Bowman et al. (2008) found that the association between major depressive episodes and self-reported role functioning (ability to work or carry out normal activities) was mediated by subjective cognitive symptoms and (to a lesser extent) embarrassment, and that these two mediators together accounted for approximately half of the impact of depression on role functioning.

Objectively-measured cognitive function in major depressive disorder has been extensively investigated. Systematic reviews and meta-analyses (Trivedi & Greer, 2014; Roca et al., 2015; Kriesche et al., 2023) have identified strong evidence of deficits in a range of cognitive domains amongst patients during major depressive episodes compared with healthy control participants. Although poor performance on cognitive tests during a major depressive episode could arise due to affective factors such as reduced motivation or catastrophic response to failure, and potentially interpreted as measurement error, some observed deficits (including deficits on non-effortful tasks such as recognition memory) are not readily explained in these terms (Porter, Bourke & Gallagher, 2007).

Greater severity of depression is associated with poorer cognitive performance. McDermott & Ebmeier (2009) meta-analysed studies which reported a correlation value between cognitive function and depression severity (quantified using recognised observer-rated scales) in currently-depressed patients with DSM-5 (APA, 2013) diagnoses (either major depressive episode, or the diagnostic category 'minor depression' which features in DSM-IV (APA, 1994) only). Of the fourteen studies included, most were of participants aged below 50. Greater severity of depression was associated with poorer cognition across all cognitive domains, and these associations were statistically significant (with 95% confidence) in the domains of episodic memory, executive function and processing speed but not semantic memory or visuospatial memory (although these latter two domains were each assessed in only two studies). Bierman et al. (2005) investigated cognitive function and depressive symptomatology in 2,615 participants aged over 55 in the Longitudinal Ageing Study Amsterdam (LASA). Cognitive measures included the Mini Mental State Examination (MMSE: Folstein, Folstein & McHugh, 1975), a 15-word recall test, a test of nonverbal reasoning (Raven's coloured progressive matrices:

Raven, Court & Raven, 1995) and a coding task to assess speed of information processing. Depression symptoms were measured using the Center for Epidemiological Studies – Depression scale (CES-D: Radloff, 1977), a self-report scale consisting of 20 items each scored from 0 to 3 (thus yielding a range from 0 to 60), on which 321 participants scored at or above the conventional clinical threshold of 16. Using a second threshold of 24 to differentiate between milder and more severe depression, they reported that, on all cognitive tests, performance was best in the nonclinical group, somewhat poorer in the mildly depressed group, and poorest in the more severely depressed group.

In a minority of cases, the cognitive deficits observed during a major depressive episode may be sufficiently severe to be classified as cognitive impairment. Gualtieri & Morgan (2008) reported that, in cognitive assessments of 285 patients with major depressive disorder and no comorbid conditions that might affect cognition, 21% (as compared with 4% of healthy control subjects) were found to perform two or more standard deviations below the mean in at least two cognitive domains. This level of cognitive deficit, if combined with evidence of functional disability, is equivalent in severity to the diagnostic criteria for dementia/major neurocognitive disorder. Historically, the term ‘pseudodementia’ has been used to denote impairments which mimic dementia, but which are attributable to psychiatric disorders (most commonly depression) rather than to neurodegenerative conditions (Brodaty & Connors, 2020).

In contrast, in most cases of major depressive disorder, cognitive function is not impaired to a clinically significant extent. Some reports have made the stronger claim that amongst depressed patients without frank cognitive impairment, no cognitive deficit at all (even at subclinical levels) may be detectable. Iverson et al. (2011) reported that, after excluding a subgroup of depressed patients with obvious cognitive impairment, levels of cognitive performance amongst the remaining patients were similar to those of healthy controls. Using hierarchical cluster analysis to account for neurocognitive heterogeneity, Pu et al. (2018) reported that, of 170 patients with major depressive disorder, 90 fell into a cluster with no cognitive deficit in comparison with age- and sex-corrected test norms.

There are theoretical grounds to hypothesise that depression might be more strongly associated with certain cognitive functions (in particular, executive function: Snyder,

2013) than with others. In a minority (around 30%) of cases of late-life depression, a 'depression executive function' syndrome has been described with a distinct profile of clinical features including anhedonia and psychomotor retardation (Alexopoulos, 2019). In a nonclinical laboratory study of college students, Quinn and Joormann (2015) administered a test of executive function (the n-back task) before and after a stress induction procedure, and found that those whose performance declined under conditions of stress went on to experience higher levels of depressive symptoms shortly before final exams. They hypothesise that the tendency to experience a temporary lapse in executive function when under stress may be a trait risk factor for depression.

More generally, however, empirical findings have not consistently supported a particular profile of cognitive deficits associated with depression. A meta-analysis by Parkinson et al. (2020) reported a significant effect of depression on every cognitive test paradigm evaluated, with some of these effects being moderate to large whilst the magnitude of the remainder could not be specified due to variance heterogeneity across studies. A recent systematic review of cognitive deficits in depression (Kriesche et al., 2023) concluded that the evidence is consistent with a global-diffuse hypothesis of reduced cognitive performance in multiple cognitive domains.

Conversely, depression is common in conditions which cause cognitive impairment, including dementia (Zubenko et al., 2003), stroke (Medeiros et al., 2020) and traumatic brain injury (Rapoport, 2012). Alongside the possibility that the depression may have arisen as a psychological reaction to the loss of cognitive function, or to the condition which caused the cognitive impairment, the association may also arise via biological mechanisms. For example, in Parkinson's disease, Bohnen et al. (2007) found that cortical acetylcholinesterase activity had an independent association with depressive symptomatology after controlling for cognitive function. Furthermore, pre-existing cognitive deficits (such as low premorbid IQ: Zammit et al., 2004; Koenen et al., 2009) are associated with an increased risk of developing depression. Thus, when cognitive deficits are concurrent with depression, causal relationships between them may be multidirectional and may differ between cases.

In late-life depression, cognitive deficits may be prodromal symptoms of dementia. Alzheimer's disease has a long preclinical phase during which cerebral

neuropathology accumulates for years or decades before dementia emerges (Braak & Del Tredici, 2015). Gradual cognitive decline is evident during this phase, and may be considered prodromal to the full manifestation of dementia (Wilson et al., 2011). Heser et al. (2013) used data from a longitudinal study of primary care patients over the age of 75, the German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe) to investigate cognitive function in 2,709 individuals without dementia, of whom 311 were classified as depressed when first assessed and 404 subsequently developed dementia within a six-year follow-up period. Compared to those with neither current depression nor subsequent dementia, those with both depression and subsequent dementia showed significantly poorer cognitive function at the time of the depression assessment. Those with subsequent dementia but not depression showed intermediate cognitive function. Amongst depressed participants who did not progress to dementia, cognitive deficits were minimal. These results suggest that cognitive deficits arising as prodromal symptoms of dementia are substantially greater than those due to depression alone. In this study, cognitive deficits in late-life depression were predominantly (though not entirely) attributable to the incipient dementia rather than to depression.

The depression executive syndrome in late-life depression responds poorly to antidepressants (Alexopoulos, 2019). It is unclear whether cognitive function at younger ages and in other cognitive domains predicts response to treatment (Groves, Douglas and Porter, 2018). Conversely, antidepressant treatment may be associated with either positive or negative changes in cognitive function (Prado, Watt & Crowe, 2018; Wang et al., 2023; Ainsworth et al., 2024).

With respect to functional disability, a study of 77 severely depressed patients (average age of 57 years, mostly with a history of prior recurrences and resistance to antidepressant medication) reported that objective measures of cognitive function predicted functional impairment (McCall & Dunn, 2003). Amongst 48 patients hospitalised with major depressive disorder (average age 40 years), Jaeger et al. (2006) measured functional disability six months later (by which time depressive symptoms had partly but not fully remitted), and reported that functional impairment was associated with cognitive impairments which persisted from the original hospital admission to the six-month follow-up, but not with cognitive impairments at the original assessment which had remitted by the time of the follow-up. Amongst 21

outpatients with depressive episodes of moderate to high severity, Naismith et al. (2007) reported a robust association between psychomotor speed and physical functioning (such as ability to climb stairs). In the same study, memory retention showed an association with role functioning which became insignificant after controlling for depression severity.

### **1.3.2 Cognitive function concurrent with subclinical depressive symptoms**

Amongst individuals who do not meet diagnostic criteria for major depressive disorder, depressive symptoms may nevertheless be associated with cognitive function. Amongst 4,243 participants (aged 50 to 93) in a study of cognitive performance in healthy older people, Rabbitt et al. (1995) found that most participants scored well below clinical thresholds on the BDI depression measure, and that after adjustment for age, sex and socioeconomic status, these predominantly subclinical scores showed small but significant negative correlations with all components of a battery of cognitive tests administered within three months.

Cognitive deficits and subclinical depressive symptoms may also arise concurrently during the preclinical phase of a dementia process. This is discussed in section 1.4.3.

The possibility that subclinical or nonspecific depressive symptoms may be associated with concurrent cognitive function is an essential consideration in the interpretation of longitudinal associations between depression and cognitive function at different timepoints, to be discussed in section 1.4.

## **1.4 Longitudinal associations between depression and cognitive function**

### **1.4.1 Concurrent changes in depression and cognitive function**

The presence of cognitive deficits (relative to healthy control participants) during depressive episodes does not indicate whether cognition declined at the time of the episode or whether, instead, a deficit was already present before the onset of depression. To differentiate between these possibilities, it would be necessary to measure cognitive function prior to the onset of the depressive episode and to compare this with cognitive function during the episode. This analysis appears to be almost entirely absent from the literature. Longitudinal cohort studies drawn from the

general population are a potentially suitable source of participants not depressed at baseline amongst whom, because depression is common, some cases of incident depression during follow-up may be expected. However, to date, analyses of such data sources have instead investigated other types of longitudinal association, for example whether baseline depression predicts future change in cognition or vice versa (Gale, Allerhand & Deary, 2012) rather than investigating associations of incident depressive symptoms with cognitive decline. One study (Jindra et al., 2020) investigated lagged associations between depression at one timepoint and cognitive function at a different timepoint whilst controlling for previous levels of depression, in two cohorts (the Health and Retirement Study (HRS: Fisher & Ryan, 2018) and the English Longitudinal Study of Ageing (ELSA: Steptoe et al., 2013). In HRS, but not ELSA, depressive symptoms were associated with future cognition after controlling for prior cognition. The analysis did not report or adjust for levels of depression at the time of the measure of prior cognition, hence it is unclear whether the prior cognitive measure was taken before, or during, a PEDS.

A converse question is whether recovery from depression is accompanied by improvement in cognitive function. Bernhardt, Klauke & Schröder (2019) conducted a meta-analysis of studies evaluating change in cognitive test performance amongst patients receiving treatment for major depressive disorder, and found that, in most cognitive domains, improvements did not differ from those found in healthy control subjects. They concluded that the improvements may reflect practice effects rather than response to treatment. The exception was the domain of verbal memory, in which improvements might represent a true treatment effect over and above the effects of practice. These verbal memory improvements were more strongly evident in younger than older patients. Butters et al. (2000) reported that, in a group of 45 elderly depressed patients treated successfully with antidepressants, recovery from depression was associated with partial improvement, but mild deficits persisted.

#### **1.4.2 Cognitive function following remission of a depressive episode**

Narrative reviews (Hammar & Årdal, 2009; Roca et al., 2015), systematic reviews (Douglas & Porter, 2009; Hasselbalch, Knorr & Kessing, 2011) and meta-analyses (Bora et al., 2013; Kriesche et al., 2023) have consistently concluded that objective cognitive deficits are found following remission from a depressive episode. The effect is strongest in late-life depression, whereas evidence for the effect in younger

populations is weaker or less consistent (Bora et al., 2013; Casteneda et al., 2008a, 2008b).

Potential explanations of the presence of cognitive deficits in remission include ‘trait’ and ‘scar’ hypotheses (Allott et al., 2016; Ahern & Semkovska, 2017). The trait hypothesis posits that long-standing cognitive deficits may increase the risk of incident depressive episodes. Under this hypothesis, the deficit observed after a depressive episode was already present before the onset of the episode, as a pre-existing vulnerability factor which may have contributed causally to the onset of the depressive episode. The scar hypothesis proposes the opposite direction of causality, i.e. that a depressive episode causes cognitive decline which persists after the depressive episode is resolved.

To avoid assumptions regarding causality, the following sections will address related issues purely in terms of temporality. Specifically, section 1.4.3 will discuss the possibility that cognitive deficits may arise during or after the depressive episode and persist after its resolution, whilst section 1.4.4 will consider the possibility that cognitive deficits may precede depressive episodes.

An important issue in the interpretation of these associations is the definition of remission. Residual subclinical symptoms often persist after remission from a major depressive episode, and these residual symptoms predict more rapid relapse or recurrence of a further major depressive episode (Conradi, Ormel and De Jonge, 2011; Judd et al., 1998). This observation has led some commentators to propose that individuals with residual symptoms should be considered only ‘incompletely’ or ‘partially’ remitted, and that patients should not be described as having fully remitted or recovered unless they are entirely asymptomatic (Judd et al., 1998). In their three-year prospective study, Conradi, Ormel and De Jonge, (2011) found that the symptoms most frequently reported by remitted patients were subjective cognitive symptoms, which were present for 44% of the time during remission.

### **1.4.3 Depression as a predictor of cognitive decline, including dementia**

Prospective associations between depression and the subsequent onset of dementia are well-established (da Silva et al., 2013). Byers and Yaffe (2011) provide an

overview of biological mechanisms with the potential to explain associations between depression and subsequent dementia, including chronic HPA hyperactivation and glucocorticoid elevation, vascular disease, inflammation, amyloid plaques, decreased neurotrophic agents such as brain-derived neurotrophic factor (BDNF), and structural brain abnormalities. The hypothesis of inflammation as a link between depression and dementia is also discussed by Leonard (2007).

Prospective associations between depression and subsequent onset of dementia are not sufficient to demonstrate direction of causality. Reverse causation is possible, as it has been proposed that depression may arise as a prodromal symptom of dementia. This hypothesis has been postulated primarily on the basis of longitudinal cohort studies in which depressive symptoms have been observed to increase over a period of ten to twelve years prior to a diagnosis of dementia. Amieva et al. (2008) observed gradually increasing CES-D (Radloff, 1977) scores (below the conventional clinical threshold of 16), with concomitant gradual cognitive decline in 350 participants in the PAQUID longitudinal cohort study who went on to develop dementia during a subsequent 14-year follow-up period, compared with 350 matched participants who did not develop dementia. Amongst 6,728 participants followed up from 1985 to 2003 in the Whitehall II study, Singh-Manoux et al. (2017) demonstrated gradually increasing trajectories of (mostly subclinical) scores on questionnaire measures of depression or mental health in the twelve years preceding a diagnosis of dementia, compared to participants who remained free of dementia. Similar patterns of increasing trajectories of depressive symptoms in the years leading up to a dementia diagnosis have been reported by Paris et al. (2025) using data from the UK Biobank study and linked health records, and by Hachem et al. (2025) in the French Three-City Study. The predominantly subclinical severity of the symptoms in these studies suggests that depressive symptoms associated with the subsequent development of dementia do not always manifest as the full syndrome of major depressive disorder.

The prodromal observations could be explained by the hypothesis that the underlying progressive neuropathology which eventually leads to dementia first manifests, at earlier stages, in depressive symptoms. However, evidence for this hypothesis is inconclusive. Based on a sample of 995 homebound older people (mean age 75), Sun et al. (2008) reported a difference in plasma amyloid ratios

between those with high vs low levels of depressive symptoms, and argued that a subgroup of these may comprise an amyloid-associated depression syndrome representing a prodromal manifestation of Alzheimer's disease. In contrast, post-mortem studies have not supported the hypothesis. Amongst 130 Catholic clergy, Wilson et al. (2003) found that depression scores proximate to death were associated with cognitive function but not with post-mortem counts of Alzheimer pathology. Using autopsy data from 436 participants in the Honolulu-Asia Aging Study who died at a mean age of 85.9 years, Royall and Palmer (2013) found that CES-D scores at a mean age of 79.6 years were not associated with post-mortem counts of neurofibrillary tangles, cortical Lewy Bodies or ischaemic lesions.

Depression at younger ages (when an underlying dementia process is unlikely) may also be associated with eventual dementia. Yang et al. (2021) analysed associations between depression and dementia incidence amongst 41,727 participants in the Swedish Twin Registry (ascertained using the Swedish National Patient Registry, which contains all medical diagnoses from inpatient admissions and, since 2001, outpatient specialist clinics). Participants with depression in mid-life (between the ages of 45 and 64 years) were found to be more likely to develop vascular dementia over an 18-year follow-up period, even if no further depression was recorded over the age of 64. Co-twin matched analysis suggested that the association was not attributable to genetic and early-life environmental factors. Possible explanations considered by the authors include a common cause hypothesis whereby underlying vascular disease increases the risk of both depression and dementia, and HPA dysregulation or inflammation as potential mediating mechanisms (heightened in depression and increasing the risk of dementia).

In contrast to the association with vascular dementia, Yang et al. (2021) did not find an association between midlife depression and Alzheimer's dementia. Another study which also used the Swedish National Patient Registry, with a larger cohort (119,386 individuals with depression and an equal number of matched nondepressed individuals), reported that depression predicted both vascular and Alzheimer's dementia over shorter intervening timespans but that, when restricted to timespans of over 20 years, the association persisted only for vascular dementia (Holmquist, Nordström & Nordström, 2020).

Mendelian randomization studies have reported no evidence of a causal association between major depressive disorder and Alzheimer's disease but that depression could contribute causally to vascular dementia (Huang et al., 2020; Hu et al., 2024).

Amongst individuals with clinical levels of depression who do not develop dementia, evidence of subsequent decline is often absent or found only in subgroups of individuals. Geerlings et al. (2000) found that, amongst 2,399 cognitively unimpaired longitudinal study participants with a mean age of 74, a CES-D score of 16 or higher predicted subsequent MMSE decline, but the effect was evident only in the more highly educated participants. Olaya et al. (2019) assessed depression and cognitive function on two occasions (three years apart), in 1,027 individuals aged over 60, using depression questions from the World Mental Health Survey Initiative version of the WHO Composite International Diagnostic Interview (WMH-CIDI; Kessler & Üstün, 2004), a widely used structured interview schedule, and word-list recall and verbal fluency tests. At both timepoints, cognitive function was poorer amongst those who were depressed than those who were not, but the two groups did not differ in the rate of change over time. In a clinic sample of 67 patients aged over 60 with DSM-IV diagnoses of major depressive disorder, Köhler et al. (2010) found that cognitive deficits persisted but did not increase over 18 months of follow-up. Based on a study of 1,265 adults aged over 67 years and free of dementia at baseline, Ganguli et al. (2006) proposed that where substantial cognitive decline occurs in late-life depression, it is likely to be attributable to prodromal symptoms of dementia rather than to the depression.

Formánek et al. (2020) analysed trajectories of depressive symptoms and cognitive function in a sample of 69,066 individuals with a mean age of 64 years (drawn from the pan-European SHARE study: Börsch-Supan et al., 2013). Although the researchers did not set out to classify individuals using a clinical threshold, their statistical procedure for classifying trajectories of depressive symptoms (latent growth mixture modelling) yielded four groups which corresponded to clinical descriptors: a “constantly high” group who presented with clinical levels of depression at all timepoints, a “constantly low” group whose depressive symptoms never reached clinical levels, a “decreasing” group who transitioned from clinical to subthreshold depression, and an “increasing” group who transitioned from subthreshold to clinical levels. Compared with the constantly low group, increasing

or constantly high levels of depression were associated with faster cognitive decline, but decreasing levels of depression were not.

Systematic reviews (Hasselbalch et al., 2011; Kriesche et al., 2023) have concluded that the potential contribution of premorbid cognitive function (before the onset of depressive illness) has not been adequately addressed in studies to date. With respect to the residual cognitive deficits observed following remission from a depressive episode, I have found no studies in which cognition was measured before the onset of the episode.

#### **1.4.4 Cognitive function as a predictor of future depression**

Depression is common in dementia (Cipriani et al., 2015) and in mild cognitive impairment (Ismail et al., 2017) but, once substantial cognitive impairment is established, its multidirectional associations with depression create difficulties in the ascertainment of temporality. Studies of individuals without cognitive impairment are more suitable for the investigation of cognitive function as a predictor of future depression.

In a sample of 500 individuals aged over 85, Vinkers et al. (2004) found that, amongst those without significant depressive symptoms at baseline (measured using the 15-item version of the Geriatric Depression Scale: Yesavage et al., 1982), poorer baseline performance on Stroop and word-list recall tests predicted an increase in depressive symptoms over the next one to four years. Similarly, amongst 273 older Hispanics, Perrino et al. (2008) found that, over successive annual timepoints, cognitive function at each timepoint predicted depressive symptoms (measured using the CES-D) at the next timepoint. The authors speculate that this could reflect a psychological reaction to awareness of cognitive decline, or that weaker cognition might be associated with a poorer capacity for functional or emotional coping and hence greater risk of depression.

Amongst 1,506 participants aged over 65 in the Longitudinal Study of Ageing Amsterdam, poorer delayed recall at baseline predicted a steeper increase in depressed affect over time (Brailean et al., 2017). Similarly, amongst 14,789 participants in the Health & Retirement Study, Jajodia and Borders (2011) found an association between performance on a delayed word-recall task and depression

(abbreviated CES-D) scores two years later. In contrast, using a slightly different cognitive measure (sum of immediate and delayed recall) from the same study, Jindra et al. (2020) reported no such association.

In a population-based sample of 708 non-depressed adults aged 20 to 64, Airaksinen et al. (2007) reported that poor episodic memory performance was associated with increased risk of a depression diagnosis three years later. Amongst children, sustained attention at the age of 8 has been reported to be negatively associated with depressive symptoms at 17 to 18 (Morales- Muñoz et al., 2021). Birth cohort studies in the UK (Gale et al., 2009) and New Zealand (Koenen et al., 2009) have found low IQ in childhood to be associated with increased risk of depression in adulthood.

Scult et al. (2017) conducted a systematic review and meta-analysis of studies evaluating associations between cognitive function and subsequent depression. Whilst the prospective association was confirmed, the result was not found in sensitivity analyses which adjusted for levels of subclinical depressive symptoms at the time of the cognitive assessment.

Cognitive function has been investigated in individuals at familial risk of (but without personal history of) depression. Mannie et al. (2009) administered a word-list recall test to 35 young women who had no personal history of depression but had a depressed parent (and were thus at increased familial risk of depression). This at-risk group performed more poorly than an age- and gender-matched control group. Cognitive function has also been investigated in twins discordant for history of depression. Christensen, Kyvik & Kessing (2006) investigated cognitive function in never-depressed twins of individuals with or without a history of depression. Twins of depressives performed more poorly on several cognitive measures than those whose twin had never been depressed. Hsu et al. (2014) compared cognitive function in monozygotic twins discordant for lifetime history of depression. Twins of depressives performed at similar levels to their twins with a history of depression and, on measures of attention and working memory, more poorly than a control group of pairs of never-depressed twins. A meta-analysis of 54 studies of cognitive performance in (mostly young: mean age 15 years) first-degree relatives of individuals with major depressive disorder (MacKenzie, Uher & Pavlova, 2019)

concluded that some cognitive deficits are familial traits disposing individuals to risk of depression.

#### **1.4.5 Cognitive function in recurrent or chronic depression**

Amongst 1,003 longitudinal research participants aged 59 to 71 with follow-up measures of both cognition and depression, Paterniti et al. (2002) found that cognitive decline was associated only with persistent or recurrent depression and not with single-episode depression. Amongst 4,271 participants in the Whitehall II longitudinal cohort study, the presence of persistent depressive symptoms (at four or more of a total of six observations over 18 years) was associated with a range of cognitive deficits at the final observation at a mean age of 61 years (Singh-Manoux et al., 2010). Symptoms at a single timepoint were weakly associated with poorer performance on some cognitive tests. In a sample of over 8,000 outpatients with major depressive disorder, Gorwood et al. (2008) reported that patients' (retrospectively assessed) number of previous episodes of depression predicted performance on a cognitive test (delayed recall of a story). Using contemporaneous clinical records both to select participants and to confirm their retrospective self-report of past depressive episodes, Hasselbalch et al. (2013) found that, amongst participants in remission from depression, cumulative duration of past depressive episodes predicted current cognitive performance.

Where unrelenting chronic depression is associated with persistent cognitive decline, the notion of investigating temporal relationships between two distinct phenomena may lose its meaning as, instead, what is observed is a composite cognitive-affective syndrome. Where depression is episodic with periods of remission between recurrences, it may be possible to distinguish between concurrent and longitudinal associations with cognition, and to investigate temporality, if measures of cognition are available before, during and after depressive episodes. In the absence of this information, the association of recurrent or chronic depression with greater cognitive deficits is open to interpretation. The Gorwood et al. (2008) finding is frequently cited (e.g. by Ahern & Semkovska, 2017) as evidence of a scar effect (i.e. that each episode of depression causes further decline in cognitive function), without consideration of other plausible interpretations including the reverse hypothesis that

pre-existing poor cognitive function may be a risk factor for more frequent recurrences of depression. Whilst the association between poorer cognitive function and more chronic, persistent or recurrent depression appears robust, analyses which have demonstrated this association have, to date, lacked the repeated measures necessary to draw conclusions regarding temporality.

## **1.5 Summary of the literature on associations between depression and cognitive function**

### **1.5.1 What is known**

Individuals who are currently depressed (i.e. experiencing an episode of Major Depressive Disorder) have poorer cognitive function (on average) than other individuals who are not currently depressed. Greater severity of depression is associated with poorer cognitive function. (Section 1.3.1.)

Subclinical or nonspecific depressive symptoms are associated with poorer cognitive function in some circumstances (Section 1.3.2).

Individuals who have recovered from an episode of Major Depressive Disorder have poorer cognitive function (on average) than individuals who have not been depressed (Section 1.4.2). A greater number or duration of previous depressive episodes is associated with poorer cognitive function (Section 1.4.5).

Major Depressive Disorder is a risk factor for the future development of dementia. Depressive symptoms may arise as prodromal symptoms of incipient dementia (Section 1.4.3).

Amongst people who are not depressed, cognitive deficits are associated with increased risk of future depression (Section 1.4.4).

### **1.5.2 What is uncertain**

Where depression is associated with future cognitive decline, it is uncertain whether this association is fully accounted for by prodromal dementia and/or other known risk factors for dementia (Section 1.4.3).

### **1.5.3 What has not been investigated**

Studies have not compared cognitive performance during and after recovery from an episode of depression with cognitive function prior to the onset of the episode (Sections 1.3.1 and 1.4.3). It is therefore not known to what extent the cognitive deficits observed during and after an episode of depression reflect a decline from previous function.

### **1.6 Aims, objectives and research questions**

The aim of the study is to determine whether periods of elevated depressive symptoms (PEDS) are associated with cognitive decline and, if so, its temporal relationship to the PEDS. Specifically, the primary objective is to compare levels and trajectories of cognitive function within the same individuals before, during and after PEDS. Secondary objectives are to repeat these comparisons after excluding the potential contributions of prodromal symptoms of dementia, and of the persistence of subclinical depressive symptoms after PEDS. We also aim to evaluate the extent to which these comparisons differ by age of observation and/or age of onset of PEDS.

Because the largest available sources of the data required for this analysis (i.e. data obtained from participants followed up from a nondepressed starting point) are longitudinal cohort studies of participants sampled from the general population, we conduct the research in a general population sample. The study investigates PEDS rather than clinical depressive episodes because, in general population studies, data on depression are usually collected by means of questionnaires rather than clinical diagnostic assessment.

The research questions are:

In a representative general population sample, is age-adjusted cognitive function during, and after recovery from, a PEDS poorer than age-adjusted cognitive function within the same individuals before the start of the PEDS?

If so, does this difference remain evident after excluding the contributions of prodromal symptoms of dementia, and of persistent post-episode depressive symptoms?

Do the answers to the above questions vary by age of observation and/or by age of onset of PEDS?

### **1.7 Structure of the thesis**

Section 2, General Methods, presents the rationale for selecting the source of the data used for the study, namely the Health and Retirement Study, describes its features, and identifies the variables selected from the study for the project.

Section 3 presents descriptive and exploratory analyses of the data, including characteristics of the sample, features of the cognitive data, features of the depression data, associations of cognition and depression with relevant covariates, and cross-sectional associations between cognition and depression.

Section 4 presents analyses of longitudinal trajectories of cognition in participants followed up from a nondepressed baseline into PEDS and subsequent remission.

Finally, the findings and their implications are discussed in section 5.

## Chapter 2: General Methods

### 2.1 Data source

Data from the Health and Retirement Study (HRS) was used for the analyses. HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan (<https://hrs.isr.umich.edu>). It is a longitudinal study of United States household residents over the age of 50 and their co-habiting partners.

HRS was chosen because it is a general population study with repeated concurrent measures of depression and cognitive function. General population cohorts (unlike follow-up studies of depressed patients) have the potential to include some observations of individuals prior to their first depressive episode. Searches of catalogues of cohort studies including Maelstrom ([www.maelstrom-research.org](http://www.maelstrom-research.org)) and The Cohort and Longitudinal Studies Enhancement Resources (CLOSER) consortium ([www.closer.ac.uk](http://www.closer.ac.uk)) revealed that measures of cognitive function were rare and infrequent in younger adult cohorts, but more frequently available in some cohorts of individuals aged 50 and over. Amongst studies with repeated concurrent measures of depression and cognition, HRS had the largest sample and the longest follow-up period.

HRS used a multi-stage household sampling procedure with intentional oversampling of ethnic minority participants to recruit participants aged 50 years and over in 1992, with periodic further recruitment to maintain a full age-range from 50 upwards at subsequent timepoints, and followed them up every two years (Sonnega et al., 2014; Fisher & Ryan, 2018). Each data collection timepoint is referred to as a 'wave', beginning with wave 1 in 1992. Consistent repeated measures of depression have been taken since 1994, and consistent repeated measures of cognition have been taken concurrently with the depression measures since 1996 (see sections 2.2 and 2.3). Co-habiting partners of participants were recruited irrespective of their age, thus resulting in the inclusion of some participants aged under 50. Over 40,000 individuals have participated in study at least once, and most of these have participated on six or more occasions over a period of ten or more years.

Each participant's first interview was conducted face-to-face in the participant's home. Until 2004, follow-up interviews were conducted by telephone, except for

participants aged over 80 who were always offered face-to-face interviews. Since 2006, HRS has adopted an alternating pattern of face-to-face and telephone interviews for each participant (except for those over 80 for whom all interviews are conducted face-to-face). During each telephone interview the participant is asked a wide range of questions about their health and socioeconomic circumstances, and a cognitive battery (described in section 2.3) is administered. During the face-to-face interview, the same questions are asked and several physical measures and samples for biomarker analysis are also taken.

HRS data are available in a format cleaned and longitudinally collated by the RAND research organisation ([www.rand.org](http://www.rand.org)). The 2020(V1) version of the RAND longitudinal dataset was used for this thesis. This dataset included most data up to 2020 but cognitive data only up to 2016. All relevant data available in this dataset were used, including cognitive data collected between 1996 and 2016 and other data collected between 1992 and 2020. (Some of the cognitive data scheduled for collection in 2016 were collected late, up to 2018. These were used in the analyses.) One measure of depression, a short form of the World Health Organization's Composite International Diagnostic Interview (CIDI: Robins et al., 1988), was not included in the RAND collated dataset, and was the only item which was instead obtained directly from the original HRS data.

## **2.2 Depression data in HRS**

The consistently repeated measure of depression in HRS is an abbreviated version of the Center for Epidemiological Studies Depression scale (CES-D). The original full CES-D scale (Radloff, 1977) is one of the most widely used scales in epidemiological research into depression in the general population (Vilagut et al., 2016). It consists of 20 items, for each of which the respondent is asked to indicate 'how often you have felt this way during the past week', with four response options ranging from 'Rarely (less than one day)' to 'Most or all of the time (5-7 days)'. Responses are scored 0 to 3, thus yielding a total score between 0 and 60. A score of 16 is conventionally used as an indicator of probable depressive disorder (Weissmann et al., 1977; Beekman et al., 1997) although a recent meta-analysis (Vilagut et al., 2016) provided support for a higher cut-point of 20.

The abbreviated version of the CES-D scale used in the HRS from 1994 onwards (Steffick, 2000) includes eight of the original 20 items and asks the respondent to respond yes or no to a statement beginning ‘Much of the time during the past week, you...’, for example: ‘Much of the time during the past week, you felt depressed. Would you say yes or no?’ Each item is scored either 0 or 1, thus yielding a total score between 0 and 8. The eight items are:

- you felt depressed
- you felt everything you did was an effort
- your sleep was restless
- you were happy (reverse-scored)
- you felt lonely
- you enjoyed life (reverse-scored)
- you felt sad
- you could not get going

Throughout this thesis, the above measure of depression is referred to as CES-D8.

Steffick (2000) and colleagues cross-referenced HRS participants' CES-D8 responses in 1994 with the same participants' responses on a different version of CES-D administered in 1992 in which a subset of items from the full (20-item) version was used. In turn, using data from another study in which the full CES-D was administered (the National Longitudinal Survey of Mature Women <https://www.nlsinfo.org/content/cohorts/mature-and-young-women>), they derived correspondences between the 1992 version and the full CES-D. Through this two-step process they concluded that a cut-point of 4 or higher on the CES-D8 corresponded to the conventional cut-point of 16 or higher on the full 20-item CES-D scale.

The CES-D8 was administered at every visit. In addition, a short form of the CIDI (Robins et al., 1988) was administered at each participant's first visit from 1996 onwards, and at every visit from 2008 onwards. The short form (CIDI-SF) follows the diagnostic criteria for major depressive episode specified in the third edition (revised) of the DSM (DSM-III-R: APA, 1987) and is designed to establish whether the

participant has met diagnostic criteria for a depressive episode at any point in the past year. The interview begins with two screening questions to determine whether the participant has experienced either low mood or anhedonia persistently for any period of two weeks in the past year. If the participant denies both, no further questions are asked. If either is answered yes, the CIDI-SF continues with questions about other depressive symptoms. The measure indicates the presence or absence of a depressive episode within the past year, without specifying whether the episode is still present at the time of assessment. The CIDI-SF was not included in the RAND longitudinal dataset, and was the only data item which was obtained directly from the original HRS dataset for the current thesis.

Alongside the above, participants were asked at every assessment whether a doctor had ever told them they had psychiatric problems and, if yes, whether they were currently receiving treatment for those problems.

### **2.3 Cognitive function data in HRS**

Cognition was assessed objectively at each wave using a version of the Telephone Interview for Cognitive Status (TICS: Brandt, Spencer & Folstein, 1988; Plassman et al., 1994). Originally intended as a screening test to aid the detection of dementia, the TICS (and various modified versions collectively referred to as TICS-M) also has psychometric properties suitable for its use as a continuous measure of cognitive function amongst older people without dementia (De Jager, Budge & Clarke, 2003).

The version of the TICS used in HRS (Crimmins et al., 2011) includes recall of a list of words, subtraction and counting backwards, orientation, and naming to description. The verbal recall and subtraction/backwards counting items were administered at every assessment. The orientation and naming questions were asked at participants' first assessment and then at each visit over the age of 65.

The HRS cognitive assessment also included a vocabulary test (not included in the TICS).

Each of the above components is discussed further below. Other cognitive tests were administered only at limited numbers of timepoints or to a small sample of participants, and are not discussed here.

### **2.3.1 Word-list recall**

TICS-M includes a list of ten words which are read to the participant who is then asked to recall the words immediately, and again after a five-minute delay. In the first two waves of HRS (1992, and 1993-4), a list of 20 words was used instead. The standard ten-word format was used from 1996 onwards.

The utility of TICS-M as a continuous measure in people without dementia is due largely to the word-list recall component, which yields an approximately normal distribution of scores amongst the general older population and avoids the ceiling effect observed in other dementia screening tests (whereby a test is easy for individuals without significant impairment and thus fails to discriminate between them: De Jager et al., 2003).

The ability to learn and recall a list of words is an example of episodic memory (Baddeley, 2001). Episodic memory impairments are prominent in many cases of dementia, particularly dementia due to Alzheimer's disease, and word list recall tasks are commonly used in the diagnosis and differential diagnosis of dementia (Aretouli & Brandt, 2010). Amongst older people without dementia, a meta-analysis (Bäckman et al., 2005) identified several types of cognitive deficit which predict subsequent development of dementia due to Alzheimer's disease, including deficits in episodic memory. A more recent study (Boraxbekk et al., 2015) suggested that episodic memory deficits are not specifically associated with risk of Alzheimer's dementia but also predict subsequent development of vascular dementia.

Kriesche et al.'s (2023) systematic review and meta-analysis of cognitive deficits in depression concluded that a wide range of deficits, including verbal episodic memory deficits (which were assessed by means of word-list recall tasks in many of the original studies included in the analysis), may be observed during and (to a lesser extent) after recovery from a depressive episode.

### **2.3.2 Subtraction and backwards counting items**

The HRS cognitive assessment includes the TICS 'serial sevens' task (which also forms part of the widely used Mini Mental State Examination (MMSE): Folstein,

Folstein & McHugh 1975). The participant is asked to subtract 7 from 100 and to continue subtracting 7 from the answer for a further four iterations, with one point awarded for each correct response (hence yielding scores between 0 and 5). Participants are also asked to count backwards from 20, and are awarded two points if this is completed without error at the first attempt, or one point if completed correctly on a second attempt.

Counting and subtraction tasks do not correspond clearly to a specific cognitive domain. They have been variously described as tests of attention, concentration and/or working memory (Bristow et al., 2016). Serial sevens may not be a pure test of these functions, as performance has been reported to be determined primarily by basic arithmetical skill rather than by concentration, cognitive impairment or psychopathology (Karzmark, 2000). Findings based on this task may therefore be open to interpretation. Nevertheless, whilst better numeracy skills have been suggested to be a potential protective factor against the development of depression in later life (Fastame et al., 2019), acquired mathematical deficits associated with ageing or cognitive impairment are commonly considered to reflect deficits in attentional or executive function rather than a decline in basic arithmetical ability (Cappelletti et al, 2014; Benavides-Varela et al., 2015). Depression has been reported to be associated with poorer performance on tests of attention, whereas findings regarding working memory are heterogeneous (Hammar & Årdal, 2009; Lee et al., 2012). Investigations of arithmetical skills in depression are rare (Nelson & Shankman, 2016) and deficits in this domain have not, to date, been identified in systematic reviews or meta-analyses of cognitive function in depression. Thus if depression is found to be associated with longitudinal changes in serial sevens performance, this may be likely to represent changes in attention and not necessarily in arithmetical ability.

### **2.3.3 Orientation and Object Naming**

At their first interview (regardless of age) and at all interviews when aged 65 or older, participants were asked two object naming questions, 'What do you usually use to cut paper?' and 'What do you call the kind of prickly plant that grows in the desert?', and orientation questions comprising the date (including month, day, year,

and day of the week) and the names of the current President and Vice-President of the United States. Disorientation in time is associated with dementia and other neurological cognitive impairments but rare amongst cognitively unimpaired individuals (Ryan et al., 2015). Neither disorientation nor naming deficits are identified in systematic reviews of cognitive deficits associated with depression (e.g. Kriesche et al., 2023).

### **2.3.4 Vocabulary**

At their first interview (regardless of age) and at all interviews when aged 65 or older, participants were asked to define five words (gaining a score from 0 to 5). This test was an adaptation of the Vocabulary subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R: Wechsler, 1981). The vocabulary subtest is one of four WAIS-R tests considered to be resistant to neurological or psychological impairment (Bright & van der Linde, 2020). According to this rationale, if vocabulary deficits were found to be cross-sectionally associated with depression, this may be more likely to represent a long-term deficit rather than a consequence of the depression, whilst a decline in vocabulary performance over time or in association with depression would be an unexpected finding. In fact, Kriesche's (2023) systematic review identified only one study of cognitive function in depression in which a vocabulary test was administered (Bhardwaj et al., 2010) and its purpose in that study was to obtain an estimate of premorbid ability rather than to measure change.

### **2.4 Time and age variables**

Assessments were scheduled every two years, but the actual interval between assessments was sometimes longer or shorter than this. The participant's age was recorded at each assessment, thus enabling a calculation of the time between assessments. The participant's year of birth was also available.

### **2.5 Other data available in HRS**

The core survey completed at every visit covers a broad range of topics. Participants are asked about their education and employment history, financial

circumstances, retirement, health status (including self-report of medical diagnoses), height and weight, physical functioning, disability, and demographic and family characteristics.

From 1998 until 2008, the questions about medical diagnoses included ‘Has a doctor ever told you that you have a memory-related disease?’ From 2010 onwards this question was replaced by two separate questions: ‘Has a doctor ever told you that you have Alzheimer’s disease?’ and ‘Has a doctor ever told you that you have dementia, senility or any other serious memory impairment?’

Since 2006, additional measures (not used in the current study) have been taken at face-to-face interviews, including biometrics (height, weight, blood pressure), physical performance measures (e.g. grip strength), and blood spots to test for cholesterol, C-reactive protein and blood sugar). A subsample provided salivary samples for genotyping to derive summary polygenic scores for a range of phenotypes, including depressive symptoms, major depressive disorder, Alzheimer’s disease, and general cognition.

## **2.6 Selection of HRS data for the study**

Within the HRS, consistent repeated measures of depression were collected from wave 2 (1993-94) to wave 15 (2020), and consistent, repeated, cleaned cognitive performance data were available from 1996 until 2016. The depression measure used throughout the current thesis is the CES-D8. The CIDI-SF and responses to self-report questions are also used for secondary purposes. The cognitive measures selected are the ten-word list immediate and delayed recall, the counting and subtraction items, and the orientation and naming test, administered between 1996 and 2016.

For other covariates, the following (all self-reported by the participant) were selected for inclusion in the analysis of relationships between depression and cognitive function:

- Age
- Sex
- Years of education completed

- History of memory disorder, Alzheimer's disease or dementia
- History of psychiatric disorder
- History of vascular health conditions, specifically high blood pressure, diabetes, heart disease, and stroke
- Smoking status, coded as current, past, never or missing.
- BMI (derived from participants' self-reported height at their first HRS assessment and their self-reported weight at every assessment)
- Alcohol consumption, self-reported as the average number of days per week when alcohol was consumed and the average number of alcoholic drinks consumed on each of those days. For the purposes of this thesis, the number of drinks per drinking day was capped at 12 and multiplied by the number of drinking days per week, resulting in a figure from 0 to 84.

For history of health conditions, missing data was minimized at source by 'pre-loading' from the previous assessment during data collection: the interviewer presented the participant's previous answer to the participant, asked whether it was still true, and presumed it to be so unless updated or disputed by the participant.

For history of memory disorders, dementia or Alzheimer's disease, different wordings of the question were used at different timepoints (so each item was missing at observations when a different wording was used instead). For the purposes of the current thesis, the three different wordings of the question were combined into a single variable, coded as 'Yes' if a positive response to any of the three items was present, or 'No' if at least one negative and no positive response was present, or 'missing' if none of the three was present.

No imputed values were used in the current thesis. The decision not to use imputation was made because of the high level of data completeness. The potential implications of this decision are considered in the discussion and interpretation of results.

## 2.7 Derived variables

The raw measures of cognitive performance and depression were used to derive variables constructed for the purpose of this thesis.

### 2.7.1 Composite measures of cognitive performance

The different cognitive measures (immediate and delayed word-list recall, subtraction and backwards counting, and orientation and naming) were observed to be inter-related and show similar patterns of association with depression and other measures. (Details are presented in section 3). In the light of these observations, and because previous research has failed to identify specific or distinctive patterns of cognitive deficit associated with depression (section 1.3.1), the separate cognitive measures were combined into a composite measure for the longitudinal analyses. The construction of the composite was implemented using a commonly-used procedure (e.g. Harrison et al., 2007; Wilson et al., 2015), whereby each cognitive test score was converted into a z-score based on the distribution of scores within a reference set of observations, and the composite score was defined as the mean of these z-scores. In applying this to the HRS data, the following steps were taken.

- Cognitive test scores obtained in 1996 of participants aged between 50 and 80 were used as the reference values.
- On the word-list recall task, the immediate and delayed recall scores were observed to be closely correlated and their sum normally distributed (section 3.2.3). The sum of the raw scores on these two related tests was converted into a z-score based on its distribution in the reference group.
- The other cognitive measures (serial sevens and backwards counting, and orientation and naming) were heavily skewed. For these measures, the percentile range associated with each value of the measure was obtained, a z-score equivalent corresponding to the midpoint of this percentile range was assigned. For example, if 60% of participants achieve the maximum possible score on a test, this score is treated as the midpoint between the 40<sup>th</sup> and 100<sup>th</sup> percentiles, i.e. the 70<sup>th</sup> percentile.

For some analyses, the composite score was the mean of three z-scores: immediate plus delayed recall, serial sevens plus backwards counting, and orientation plus naming. However, the orientation and naming measure was collected less frequently

than the other measures. Therefore the composite of the other two z-scores was also used (alongside or instead of the three-component composite), in order to include observations where the orientation and naming measure was not available.

### **2.7.2 Definitions of ‘PEDS’, ‘pre-PEDS’, ‘post-PEDS’ and ‘fully-observed PEDS’**

The primary aim of the thesis was to compare cognition before, during and after PEDS. A working definition of PEDS was constructed as follows. Using the cut-point derived by Steffick (2000), when a participant's CES-D8 score was 4 or higher the observation was classified as in a PEDS. When a participant scored 0 or 1 on the CES-D8, the observation was classified as not in a PEDS. When the score fell between these two ranges (i.e. CES-D8 scores of 2 or 3) or was missing, the previous status was presumed not to have changed, i.e. the participant's most recent preceding classification was carried forward. At any observations prior to the participant's first CES-D8 score of 0, 1 or 4 or higher, the participant's PEDS status was unclassified.

The analyses also require definition of the pre-PEDS and post-PEDS phase associated with each PEDS. For this purpose, any continuous nondepressed period (i.e. any continuous series of observations classified as not currently in a PEDS) was defined as a pre-PEDS phase where it occurred immediately before a PEDS, and as a post-PEDS phase where it occurred immediately after a PEDS. It was possible for participants to have multiple PEDS, with nondepressed observations in between. In longitudinal analyses, each such observation was assigned to the post-PEDS phase of the preceding PEDS and also to the pre-PEDS phase of the following PEDS.

Participants were classified as having ‘no observed depression’ if they had at least three CES-D8 measures of depression, had no observed PEDS based on the CES-D8 definition or depressive episodes according to the CIDI-SF, and never self-reported any psychiatric history. In analyses comparing cognition before and after PEDS, participants with no observed PEDS were included but the reference group was the pre-PEDS observations of the participants with PEDS. To compare pre- and post-PEDS measures within the same group of participants, PEDS were included only if cognitive measures were available in both the pre-PEDS and post-PEDS phases (referred to hereafter as ‘fully observed’ PEDS).

Participants for whom depression was measured fewer than three times, or whose depression scores were indeterminate (i.e. CES-D8 scores of 2 or 3) at every observation, were unclassified. These participants' depression status was missing at all observations.

## **2.8 Accounting for age in the analyses**

### **2.8.1 Cross-sectional analyses**

Chapter 3 (Descriptive and exploratory analyses) presents cross-sectional analyses which do not estimate intra-individual change across multiple observations. These include analyses of concurrent associations (for example, associations between measures of depression and cognitive performance at the time of the observation), as well as associations with data which were retrospectively ascertained via current recall (for example, the CIDI-SF depression measure). They also include comparisons of data collected at different time points: for example, comparing levels of depression amongst participants classified according to whether or not they eventually report a diagnosis of dementia at a later observation.

In these analyses, relationships with age are reported by conducting regression analyses with age group as a factor variable, then deriving the marginal value of the dependent variable at each age group. Where participants contribute repeated measures to these analyses, a multilevel regression model is used, with participant identifier as the class variable. Different age groups include different individuals, and the results presented are derived from comparisons between different participants within the same age group.

### **2.8.2 Longitudinal analyses**

In the cross-sectional analyses (presented in section 3), nonlinear associations of cognitive function with age were observed. To model the shape of the association, the age-group factor was reclassified into ten-year age groups and included alongside its interaction with a continuous variable representing the year within the age group (from 0 to 9). This successfully modelled the nonlinear association (Figure 3.13) and was thereafter used to adjust for age in the longitudinal analyses.

## 2.9 Age inclusion criteria

All analyses presented in this thesis include observations of participants aged 45 to 94 and exclude observations outside this age range. This age range was chosen for the following reasons. The chosen method for accounting for nonlinear associations of cognition with ageing involves stratifying participants into ten-year age groups. Because some assessments are repeated only from age 65 upwards, some analyses will be necessarily restricted to over-65s, so age 65 was designated as a stratification point. Consequently, the ten-year age strata run from mid-decade (e.g. 65 to 74). Observations in the age strata below 45 and over 94 are much rarer than those between these ages, and it is likely that observations in these outer age strata might be unrepresentative of the overall sample. Younger participants were selected through a different mechanism (as partners of target participants rather than as target participants in their own right) whilst older participants are increasingly likely to be affected by survivor bias. Observations at ages below 45 and over 94 were therefore excluded from all analyses.

In the following specific circumstances, data from observations at ages outside this age range were used to classify participants or observations. For the primary analyses, participants were required to have at least three CES-D8 depression measures, and this count may include instances which fall outside the age range. Furthermore, when classifying depression status (section 2.7.2), participants are classified as having no observed depression only if no depression is observed at any point within or outside the included age range. Where a participant's depression status cannot be inferred at the current observation (because their depression score at that observation is either at an indeterminate value or missing), the depression status from the preceding observation is carried forward, and that preceding observation may have occurred below the age of 45. Finally, for some analyses individuals were classified according to whether they report dementia at a later observation. For this purpose all self-reports of dementia were used, including those over the age of 94.

## Chapter 3: Descriptive and exploratory analyses

Data summaries and analyses to evaluate the suitability of the dataset for the study and plan the primary analyses are presented below. These include descriptions of the size and characteristics of the sample and the duration of follow up (section 3.1), and the availability and frequency of measures of depression (section 3.2), cognition (section 3.3) and potential confounders. This information was used to inform the selection of variables to be used in the primary analyses, to plan their modelling in the analyses, and to provide context for the interpretation of the results.

Two specific sources of potential confounding identified in the research question were the potential for depression to arise in the prodromal period before a diagnosis of dementia, and the potential for cognitive deficits to be attributable to subclinical depressive symptoms. The former is considered in the course of sections 3.2 and 3.3. To evaluate the latter, cross-sectional associations between concurrent measures of depression and cognition were evaluated (section 3.4).

Conclusions and implications for the planning of the longitudinal analyses are considered in section 3.5.

### 3.1 Characteristics of the sample

At assessment waves scheduled from 1996 to 2016, 37,662 participants completed at least one measure of cognition between the ages of 45 and 94, and at least one CES-D8 measure of depression (at any age). Because some assessments took place earlier or later than scheduled, assessment dates ranged from 1993 to 2018. Participants joined and left the study at different points, with additional recruitment every six years from 1998 (Table 3.1). Overall, 53% of the participants left the study during this period, with 47% remaining in follow-up beyond the end of the period.

Participants were observed between one and eleven times, with a mean of 5.6 (median 5) observations. Lower levels of depression, and better cognition, were associated with more frequent observation (Figures 3.1 and 3.2).

Participants were predominantly of White ethnicity (72%) and female (57%). They were born between 1900 and 1972 with an average age of 60 years at first observation, and had attended twelve years of education on average (Table 3.2).

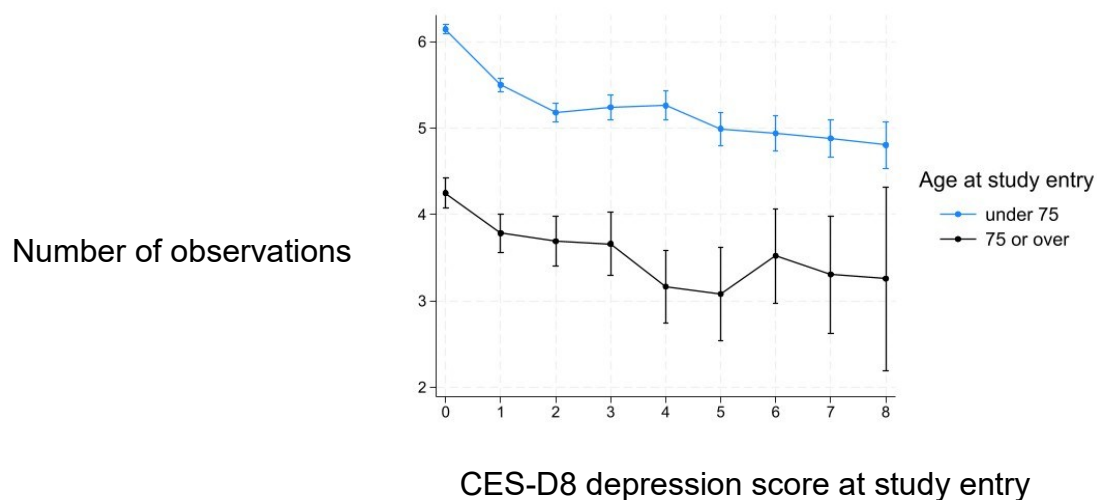
Higher rates of psychiatric history were observed amongst women, and higher rates of heart disease and past smoking amongst men.

**Table 3.1:** Numbers of participants in the HRS cohort by first and last scheduled<sup>1</sup> participation year

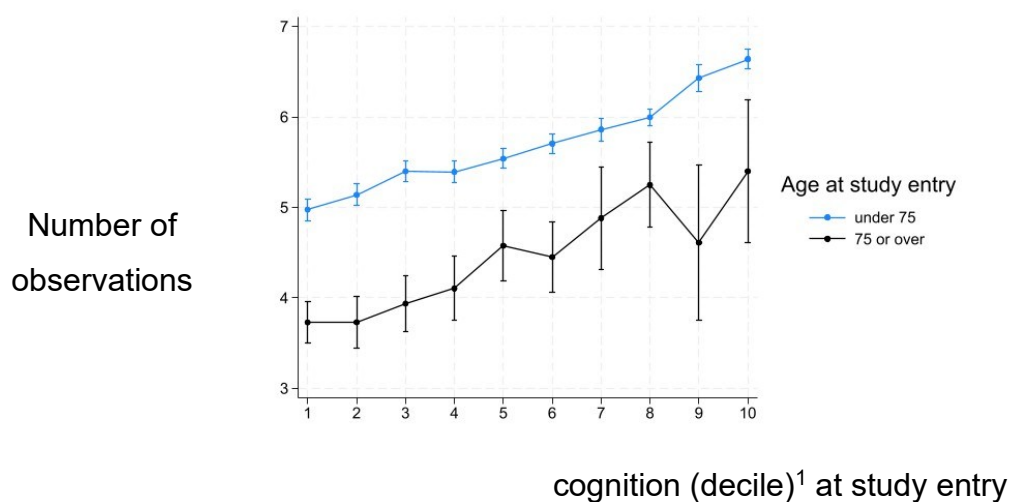
|                      |             | Final observation |             |             |             |             |             |             |             |             |             |             |              | Total        |
|----------------------|-------------|-------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|--------------|--------------|
|                      |             | 1996              | 1998        | 2000        | 2002        | 2004        | 2006        | 2008        | 2010        | 2012        | 2014        | 2016        | Later        |              |
| First<br>observation | Before 1993 | 518               | 507         | 544         | 427         | 475         | 497         | 669         | 578         | 724         | 855         | 915         | 4363         | <b>11072</b> |
|                      | 1993/4      | 743               | 794         | 797         | 686         | 638         | 585         | 600         | 367         | 299         | 300         | 206         | 294          | <b>6309</b>  |
|                      | 1996        | 8                 | 11          | 15          | 9           | 12          | 12          | 17          | 13          | 17          | 21          | 24          | 49           | <b>208</b>   |
|                      | 1998        |                   | 254         | 267         | 243         | 246         | 260         | 301         | 263         | 367         | 415         | 399         | 1926         | <b>4941</b>  |
|                      | 2000        |                   |             | 23          | 8           | 11          | 12          | 10          | 22          | 16          | 21          | 13          | 93           | <b>229</b>   |
|                      | 2002        |                   |             |             | 9           | 9           | 8           | 10          | 12          | 17          | 18          | 23          | 100          | <b>206</b>   |
|                      | 2004        |                   |             |             |             | 164         | 114         | 138         | 150         | 141         | 215         | 264         | 2190         | <b>3376</b>  |
|                      | 2006        |                   |             |             |             |             | 7           | 10          | 13          | 16          | 19          | 15          | 112          | <b>192</b>   |
|                      | 2008        |                   |             |             |             |             |             | 7           | 4           | 9           | 16          | 11          | 87           | <b>134</b>   |
|                      | 2010        |                   |             |             |             |             |             |             | 289         | 323         | 409         | 589         | 4659         | <b>6269</b>  |
|                      | 2012        |                   |             |             |             |             |             |             |             | 31          | 29          | 34          | 194          | <b>288</b>   |
|                      | 2014        |                   |             |             |             |             |             |             |             |             | 14          | 28          | 111          | <b>153</b>   |
|                      | 2016        |                   |             |             |             |             |             |             |             |             |             | 613         | 3672         | <b>4285</b>  |
| <b>Total</b>         |             | <b>1269</b>       | <b>1566</b> | <b>1646</b> | <b>1382</b> | <b>1555</b> | <b>1495</b> | <b>1762</b> | <b>1711</b> | <b>1960</b> | <b>2332</b> | <b>3134</b> | <b>17850</b> | <b>37662</b> |

<sup>1</sup>Participants who attended earlier or later than the scheduled year are counted in the scheduled (not actual) year of attendance.

**Figure 3.1:** Average number of observations per participant (with 95% CI) by CES-D8 depression score at study entry



**Figure 3.2:** Average number of observations per participant (with 95% CI) by cognition at study entry



<sup>1</sup>Decile of two-component cognitive composite at first observation

**Table 3.2:** Participants' characteristics at study entry<sup>1</sup>

Figures are stratified by sex, and expressed as percentage of the sex-specific subsample or as mean (standard deviation); median [range]

|                       | Female                                             | Male                                              |
|-----------------------|----------------------------------------------------|---------------------------------------------------|
| n                     | 21,388                                             | 16,274                                            |
| Total 37,662          | (57% of sample)                                    | (43% of sample)                                   |
| Ethnic group:         |                                                    |                                                   |
| White                 | 72%                                                | 73%                                               |
| Black                 | 20%                                                | 18%                                               |
| Other                 | 8%                                                 | 9%                                                |
| Missing               | 0.2%                                               | 0.3%                                              |
| Age (years)           |                                                    |                                                   |
|                       | Mean 60.1 (s.d. 10.6);<br>Median 56 [45 to 94]     | Mean 60.6 (s.d. 9.6);<br>Median 57 [45 to 94]     |
| Decade of birth:      |                                                    |                                                   |
| Pre-1920              | 11%                                                | 9%                                                |
| 1920s                 | 14%                                                | 15%                                               |
| 1930s                 | 20%                                                | 23%                                               |
| 1940s                 | 19%                                                | 18%                                               |
| 1950s                 | 22%                                                | 22%                                               |
| 1960 or later         | 15%                                                | 14%                                               |
| Education (yrs):      |                                                    |                                                   |
| <9                    | 12%                                                | 13%                                               |
| 9 to 11               | 14%                                                | 12%                                               |
| 12                    | 33%                                                | 29%                                               |
| 13 to 15              | 23%                                                | 22%                                               |
| >15                   | 19%                                                | 24%                                               |
| Missing               | 0.3%                                               | 0.4%                                              |
| Body Mass Index (BMI) |                                                    |                                                   |
|                       | Mean 27.9 (s.d. 6.5);<br>Median 26.6 [9.7 to 75.5] | Mean 27.9 (s.d. 5.0);<br>Median 27.2 [10.8 to 65] |

|                                               | Female                                             | Male                                               |
|-----------------------------------------------|----------------------------------------------------|----------------------------------------------------|
| Smoking status:                               |                                                    |                                                    |
| Current                                       | 19%                                                | 22%                                                |
| Past                                          | 30%                                                | 46%                                                |
| Never                                         | 51%                                                | 31%                                                |
| Missing                                       | 0.5%                                               | 0.7%                                               |
| Self-reported history of: <sup>2</sup>        |                                                    |                                                    |
| Dementia or memory disorder                   | 1.4%                                               | 1.4%                                               |
| High blood pressure                           | 41%                                                | 42%                                                |
| Diabetes                                      | 13%                                                | 15%                                                |
| Heart disease                                 | 13%                                                | 18%                                                |
| Stroke                                        | 4.5%                                               | 5.3%                                               |
| Psychiatric disorder                          | 14%                                                | 9%                                                 |
| Measures of depression:                       |                                                    |                                                    |
| CES-D8 depressive symptoms                    | Mean 1.7 (s.d. 2.1);<br>Median 1 [0 to 8]          | Mean 1.3 (s.d. 1.9);<br>Median 1 [0 to 8]          |
| CIDI-SF: Depression in past year <sup>2</sup> | 10%                                                | 6%                                                 |
| Measures of cognition:                        |                                                    |                                                    |
| Immediate recall                              | Mean 5.8 (s.d. 1.7);<br>Median 6 [0 to 10]         | Mean 5.3 (s.d. 1.7);<br>Median 5 [0 to 10]         |
| Delayed recall                                | Mean 4.7 (s.d. 2.1);<br>Median 5 [0 to 10]         | Mean 4.2 (s.d. 2.0);<br>Median 4 [0 to 10]         |
| Serial sevens and counting backwards          | Mean 5.2 (s.d. 1.9);<br>Median 6 [0 to 7]          | Mean 5.6 (s.d. 1.7);<br>Median 6 [0 to 7]          |
| Orientation and naming                        | Mean 7.3 (s.d. 1.0);<br>Median 8 [0 to 8]          | Mean 7.3 (s.d. 1.0);<br>Median 8 [0 to 8]          |
| Derived cognitive composites:                 |                                                    |                                                    |
| Two-component composite                       | Mean -.07 (s.d. .77 );<br>Median .02 [-2.5 to 1.7] | Mean -.10 (s.d. .72);<br>Median -.05 [-2.5 to 1.7] |
| Three-component composite                     | Mean -.08 (s.d. .66);<br>Median .03 [-2.5 to 1.3]  | Mean -.09 (s.d. .63);<br>Median -.00 [-2.5 to 1.3] |

<sup>1</sup>Participant's first HRS observation since 1996 at age 45 or older or, where missing at that observation, at the first subsequent instance when the characteristic was recorded.

<sup>2</sup>Disorder presumed absent if data were missing at every observation for memory disorder (3.2% of females and 3.6% of males) and CIDI-SF depression classification (14% of females and 12% of males). For all other disorders, data completeness was 100%.

## **3.2 Features of the depression data**

### **3.2.1 Availability and completeness of measures of depression**

CES-D8 data were available at 94% (196,062) of all (209,616) observations.

Participants completed the CES-D8 on an average of 5.2 occasions (sd 3.4, median 4, range 1 to 11), with 75% of women and 69% of men completing the measure on at least three occasions.

The CIDI-SF diagnostic checklist for depression was completed at least once by 32,662 participants (87%). The CIDI-SF was readministered regularly from 2008 onwards, and was completed in 95% of observations from 2008 to 2016.

Participants completed the CIDI-SF on an average of 3.0 occasions (sd 2.2, median 3, range 0 to 7) between 1996 and 2016, with 55% of women and 50% of men completing the measure on at least three occasions. At 99% of CIDI-SF administrations, a concurrent CES-D8 measure was available.

### **3.2.2 Features of depressive episodes and PEDS**

Of the 37,662 participants, 14,077 (37%) had a CES-D8 score of 4 or higher on at least one occasion, and were thus classed as depressed according to the operational definition of PEDS previously described (section 2.7.2). PEDS were fully observed from pre- to post-PEDS in 4,076 participants (29% of all individuals with depression). Of these, 3,580 (88%) had one fully observed PEDS, 460 (11%) had two such PEDS, 35 (1%) had three and one participant had four fully observed PEDS, amounting to 4,609 fully observed PEDS in total.

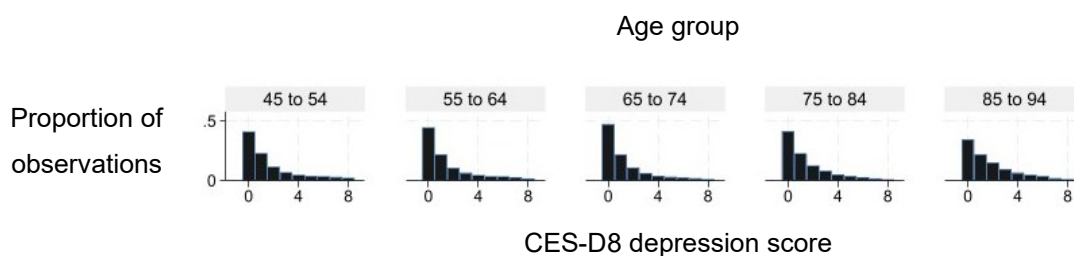
In 2,788 (60%) of the fully observed PEDS, the duration of the PEDS was a single observation wave (i.e. after becoming depressed, the participant was no longer depressed at the next wave). In 824 cases (18%) the participant was depressed at successive observations spanning a period of up to two years. For 735 participants (16%) this period spanned three to six years, and for the remaining 262 (6%) the period was seven or more years.

On the CIDI-SF diagnostic checklist, 5,670 participants (15%) were classified as depressed on at least one occasion. For 1,851 (33%) of these, nondepressed observations were available both before and after the depression. Of the latter, 79 were observed to develop and recover from a second instance of depression as classified by the CIDI-SF. Of all 1,930 fully observed periods of depression based on the CIDI-SF classification, 1,629 (84%) lasted for a single observation, 12% spanned two consecutive observations, and 3% spanned three or four observations.

### 3.2.3 Distributions and inter-relationships of the depression variables

At all ages, the distribution of the CES-D8 depression score was skewed with between one-third and one-half of participants scoring zero (Figure 3.3).

**Figure 3.3:** Distributions of CES-D8 depression scores by age group



On the CIDI-SF measure, participants were classified as depressed (i.e. as having been depressed within the past year) at 8% of all assessments. In 15% of all instances when the CIDI-SF classified participants as not depressed, the participant was classified as depressed according to the operational definition based on the CES-D8. Thus relative to the CIDI-SF, the CES-D8 definition resulted in false positive classifications. False negative misclassification relative to CIDI-SF could be

evaluated, because some individuals classified as depressed by the CIDI-SF may have recovered by the time of the assessment (in which case a low CES-D8 score would not be a misclassification).

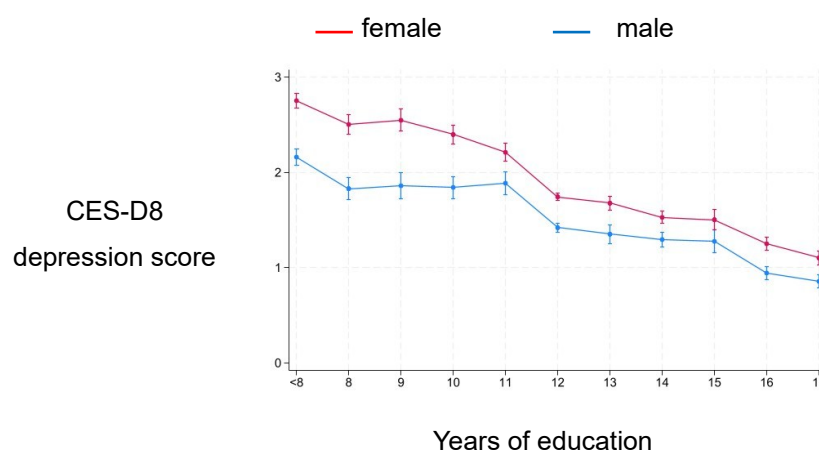
### 3.2.4 Sex differences in the depression variables

Levels of CES-D8 depressive symptoms were higher in women than in men (mean difference 0.39, 95%CI 0.35 to 0.42,  $p < .001$ , based on multilevel regression of CES-D8 depression score by sex with observations grouped by participant, unadjusted for other covariates). On the CIDI-SF, women were almost twice as likely as men (9.9% vs 5.4%) to be classified as having been depressed in the past year.

### 3.2.5 Associations of depression with years of education

Higher levels of education were associated with lower levels of CES-D8 depressive symptoms (Figure 3.4), and with lower likelihood of being classified as depressed according to the CIDI-SF diagnostic interview (logistic regression stratified by sex, unadjusted: odds ratio per year of education = 0.96 (95%CI 0.95 to 0.97) amongst males, 0.95 (95%CI 0.95 to 0.96) amongst females).

**Figure 3.4:** Average CES-D8 depression score (with 95% CI) by years of education

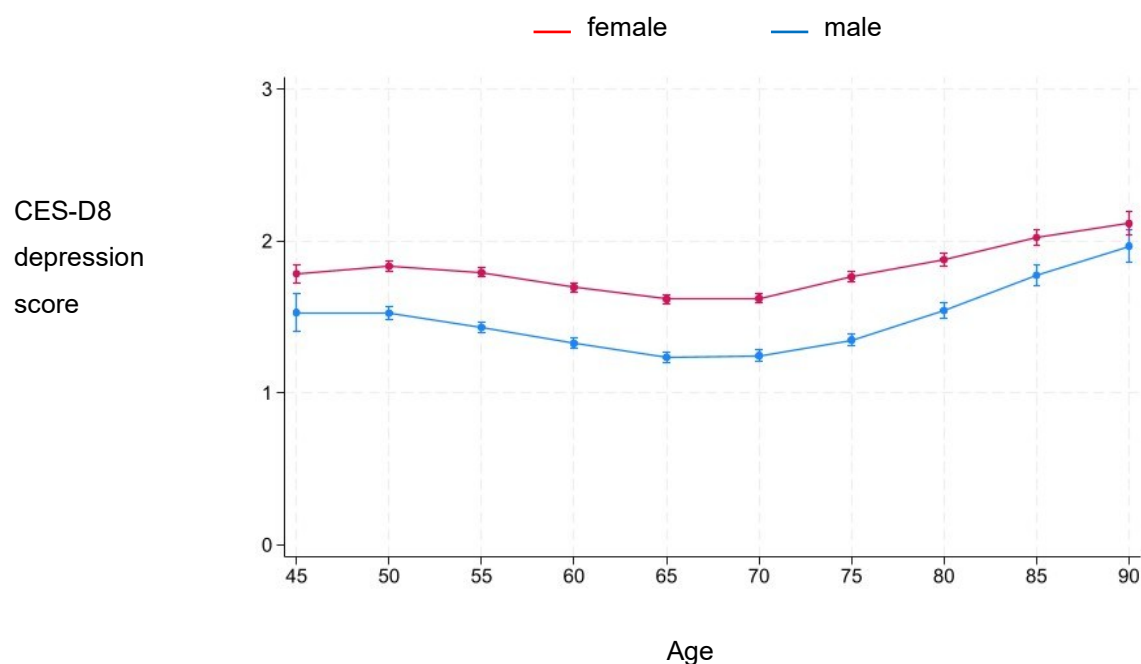


Marginal values derived from multilevel regression of CES-D8 depression score on years of education (with observations grouped by participant, unadjusted for other covariates).

### 3.2.6 Associations of depression with age

On the CES-D8 depression scale, the lowest levels of depressive symptoms were found amongst participants aged 65 to 70, with slightly higher levels at younger ages and increasing levels at older ages (Figure 3.5). Based on CIDI-SF, rates of depression were lower amongst older participants. This may have been partly due to cohort effects as, within each age group, later-born cohorts tended to have higher rates of CIDI-SF depression (Table 3.3).

**Figure 3.5:** Average CES-D8 depression score (with 95% CI) by age group



Marginal values of CES-D8 depression measure by age, stratified by sex and adjusted for years of education, based on multilevel analysis (grouped by participant) of data from all observations.

**Table 3.3:** Proportions (with 95% CIs) of participants classified as depressed at their first CIDI-SF assessment, by age group and birth decade

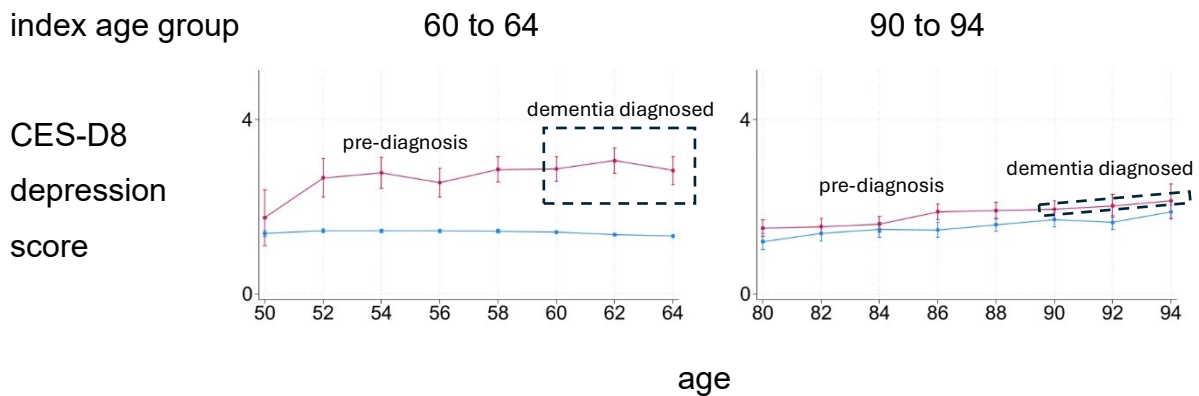
| Age      | Decade of birth  |                  |                  |                     |                     |                     |
|----------|------------------|------------------|------------------|---------------------|---------------------|---------------------|
|          | pre-1920         | 1920s            | 1930s            | 1940s               | 1950s               | 1960 or later       |
| 45 to 54 |                  |                  |                  | 10%<br>(9% to 11%)  | 13%<br>(12% to 14%) | 14%<br>(13% to 15%) |
| 55 to 64 |                  |                  | 7%<br>(6% to 7%) | 11%<br>(10% to 12%) | 13%<br>(12% to 14%) | 12%<br>(10% to 13%) |
| 65 to 74 |                  | 4%<br>(3% to 5%) | 6%<br>(4% to 7%) | 6%<br>(4% to 9%)    | 7%<br>(0% to 13%)   |                     |
| 75 to 84 | 2%<br>(0% to 7%) | 4%<br>(3% to 6%) | 4%<br>(1% to 6%) | 6%<br>(0% to 17%)   |                     |                     |
| 85 to 94 | 2%<br>(1% to 4%) | 3%<br>(2% to 4%) |                  |                     |                     |                     |

### 3.2.7 Associations of depression with dementia

Exploratory analyses (illustrated at two example age groups in Figure 3.6) suggested that diagnosis of dementia (ascertained through participant self-report of a doctor's diagnosis) was preceded by increased levels of depressive symptoms, most prominently amongst individuals diagnosed at younger ages. The time between the increase in depressive symptoms and the eventual diagnosis of dementia appeared broadly consistent with previous reports of a twelve-year prodromal period (Singh-Manoux et al., 2017).

**Figure 3.6:** Trajectories of average CES-D8 depression scores (with 95%CI) by eventual dementia status at 60 to 64 and 90 to 94

\_\_\_\_\_ participants who first reported a diagnosis within the index age group  
 \_\_\_\_\_ participants who remained diagnosis-free throughout the index age-group



Marginal values in each group, at each two-year age bracket

### 3.2.8 Associations of depression with other variables

At study entry, CES-D8 depression scores were higher amongst participants with histories of high blood pressure, diabetes, heart disease or stroke, and amongst current smokers, than amongst those without the characteristic (Table 3.4). CES-D8 score at study entry was significantly correlated with BMI ( $r=0.10$ ,  $p<.001$ ). Correlation with the measure of alcohol consumption was nonsignificant ( $r=-.01$ ,  $p=.14$ ).

**Table 3.4:** Average difference (in standard deviation units) in CES-D8 depression score at study entry associated with the presence of health conditions and smoking status

|                                   | Difference (in SD units) in CES-D8 score |
|-----------------------------------|------------------------------------------|
| Self-reported history of:         | (SD=2.02) <sup>1</sup>                   |
| high blood pressure               | .24 (.22 to .26)**                       |
| Diabetes                          | .34 (.31 to .36)**                       |
| heart disease                     | .32 (.29 to .35)**                       |
| Stroke                            | .46 (.42 to .51)**                       |
| Smoking (ref=never):              |                                          |
| Past                              | .00 (-.02 to .03)                        |
| Current                           | .33 (.31 to .36)**                       |
| Not adjusted for other covariates | **p<.001                                 |

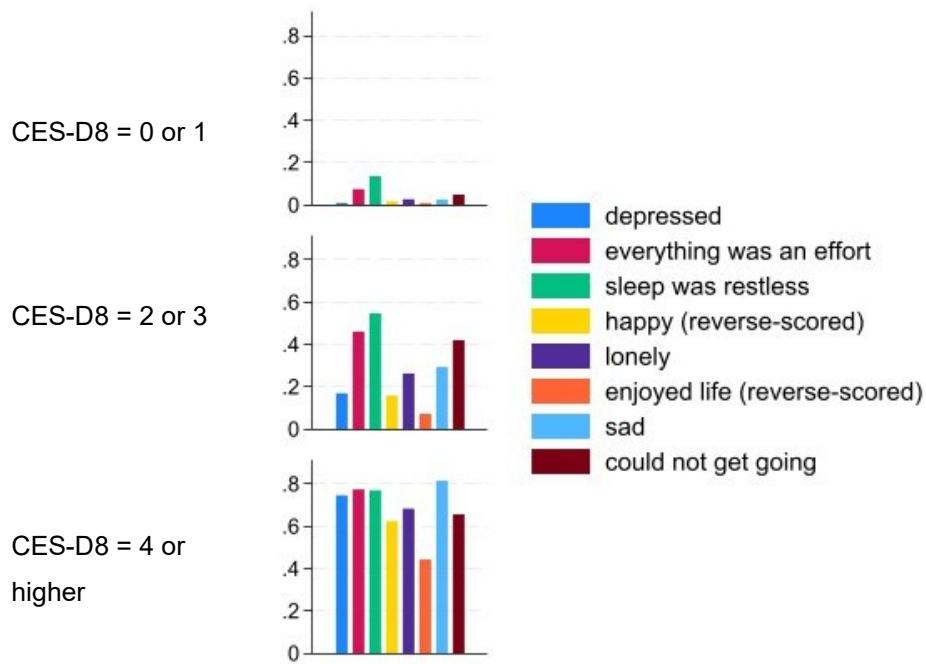
<sup>1</sup>Standard deviation of CES-D8 scores in the full sample at study entry. The figure for each condition is calculated by dividing the regression coefficient by this value.

### 3.2.9 Profiles of depressive symptoms

Amongst the individual CES-D8 items (Figure 3.7), 'sleep was restless' and 'everything was an effort' were the most frequently-endorsed items amongst individuals with low CES-D8 scores. The items 'I felt depressed' and 'I felt sad' appeared relatively more distinctive of participants with higher total scores.

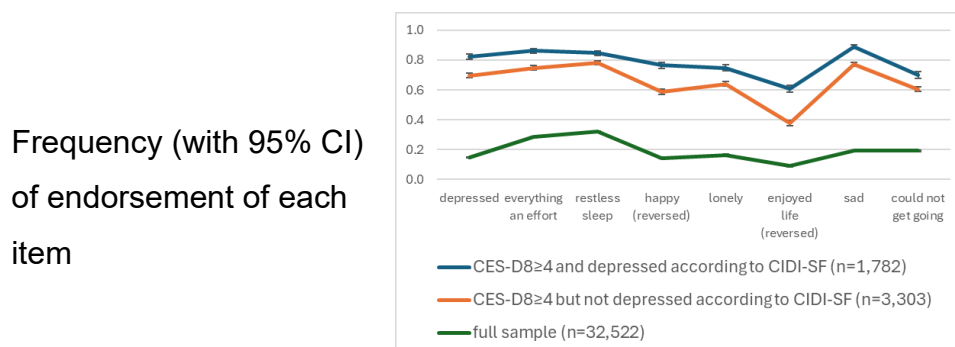
Participants with CES-D8 scores of 4 or higher (and thus classified as depressed using this measure) were often classified as nondepressed on the CIDI-SF. These discordant classifications could have arisen if some nondepressed participants' high CES-D8 scores were due primarily to nonspecific symptoms such as sleep disturbance, rather than to key symptoms of depression such as depressed mood. However, the data did not support this interpretation, as the CES-D8 symptom profile amongst these participants appeared similar to that amongst participants classified concordantly (Figure 3.8).

**Figure 3.7:** Frequency of endorsement of individual CES-D8 items, by total CES-D8 score



Proportion of all CES-D8 administrations (stratified by total CES-D8 score) in which each item was endorsed.

**Figure 3.8:** Symptom profiles amongst participants with concordant and discordant CES-D8 and CIDI-SF classifications

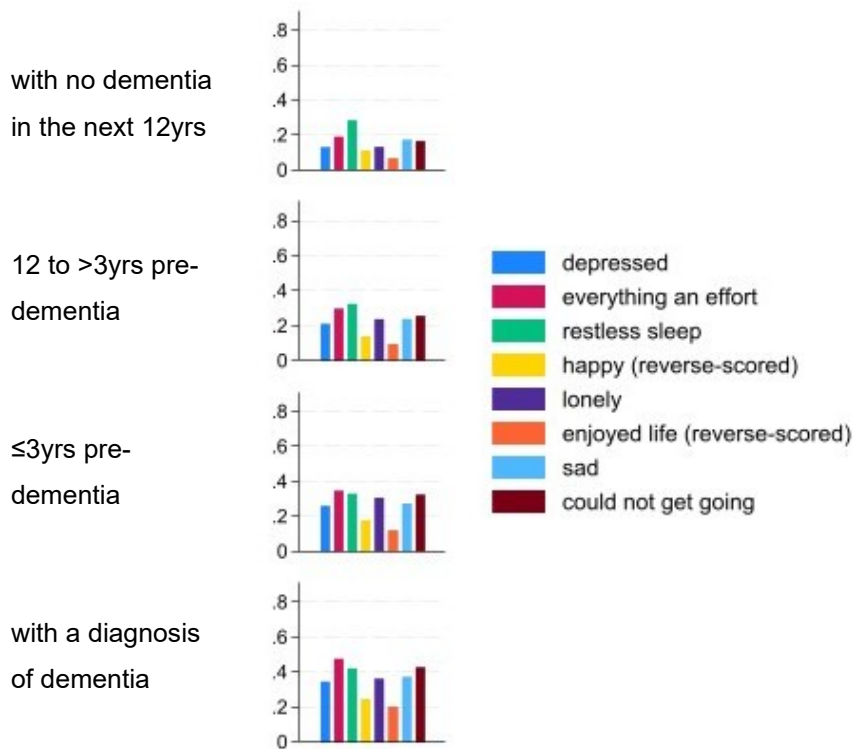


Proportions of participants endorsing each CES-D8 item at the time of their first CIDI-SF observation.

Profiles of depressive symptoms amongst individuals without, prior to, and after a diagnosis of dementia (Figure 3.9) suggested that certain depressive symptoms, in particular 'everything was an effort', may become relatively more prominent as dementia approaches.

**Figure 3.9:** Relative frequencies of individual CES-D8 depressive symptoms by proximity to dementia

Frequency of endorsement of each item, amongst participants:



### 3.3 Features of the cognitive data

#### 3.3.1 Availability and completeness of measures of cognitive performance

Tests of episodic memory (immediate and delayed recall) and working memory (serial sevens and backward counting) were usually administered at every observation between 1996 and 2016. The orientation and naming items were administered at each participant's first HRS visit and then repeated at every visit after the age of 65. Amongst all 37,662 individuals with data on cognition and depression within eligible age and date limits, full cognitive data on all tests (episodic memory, working memory and attention, and orientation and naming) were available concurrently on at least one occasion for 35,746 (95%), and on three or more

occasions for 16,326 participants (43%). Results of the episodic and working memory tests were available concurrently at 90% of all observations, on at least one occasion for 37,065 participants (98%), and on three or more occasions for 26,275 participants (70%).

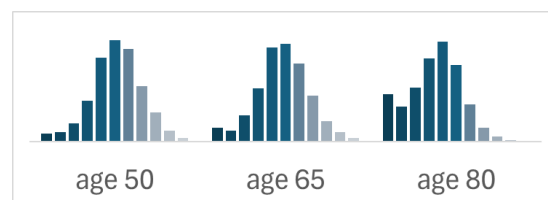
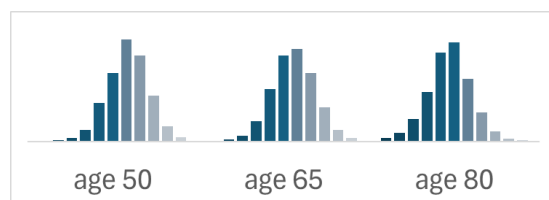
### 3.3.2 Distributions and inter-relationships of the cognitive variables

The cognitive variables differed in their distributions (illustrated below at three example ages: Figure 3.10). The distribution of immediate recall scores appeared normal. Delayed recall appeared normally distributed between 1 and 10 but, at older ages, exhibited a secondary peak at zero. For both working memory and orientation/naming, distributions were skewed with the modal value falling at the maximum possible score. Significant ( $p < .001$ ) correlations were observed between all pairs of cognitive test scores (Table 3.5).

**Figure 3.10:** Distributions of cognitive test scores in the full HRS sample

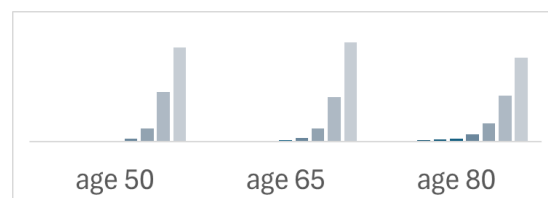
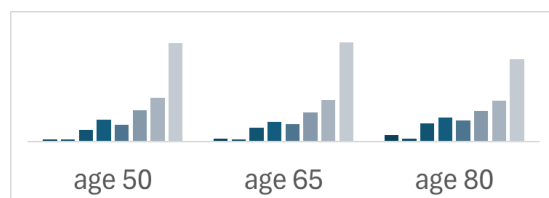
immediate recall (range 0 to 10)

delayed recall (range 0 to 10)



working memory (range 0 to 7)

orientation and naming (range 0 to 8)



**Table 3.5:** Pairwise correlation coefficients (Spearman rho) between measures of cognitive performance

|                    | immediate<br>recall | delayed<br>recall | working<br>memory |
|--------------------|---------------------|-------------------|-------------------|
| delayed recall     | 0.77                |                   |                   |
| working memory     | 0.30                | 0.30              |                   |
| orientation/naming | 0.27                | 0.26              | 0.32              |

Based on observations at age 65. For every pairwise correlation,  $p < .001$ .

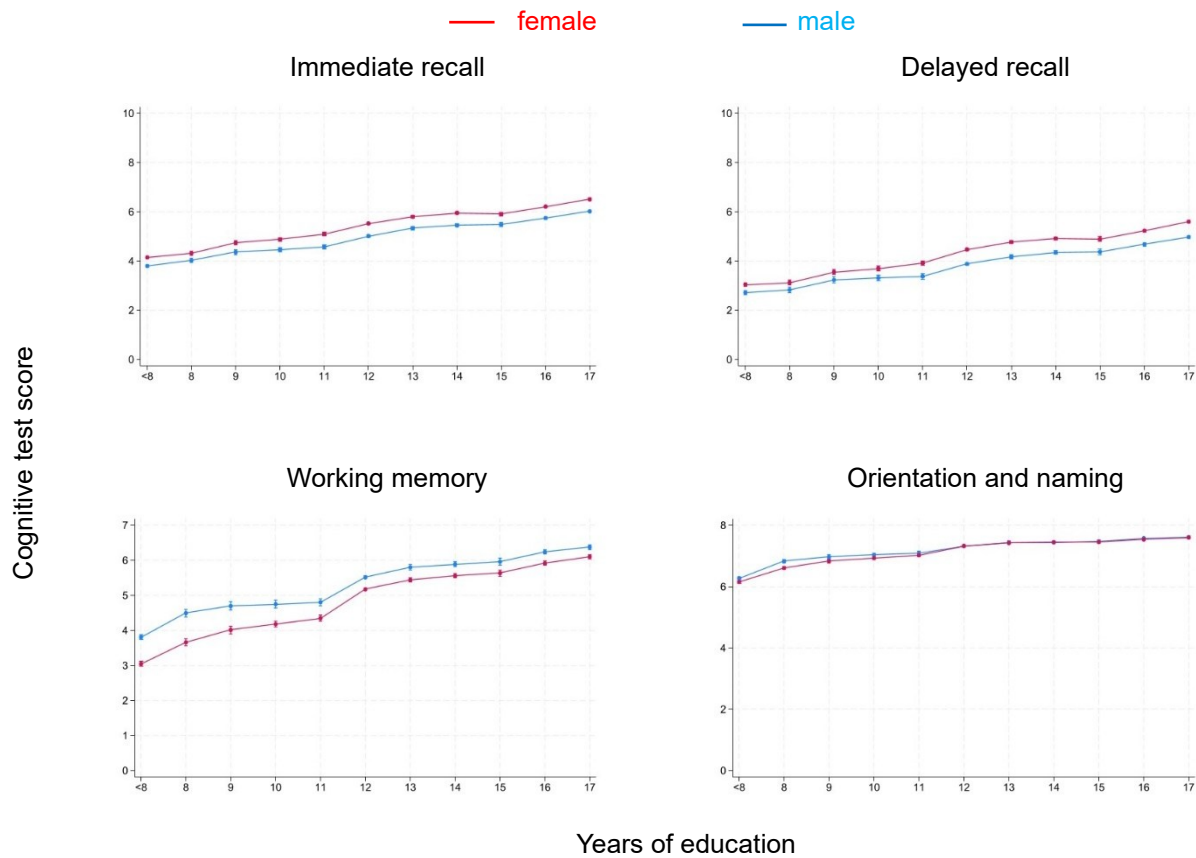
### 3.3.3 Sex differences in cognitive performance

In comparisons unadjusted for other covariates, women performed better than men on the word-list recall tests (immediate recall: mean difference .42, 95%CI .40 to .45,  $p < .001$ ; delayed recall: mean difference .48, 95%CI .45 to .52,  $p < .001$ ). Men performed better than women on working memory (mean difference .44, 95%CI .40 to .47,  $p < .001$ ) and on orientation and naming (mean difference .05, 95%CI .03 to .06,  $p < .001$ ).

### 3.3.4 Associations of cognitive performance with years of education

Relationships between education and cognitive performance appear roughly linear (Figure 3.11).

**Figure 3.11:** Average cognitive performance (with 95% CIs) by sex and years of education

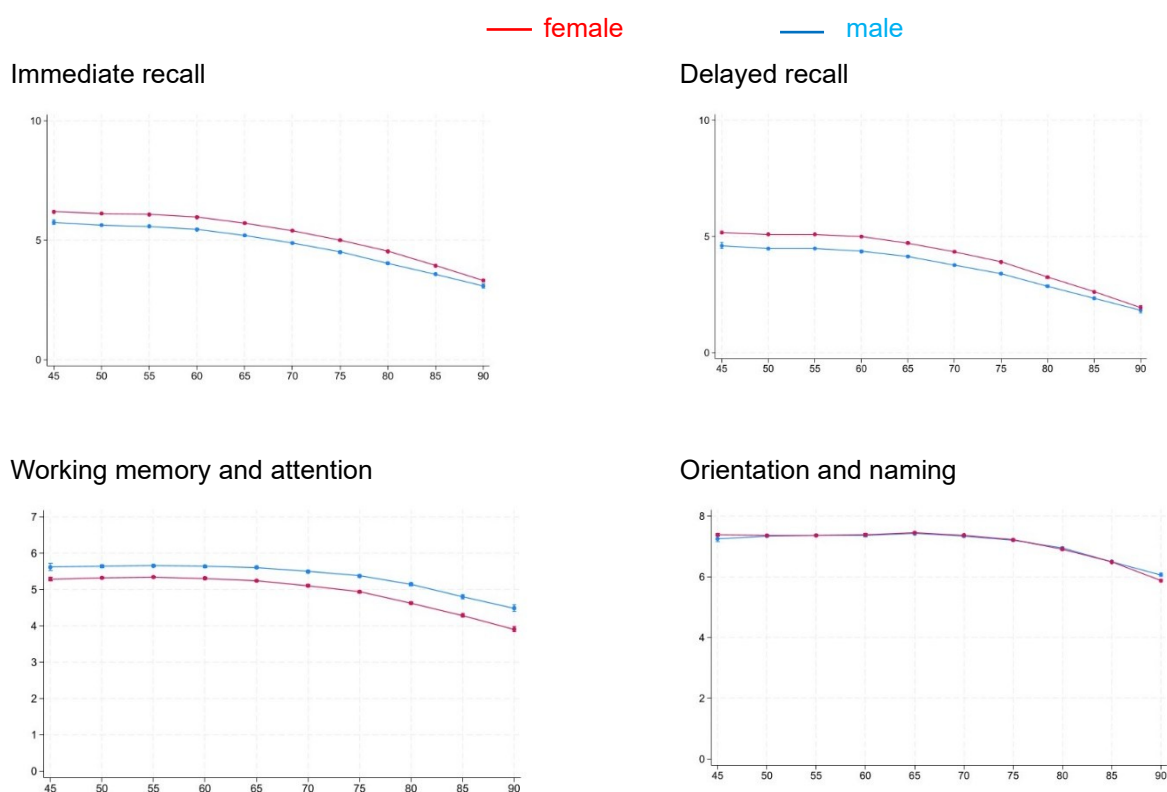


Marginal values derived from multilevel regression of cognitive performance by years of education, stratified by sex, unadjusted for other covariates

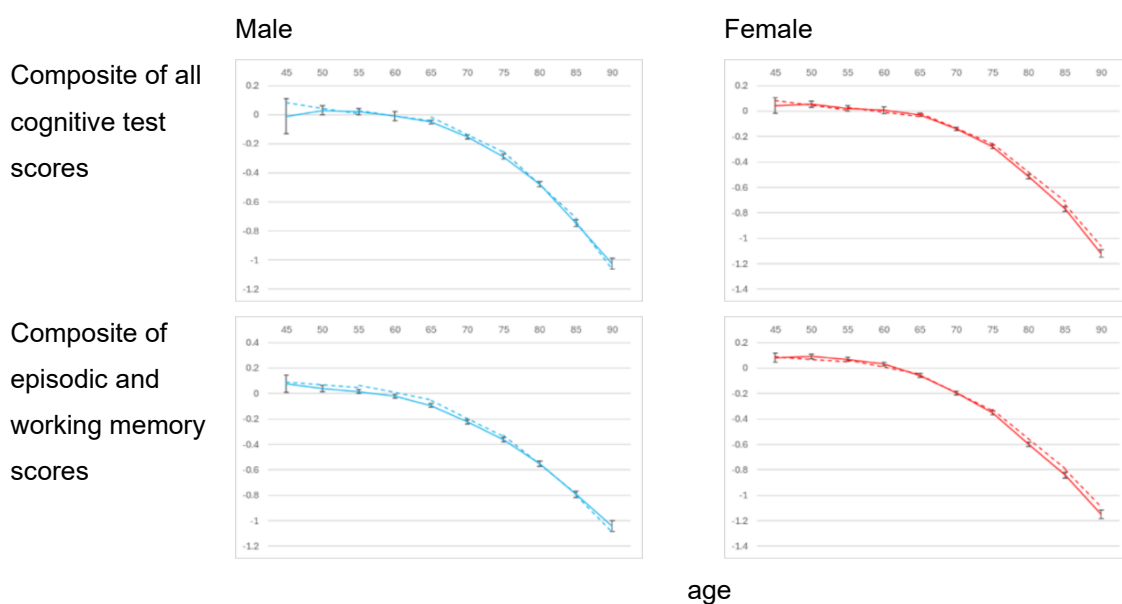
### 3.3.5 Associations of cognitive performance with age

In general, the relationship between cognition and age was monotonically negative, with steeper slopes at older ages (Figure 3.12). For longitudinal analyses, cognitive composite scores (as defined in section 2.7.1) were used, and their nonlinear associations with age were modelled in discrete ten-year age groups with a linear slope within each age group. Observed and modelled values of the cognitive composite scores are shown in Figure 3.13.

Stratification by birth decade (Figure 3.14) suggested poorer performance amongst participants born after 1950.

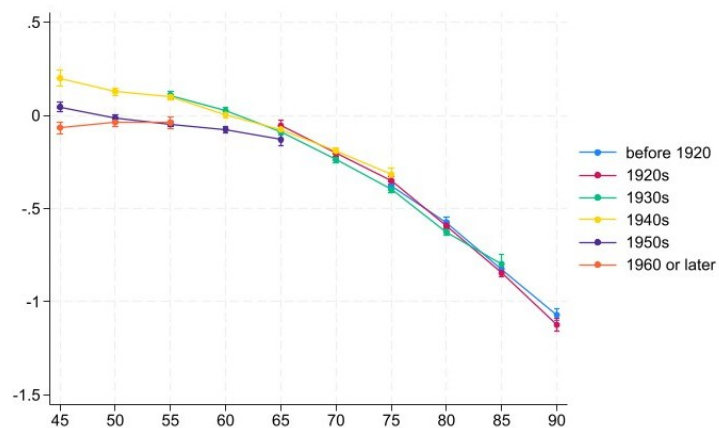
**Figure 3.12:** Average cognitive test scores (with 95% CI) by age-group

Marginal values of cognition, stratified by age and sex, based on multilevel analysis adjusted for years of education.

**Figure 3.13:** Observed and modelled average (marginal) values of cognition by age

Solid lines indicate marginal observed values, with 95% confidence intervals. Dotted lines indicate modelled values.

**Figure 3.14:** Cognitive performance<sup>1</sup> by age group, stratified by birth decade



<sup>1</sup>Marginal values of the two-component cognitive composite score

### 3.3.6 Associations of cognitive performance with self-report of diagnosis of memory disorder or dementia

On most cognitive measures, deficits and declining trajectories were evident many years before a diagnosis was reported, compared with participants who never reported such a diagnosis (Figure 3.15).

**Figure 3.15: Cognition by future dementia status**

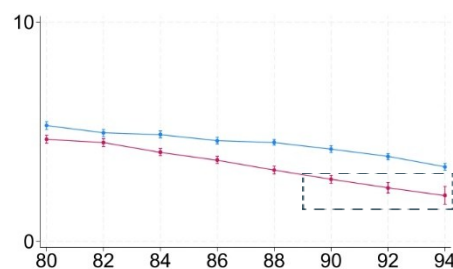
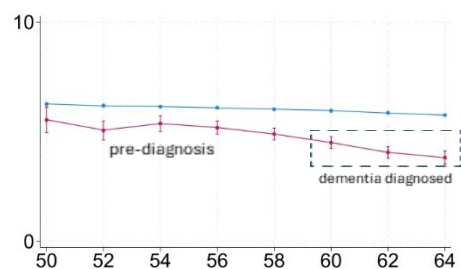
— participants who first reported a diagnosis within the index age group  
 — participants who remained diagnosis-free throughout the index age-group

index age group

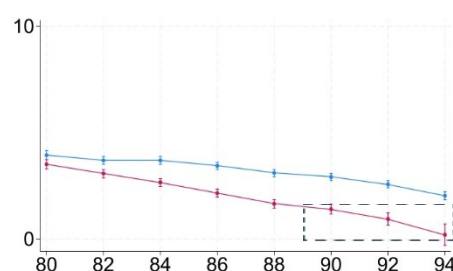
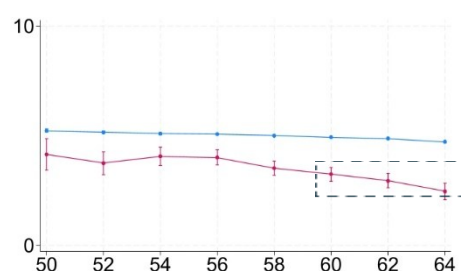
60 to 64

90 to 94

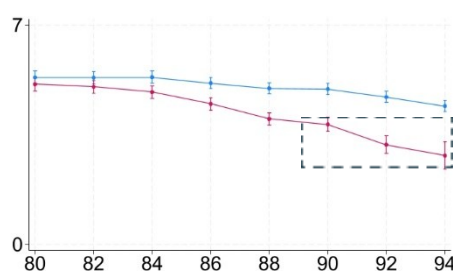
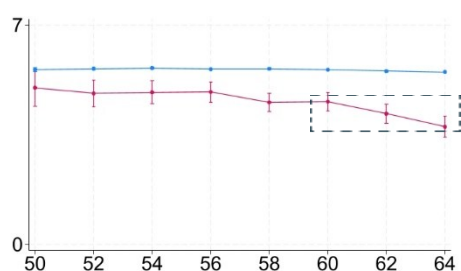
immediate  
recall



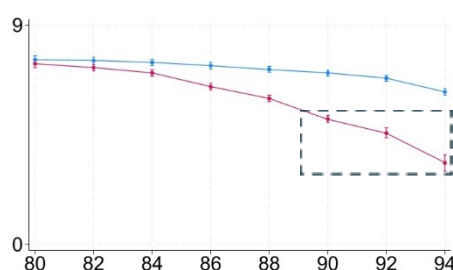
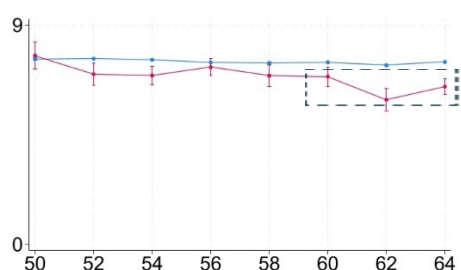
delayed recall



working  
memory



orientation and  
naming



age

Marginal values in each group, at each two-year age bracket

### 3.3.7 Associations of cognitive performance with other variables

At study entry, cognition was poorer amongst participants with histories of high blood pressure, diabetes, heart disease or stroke, and amongst current smokers, than amongst those without the characteristic (Table 3.6). Associations of cognition with BMI and alcohol consumption were small and differed across cognitive tests (Table 3.7).

**Table 3.6:** Average difference (in standard deviation units) in cognitive test scores at study entry associated with the presence of covariates

|                           | immediate recall      | delayed recall        | working memory        | orientation/naming    |
|---------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| SD <sup>1</sup>           | 1.72                  | 2.06                  | 1.84                  | 0.96                  |
| Self-reported history of: |                       |                       |                       |                       |
| hypertension              | -.21 (-.23 to -.19)** | -.22 (-.24 to -.20)** | -.21 (-.23 to -.19)** | -.14 (-.16 to -.12)** |
| diabetes                  | -.27 (-.3 to -.25)**  | -.27 (-.3 to -.24)**  | -.25 (-.28 to -.22)** | -.24 (-.27 to -.21)** |
| heart disease             | -.3 (-.33 to -.27)**  | -.29 (-.32 to -.27)** | -.1 (-.13 to -.08)**  | -.12 (-.15 to -.10)** |
| stroke                    | -.54 (-.59 to -.49)** | -.50 (-.55 to -.45)** | -.39 (-.44 to -.34)** | -.37 (-.42 to -.32)** |
| smoking (ref=never):      |                       |                       |                       |                       |
| past                      | -.05 (-.07 to -.03)** | -.07 (-.09 to -.04)** | +.08 (.06 to .10)**   | +.05 (.03 to .08)**   |
| current                   | -.08 (-.11 to -.05)** | -.07 (-.10 to -.05)** | -.12 (-.15 to -.09)** | -.10 (-.13 to -.08)** |

Unadjusted for other covariates.

\*\*p<.001

<sup>1</sup>Standard deviation of cognitive test scores in the full sample at study entry. The difference associated with each covariate is presented in SD units (i.e. the absolute difference divided by the SD). For example, on the immediate recall score, the deficit amongst participants with hypertension (compared to those without) is equivalent to 0.21 standard deviations of the distribution of immediate recall scores amongst all participants at their first assessment.

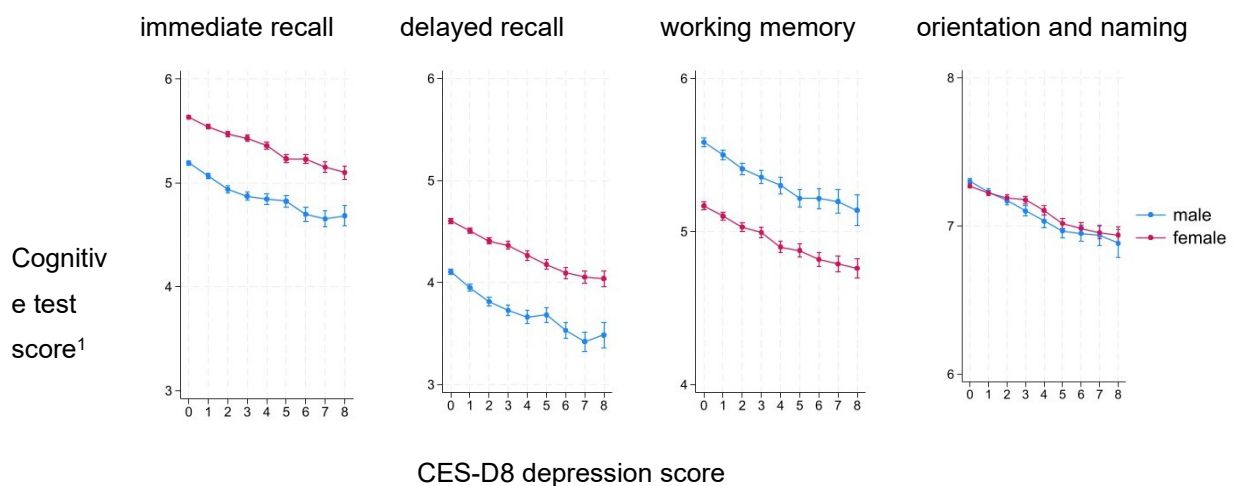
**Table 3.7:** Correlations of cognitive test scores with BMI and alcohol consumption at study entry

|                     | immediate recall         | delayed recall          | working memory           | orientation and naming    |
|---------------------|--------------------------|-------------------------|--------------------------|---------------------------|
| BMI                 | $r=+.02$<br>( $p=.001$ ) | $r=+.01$<br>( $p=.04$ ) | $r=-.03$<br>( $p<.001$ ) | $r=-.01$<br>( $p=.028$ )  |
| Alcohol consumption | $r=+.01$<br>( $p=.139$ ) | $r=.00$<br>( $p=.749$ ) | $r=+.05$<br>( $p<.001$ ) | $r=+.023$<br>( $p<.001$ ) |

### 3.4 Cross-sectional associations between concurrent measures of cognitive function and depression

On every cognitive measure, a linear negative relationship between CES-D8 score and cognition was evident (Figure 3.16).

**Figure 3.16:** Average cognitive test score (with 95% CI) at each level of CES-D8 depression score



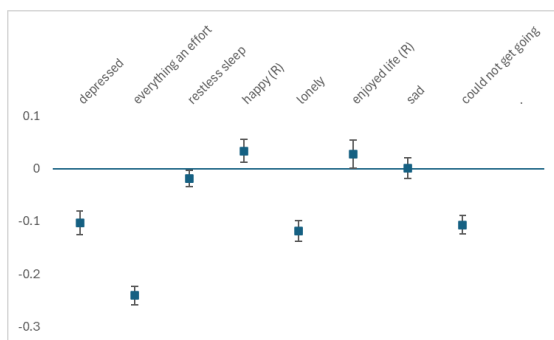
<sup>1</sup>Adjusted for age and years of education.

The association of cognition with each of the eight individual CES-D8 items was also explored, by specifying the individual item as a covariate in the regression analysis, alongside the total of the other seven items treated as a continuous variable. The coefficients of association between each CES-D8 item and each cognitive test are

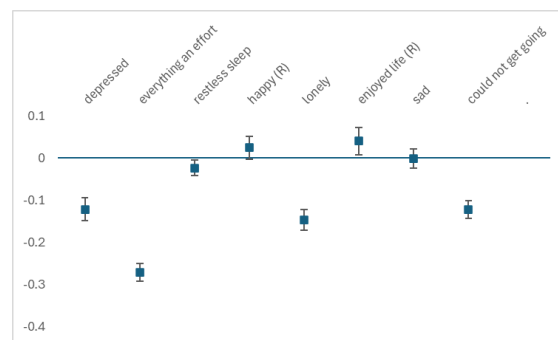
shown in Figure 3.17. The item ‘everything was an effort’ was the most strongly associated with poorer performance on all cognitive measures. The items ‘depressed’, ‘lonely’ and ‘could not get going’ were also consistently associated with poorer cognitive performance. For the remaining items, the associations were nonsignificant or in the reverse direction.

**Figure 3.17:** Average difference in cognitive test scores associated with individual CES-D8 items

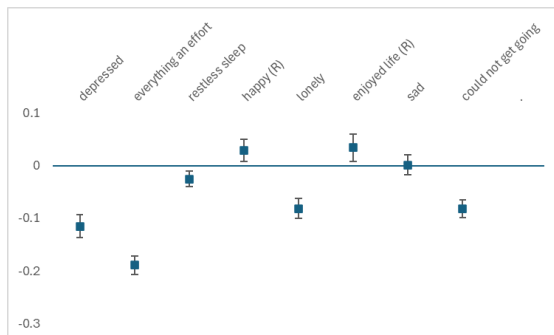
immediate recall



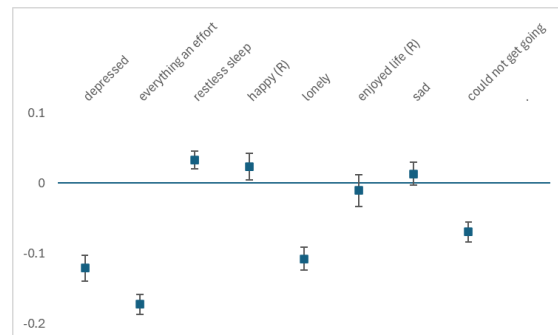
delayed recall



serial 7s and backward counting



orientation and naming



Association ( $\beta$  coefficient) of each CES-D8 depression scale item with cognitive test score in multilevel linear regression model adjusted for the total of the other CES-D8 items. Also adjusted for sex and ten-year age group. (R) indicates a reverse-scored item.

At participants' first assessment using the CIDI-SF instrument, those classified as depressed (within the past year) performed more poorly on cognitive measures than those classified as not depressed within the past year (Table 3.8). After adjustment for current CES-D8 depression score, this deficit was no longer present and, in the case of the working memory score, the association was reversed (Table 3.8).

**Table 3.8:** Associations of CIDI-SF classification at first assessment with concurrent cognitive performance

| Cognitive measure      | N total <sup>2</sup><br>(n with CIDI depression) | SD <sup>3</sup> | Cognitive deficit (in standard deviation units) associated with CIDI-SF depression classification <sup>1</sup> |                                                           |
|------------------------|--------------------------------------------------|-----------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
|                        |                                                  |                 | Adjusted for age, sex and education                                                                            | Additionally adjusted for current CES-D8 depression score |
| Immediate recall       | 32,159<br>(3,148)                                | 1.66            | -.17 (-.20 to -.13)**                                                                                          | .02 (-.02 to .05)                                         |
| Delayed recall         | 28,768<br>(3,101)                                | 2.00            | -.15 (-.19 to -.12)**                                                                                          | .03 (-.01 to .07)                                         |
| Working memory         | 28,531<br>(3,058)                                | 1.78            | -.08 (-.12 to -.05)**                                                                                          | +.12 (.08 to .16)**                                       |
| Orientation and naming | 28,709<br>(3,101)                                | 0.95            | -.16 (-.20 to -.13)**                                                                                          | .01 (-.03 to .05)                                         |

<sup>1</sup>Adjusted average difference (with 95% CI) between those classified as depressed on the CIDI-SF and those classified as not depressed, calculated by dividing the regression coefficient by the standard deviation<sup>3</sup>.

<sup>2</sup>Number of participants with complete education and CES-D8 data at first CIDI-SF assessment.

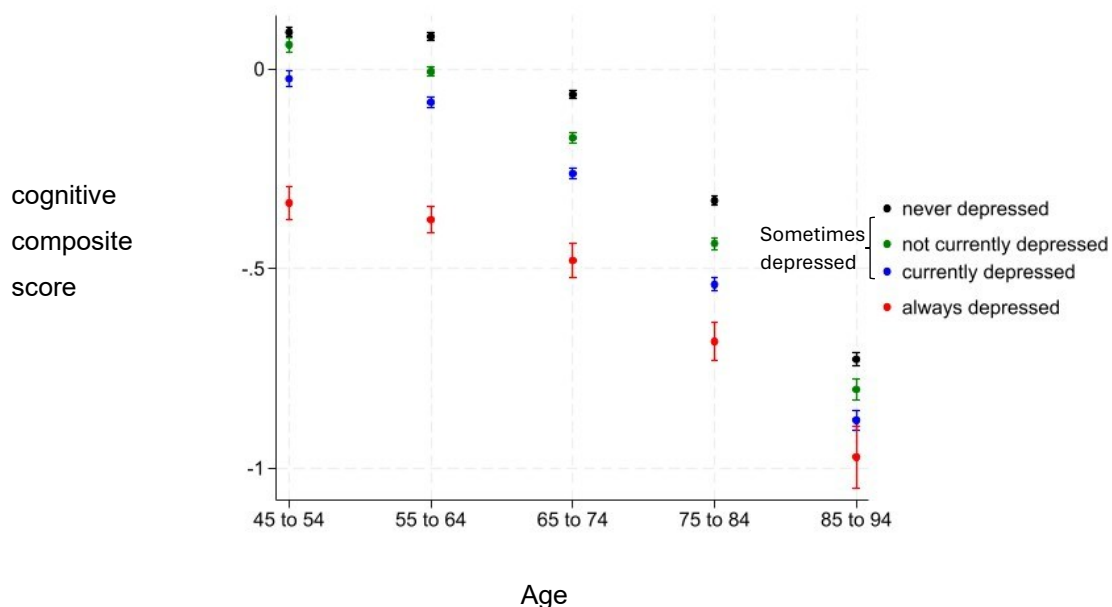
<sup>3</sup>Standard deviation of the cognitive measure at first CIDI-SF assessment amongst participants with complete education and CES-D8 data at that assessment.

\*\*p<.001

When participants were classified by observed course of depression, using the operationalised definition of PEDS previously described (General Methods, section 2.7.2), the best cognitive performance was observed amongst participants with no observed depression, and the poorest cognition was found amongst participants who were depressed at every observation (Figure 3.18). Amongst those who were

sometimes but not always depressed, cognitive performance was poorer during PEDS than when not depressed.

**Figure 3.18:** Average cognitive performance (with 95% CI) by age group and depression course



Marginal values of two-component cognitive composite (with 95% CI) at each age group by depression course, adjusted for sex and years of education.

### 3.5 Conclusions and implications for the longitudinal analyses

Based on the above, the following decisions were made for the purposes of the primary (longitudinal) analyses.

#### 3.5.1 Selection of outcome and exposure measures

Cognitive composite measures (not individual test scores) were selected as the outcome measures for the longitudinal analyses. This was on the basis that the individual cognitive measures were similar to one another with respect to their relationships with age, depression and other covariates, and because the research question included no domain-specific element requiring separate test-specific analyses.

For the evaluation of exposure, the definition of PEDS derived from the CES-D8 was selected in preference to the CIDI-SF. Because cross-sectional associations between CIDI-SF and cognition were fully explained by the concurrent CES-D8 score, the CES-D8 was considered to be the measure more directly associated with cognition. The CIDI-SF was retained as an exclusion criterion when defining a nondepressed comparison group or absence of history of depression.

### **3.5.2 Selection and modelling of covariates**

Sex was included as a covariate in all longitudinal analyses. Because the exploratory analyses did not appear to indicate that associations between depression and cognition differed by sex, analyses were not stratified by sex and did not include interactions of sex with other variables.

Education, measured in years, was related to both depression and cognition in a continuous and roughly linear manner. Accordingly, education was modelled as a continuous linear covariate in the longitudinal analyses.

With the exception of the measure of alcohol consumption, most other covariates were associated with both depression and cognition in directions likely to exaggerate the hypothesised associations (i.e. with the potential to act as positive confounders). On this basis, smoking status, BMI, and histories of high blood pressure, diabetes, heart disease and stroke were included as covariates.

### **3.5.3 Selection of variables as exclusion criteria in sensitivity analyses**

Prospective associations with dementia were observed for both depression and cognition, concordant with previous reports of a prodromal period of up to twelve years. Dementia status twelve years into the future was therefore used as a criterion for including or excluding observations in sensitivity analyses to exclude the contribution of prodromal dementia.

Subclinical symptoms, as represented by low but non-zero scores on the depression scale, were associated with poorer cognition than the complete absence of symptoms. The CES-D8 items most likely to be associated with lower cognition

(illustrated in Figure 3.17) were used as exclusion criteria in sensitivity analyses to exclude the contribution of subclinical symptoms to post-depressive cognitive deficits.

With regard to cohort effects, the descriptive analyses suggested that participants born after 1950 may differ from earlier cohorts with respect to both depression and cognitive function. As a precaution against confounding due to cohort effects, participants born after 1950 were excluded from a sensitivity analysis.

### **3.5.4 Implications for the interpretation and generalisability of the results**

The most depressed participants, and those with the poorest cognition, were expected to be underrepresented in the primary analysis. Firstly, they attended fewer follow-up assessments, and secondly, the group with poorest cognition were those who remain depressed at every observation (and for whom pre- and post-PEDS measures of cognition are therefore not available for comparison). Findings will therefore be based on participants whose depression or cognitive deficits were not severe or chronic.

## **Chapter 4: Analyses of cognitive performance before, during and after PEDS**

Cognitive function is found to be poorer both during and after depressive episodes than amongst individuals who have not been depressed (Hasselbalch et al., 2011; Bora et al., 2013; Kriesche et al., 2023), and the extent of the post-episode deficit is reported to be associated with the number or duration of previous episodes (Hasselbalch et al., 2013). A plausible but untested hypothesis is that cognition declines during each depressive episode and does not fully recover afterwards. If this is the case, it is possible that intervention at the time of the depressive episode could reduce or limit the associated cognitive decline.

However, the observed post-depressive cognitive deficits are compatible with other hypotheses. They might already have been present (or developing) before the depressive episode. They could be symptoms of incipient dementia of which the depression was a prodromal sign. They could be due to residual subclinical depressive symptoms. They might be consequences of antidepressant treatment. Furthermore, the likelihood, severity or nature of associated cognitive deficits may vary depending on age of onset of the depressive episode.

This chapter describes a series of analyses which were conducted to investigate these possibilities. The first analysis compared average levels of cognitive function before PEDS with average levels in the same individuals during and after PEDS, and amongst individuals with no observed depression. To conduct this analysis, it was necessary to identify individuals with measures of cognitive function both before and after PEDS. This analysis, and the participant selection process, are described in section 4.1.

The next analysis, described in section 4.2, used the same group of participants to compare trajectories (i.e. rates of change over time) of cognitive function before, during and after PEDS.

Sensitivity analyses were then conducted to exclude the potential contribution of prodromal symptoms of dementia to the observed association (section 4.3), and to exclude the contribution of subclinical depressive symptoms (section 4.4). Next, analyses were stratified by age of onset of the PEDS, and those occurring after the

age of 65 were further classified according to the presence or absence of prior psychiatric history. These analyses are presented in section 4.5. A combined summary of the results of all of the longitudinal analyses is presented in section 4.6.

#### **4.1 Levels of cognitive performance before, during, after and without PEDS**

##### Methods

###### *Inclusion and exclusion criteria*

Participants were included if they had no observed depression, or if they had PEDS for which cognition was measured both before and after the PEDS, using the definitions previously specified (General Methods, section 2.7.2). Participants who reported dementia at or before their first non-depressed observation were excluded.

Observations prior to the participant's first nondepressed observation and after their final nondepressed observation were not included in the analysis. For each PEDS, all associated observations (i.e. those before, during and after the PEDS) were included if (and only if) cognition was measured at least once during the pre-PEDS period and at least once during the post-PEDS period. Participants with no observed depression were included if they had measures of cognition on two or more occasions.

Participants were excluded if data on a continuously-measured covariate (education or BMI) were missing at every observation. Where they lacked data on a categorical covariate, the value of the covariate was classified as 'missing' and the participant was not excluded.

###### *Classification of depression status and epochs*

Depression status was classified as no observed depression, pre-PEDS, during PEDS or post-PEDS (as defined in section 2.7.2). Scores on the CES-D8 depression measure were used to derive these classifications, but the analysis used only the derived classifications, not the original CES-D8 scores.

The combined pre-, during and post-PEDS periods of each PEDS comprised an epoch. Participants with multiple PEDS had multiple epochs, which overlapped (with the post-episode observations of one epoch doubling as the pre-episode observations of the next epoch). Participants with no observed depression had a single epoch comprising all observations.

### *Measure of cognitive function*

Cognitive function was measured using the HRS version of the TICS cognitive assessment. The primary measure was the z-score composite of two components of the cognitive assessment (episodic memory and working memory) as described in section 2.7.1. For PEDS after the age of 65, the third cognitive component (orientation and naming) was available, and a further analysis was conducted using the full three-component z-score composite as the outcome measure.

### *Covariates*

Covariates included in the analyses were age (self-reported in whole years, rounded down), sex, years of education, BMI, smoking status, and histories of high blood pressure, diabetes, heart disease and stroke (self-reported at interview as described in section 2.5).

### *Data used for excluding participants or observations*

As per the definition in section 2.7.2, two variables were used (in addition to the absence of PEDS) to exclude participants from the group with no observed depression: the participant's self-report of any history of psychiatric disorder, and the CIDI-SF depression diagnostic checklist, at or before baseline.

Participants' self-report of a diagnosis of dementia was used to exclude participants with dementia at baseline.

### *Accounting for missing data*

No imputed values were used. Where a cognitive measure or the CES-D8 measure of depression was incomplete, its value was defined as missing. Where the CES-D8 depression score was missing, the depression status from the preceding observation was carried forward (as per the definitions in section 2.7.2). Observations with missing cognitive data did not contribute to the analysis.

Where the value of a covariate was missing at an observation, the value at the previous observation was carried forward or, if no values were available at any previous observation, the first (i.e. next) available value was used. If a categorical covariate was missing at every observation, it was classified as a 'missing' observations category, and not excluded from the analysis. Where a continuous covariate (education or BMI) was not available at any observation, the participant was excluded from the analysis.

Any self-report of dementia was carried forward to all future observations (replacing any missing or contradictory responses). These participants were presumed not to have developed dementia up to and including their last consistently negative response. If the data were missing at observations in between the last negative response and the first positive response (or at all observations before the first positive response), their dementia status at those observations was classified as missing. Participants who never reported dementia were presumed not to have dementia at any observation.

### Statistical analyses

To account for the intra-class correlation between repeated measures of the same individuals, multilevel linear regression analysis was used, with the measure of cognition as the outcome variable and the participant identifier as the class variable. The independent variable of interest was depression status, classified as no observed depression or as pre-, during or post-PEDS. The reference value of this variable was specified as the pre-PEDS value.

To account for the nonlinear association of cognition with age, age was classified into ten-year age groups (45 to 54, etc.). Age group was included in the analysis as a

factor variable alongside its interaction with a continuous variable representing the year within the age group (ranging from 0 to 9). Because of the classification into ten-year age groups, this procedure yielded a separate set of coefficients for each age group. These results were combined by deriving the marginal values of cognition before and after PEDS for the full sample (across all age ranges). A contrasts analysis was applied to these marginal values to test the statistical significance of the difference between cognition after PEDS and cognition before PEDS.

For other covariates, their values at the baseline of each epoch were included in the analysis.

Because participants born before 1950 were observed, in exploratory analyses, to differ from earlier-born cohorts in terms of age-adjusted cognitive function and on some measures of depression, a sensitivity analysis was conducted with these participants excluded in order to evaluate the possibility of confounding due to cohort effects.

History of psychiatric treatment was considered a potential confounding variable in associations between depression and cognitive function. However, data on history of psychiatric treatment were not sufficiently complete or reliable for use in sensitivity analyses. Instead, to evaluate associations amongst participants who had not received psychiatric treatment, a sensitivity analysis was restricted to participants who reported no psychiatric history (i.e. those whose responses to the question 'Has a doctor ever told you that you have any emotional, nervous or psychiatric problems?' are all negative). The rationale for this was that, amongst participants who never responded 'Yes' to this question, rates of psychiatric treatment were likely to be low. In corroboration of this it was noted that, amongst the participants for whom the data were available on at least one occasion ( $n=7,556$ ), the proportion who reported psychiatric treatment was 51% amongst those with history of psychiatric disorder and 4% amongst those without.

## Results

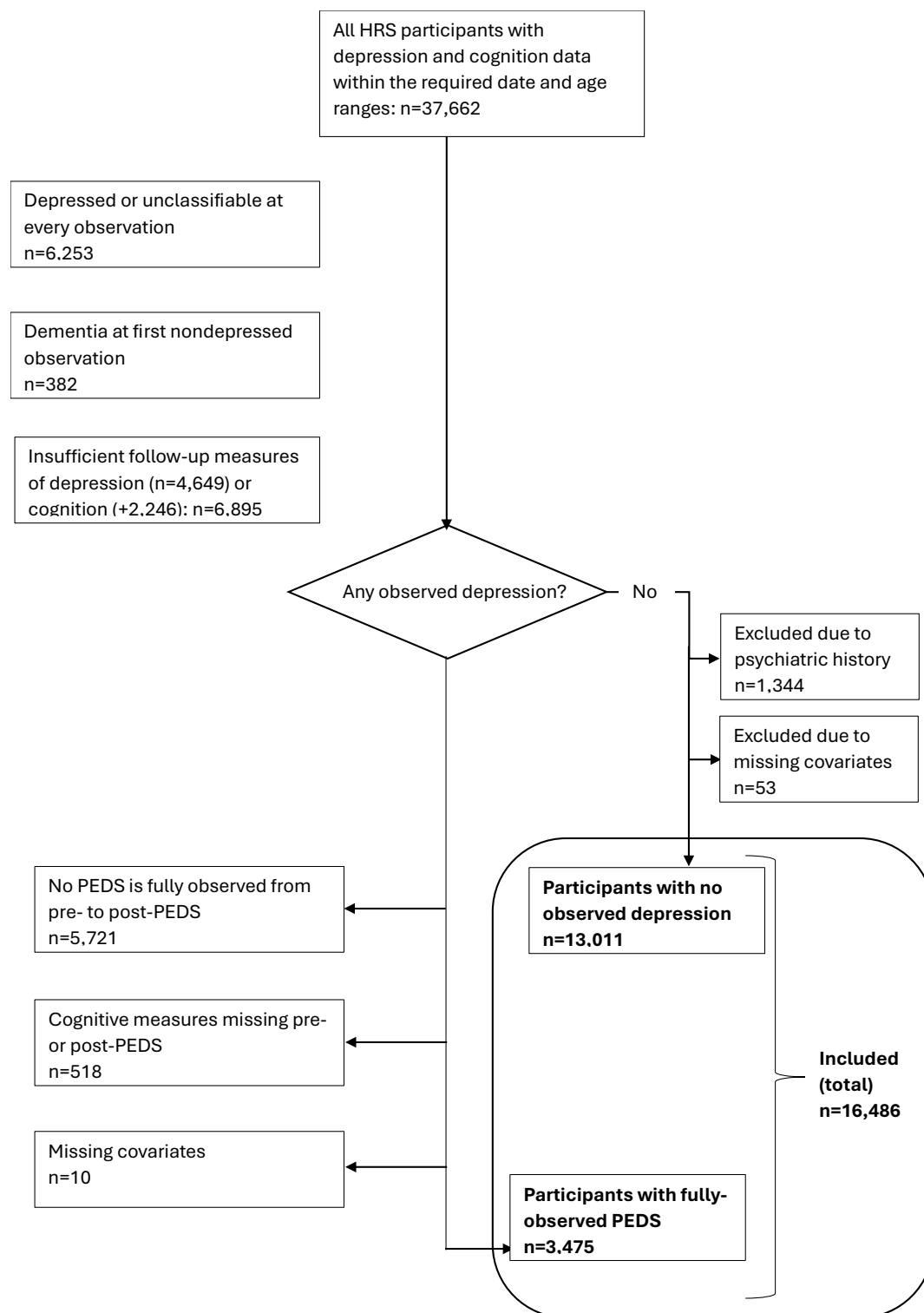
### *Participants included and excluded*

Of the original 37,662 participants, 16,486 (44%) were included in the analyses. These comprised 3,475 with PEDS and 13,011 with no observed depression. Participants who were depressed at every observation or whose PEDS were only partly observed (with observed onset but not remission or *vice versa*) constituted the majority of exclusions, and others were excluded primarily due to insufficient follow-up or missing data (Figure 4.1).

### *Participant characteristics*

On average, participants included in the analysis were followed up for 12.3 (s.d.6.0) years, during which time cognitive function was measured 6.5 (s.d. 2.9) times. Those with PEDS had longer follow-up (mean 15.0 (s.d. 4.8) years, with 7.9 (s.d. 2.5) observations of cognitive function).

At HRS study entry (defined as the participant's first HRS observation at or over the age of 45), significant differences between the included and excluded participants were observed (Table 4.1). Those included in the longitudinal analysis were more highly educated, with lower BMI, lower rates of all reported medical conditions and current smoking, fewer depressive symptoms, lower rates of recent depression according to the CIDI-SF diagnostic checklist, and better cognition. The same was true of participants with PEDS included in the analysis, compared with excluded participants with PEDS (Table 4.2). At the baseline observation of the longitudinal analysis, the included participants with PEDS were younger than those without and had somewhat lower cognitive test scores, lower levels of education, higher BMI and higher rates of current smoking (Table 4.3). Amongst the included participants, rates of medical conditions were similar amongst those with vs without PEDS. Some of the participants with depression had more than one PEDS (349 had two, 23 had three, and one had four), giving a total of 3,873 PEDS.

**Figure 4.1:** Reasons for exclusion from the longitudinal analyses

**Table 4.1:** Characteristics at study entry of the full HRS sample and those included in the longitudinal analysis

Figures are expressed as a percentage of the column or as mean (standard deviation); median [range]

|                       | Full HRS sample<br>N=37,662                     | Participants included in the longitudinal analysis<br>N=16,486 | p (excluded vs included) <sup>1</sup> |
|-----------------------|-------------------------------------------------|----------------------------------------------------------------|---------------------------------------|
| Ethnic group:         |                                                 |                                                                | <.001                                 |
| White                 | 72%                                             | 78%                                                            | ( $\chi^2(3)=593$ )                   |
| Black                 | 19%                                             | 16%                                                            |                                       |
| Other                 | 8%                                              | 5%                                                             |                                       |
| Missing               | .3%                                             | .2%                                                            |                                       |
| Sex (% female)        | 57%                                             | 54%                                                            | <.001<br>( $\chi^2(1)=107$ )          |
| Age (years)           | Mean 60.3 (s.d. 10.2);<br>Median 57 [45 to 94]  | Mean 60.3 (s.d. 9.5)<br>Median 58 [45 to 92]                   | .31<br>(t(37660)=1.03)                |
| Decade of birth:      |                                                 |                                                                | <.001                                 |
| Pre-1920              | 10%                                             | 8%                                                             | ( $\chi^2(5)=3,800$ )                 |
| 1920s                 | 14%                                             | 16%                                                            |                                       |
| 1930s                 | 21%                                             | 27%                                                            |                                       |
| 1940s                 | 18%                                             | 23%                                                            |                                       |
| 1950s                 | 22%                                             | 23%                                                            |                                       |
| 1960 or later         | 14%                                             | 3%                                                             |                                       |
| Education (yrs):      |                                                 |                                                                | <.001                                 |
| <9                    | 12%                                             | 8%                                                             | ( $\chi^2(4)=729$ )                   |
| 9 to 11               | 13%                                             | 11%                                                            |                                       |
| 12                    | 31%                                             | 33%                                                            |                                       |
| 13 to 15              | 22%                                             | 23%                                                            |                                       |
| >15                   | 21%                                             | 25%                                                            |                                       |
| Missing               | .3%                                             | n/a (excluded)                                                 |                                       |
| Body Mass Index (BMI) | Mean 27.9 (s.d. 5.9);<br>Med 27.0 [9.7 to 75.5] | Mean 27.4 (s.d. 5.1);<br>Median 26.6 [9.7 to 60.5]             | <.001<br>(t(37497)=15.3)              |

|                                                | Full HRS sample                                | Participants included in the longitudinal analysis | p (excluded vs included) <sup>1</sup> |
|------------------------------------------------|------------------------------------------------|----------------------------------------------------|---------------------------------------|
| Smoking status:                                |                                                |                                                    | <.001                                 |
| Current                                        | 21%                                            | 17%                                                | ( $\chi^2(2)=274$ )                   |
| Past                                           | 37%                                            | 39%                                                |                                       |
| Never                                          | 42%                                            | 43%                                                |                                       |
| Missing                                        | .6%                                            | .7%                                                |                                       |
| Self-reported history of: <sup>2</sup>         |                                                |                                                    |                                       |
| Dementia or memory disorder                    | 1.4%                                           | excluded                                           | n/a                                   |
| High blood pressure                            | 41%                                            | 35%                                                | <.001<br>( $\chi^2(1)=479$ )          |
| Diabetes                                       | 14%                                            | 10%                                                | <.001<br>( $\chi^2(1)=492$ )          |
| Heart disease                                  | 15%                                            | 11%                                                | <.001<br>( $\chi^2(1)=291$ )          |
| Stroke                                         | 4.8%                                           | 2.9%                                               | <.001<br>( $\chi^2(1)=242$ )          |
| Psychiatric disorder                           | 11%                                            | 2%                                                 | <.001<br>( $\chi^2(1)=2,500$ )        |
| CES-D8 depressive symptoms                     | Mean 1.5 (s.d. 2.0);<br>Median 1 [0 to 8]      | Mean .6 (s.d. 1.0);<br>Median 0 [0 to 8]           | <.001<br>( $t(37660)=84.3$ )          |
| CIDI-SF depression classification <sup>2</sup> | 8.5%                                           | 2.0%                                               | <.001<br>( $\chi^2(1)=1,600$ )        |
| Cognitive composite scores:                    |                                                |                                                    |                                       |
| Two-component composite                        | Mean -.08 (s.d. .75);<br>Med .02 [-2.5 to 1.7] | Mean .08 (s.d. .68);<br>Median .16 [-2.4 to 1.7]   | <.001<br>( $t(37067)=-38.9$ )         |
| Full composite                                 | Mean -.08 (s.d. .65);<br>Med .00 [-2.5 to 1.3] | Mean .07 (s.d. .56);<br>Median .16 [-2.4 to 1.3]   | <.001<br>( $t(35748)=-41.9$ )         |

<sup>1</sup>Comparison of characteristics of excluded (not shown) vs included participants.

<sup>2</sup>Dementia/memory disorder and CIDI-SF depression presumed absent if data were missing at every observation. For all other disorders, data completeness was 100%.

**Table 4.2:** Characteristics at study entry of participants with elevated depressive symptoms at any observation

Figures are expressed as a percentage of the column or as mean (standard deviation); median [range]

|                  | All ppts with PEDS <sup>1</sup> in<br>the full HRS sample<br>N=15,144 | Ppts with PEDS included<br>in the longitudinal<br>analysis<br>N=3,475 | p (excluded vs<br>included) <sup>2</sup> |
|------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------|------------------------------------------|
| Ethnic group:    |                                                                       |                                                                       | <.001                                    |
| White            | 70%                                                                   | 79%                                                                   | (χ <sup>2</sup> (3)=186)                 |
| Black            | 21%                                                                   | 16%                                                                   |                                          |
| Other            | 9%                                                                    | 5%                                                                    |                                          |
| Missing          | .3%                                                                   | .1%                                                                   |                                          |
| Sex (% female)   | 65%                                                                   | 69%                                                                   | <.001<br>(χ <sup>2</sup> (1)=36.1)       |
| Age (years)      | Mean 60.5 (s.d. 10.3)<br>Median 57 [45 to 94]                         | Mean 59.1 (s.d. 8.6)<br>Median 57 [45 to 88]                          | <.001<br>(t(15142)=8.92)                 |
| Decade of birth: |                                                                       |                                                                       | <.001                                    |
| Pre-1920         | 11%                                                                   | 5%                                                                    | (χ <sup>2</sup> (5)=1100)                |
| 1920s            | 14%                                                                   | 14%                                                                   |                                          |
| 1930s            | 22%                                                                   | 33%                                                                   |                                          |
| 1940s            | 20%                                                                   | 31%                                                                   |                                          |
| 1950s            | 22%                                                                   | 16%                                                                   |                                          |
| 1960 or later    | 12%                                                                   | 1%                                                                    |                                          |
| Education (yrs): |                                                                       |                                                                       | <.001                                    |
| <9               | 17%                                                                   | 11%                                                                   | (χ <sup>2</sup> (4)=185)                 |
| 9 to 11          | 17%                                                                   | 15%                                                                   |                                          |
| 12               | 31%                                                                   | 34%                                                                   |                                          |
| 13 to 15         | 20%                                                                   | 21%                                                                   |                                          |
| >15              | 14%                                                                   | 19%                                                                   |                                          |
| Missing          | .3%                                                                   | excluded                                                              |                                          |

|                                                | All ppts with PEDS <sup>1</sup> in the full HRS sample | Ppts with PEDS included in the longitudinal analysis | p (excluded vs included) <sup>2</sup> |
|------------------------------------------------|--------------------------------------------------------|------------------------------------------------------|---------------------------------------|
| Body Mass Index (BMI)                          | Mean 28.3 (s.d. 6.4)<br>Median 27.3 [10.5 to 75.5]     | Mean 27.7 (s.d. 5.4)<br>Median 26.9 [15.3 to 60.5]   | <.001<br>(t(15064)=6.80)              |
| Smoking status:                                |                                                        |                                                      | <.001                                 |
| Current                                        | 28%                                                    | 24%                                                  | ( $\chi^2(2)=43.9$ )                  |
| Past                                           | 33%                                                    | 34%                                                  |                                       |
| Never                                          | 39%                                                    | 41%                                                  |                                       |
| Missing                                        | .5%                                                    | .8%                                                  |                                       |
| Self-reported history of: <sup>3</sup>         |                                                        |                                                      |                                       |
| Dementia or memory disorder                    | 5.0%                                                   | excluded                                             | n/a                                   |
| High blood pressure                            | 46%                                                    | 36%                                                  | <.001<br>( $\chi^2(1)=202$ )          |
| Diabetes                                       | 17%                                                    | 9%                                                   | <.001<br>( $\chi^2(1)=183$ )          |
| Heart disease                                  | 18%                                                    | 12%                                                  | <.001<br>( $\chi^2(1)=123$ )          |
| Stroke                                         | 6.6%                                                   | 3.0%                                                 | <.001<br>( $\chi^2(1)=89.1$ )         |
| Psychiatric disorder                           | 21%                                                    | 10%                                                  | <.001<br>( $\chi^2(1)=296$ )          |
| CES-D8 depressive symptoms                     | Mean 2.9 (s.d. 2.4)<br>Median 2 [0 to 8]               | Mean 1.2 (s.d. 1.6)<br>Median 1 [0 to 8]             | <.001<br>(t(15142)=50.5)              |
| CIDI-SF depression classification <sup>3</sup> | 16.7%                                                  | 9.3%                                                 | <.001<br>( $\chi^2(1)=184$ )          |

|                             | All ppts with PEDS <sup>1</sup> in the full HRS sample | Ppts with PEDS included in the longitudinal analysis | p (excluded vs included) <sup>2</sup> |
|-----------------------------|--------------------------------------------------------|------------------------------------------------------|---------------------------------------|
| Cognitive composite scores: |                                                        |                                                      |                                       |
| Two-                        | Mean -.22 (s.d. .79)                                   | Mean .07 (s.d. .69)                                  | <.001                                 |
| component composite         | Median -.19 [-2.5 to 1.7]                              | Median .16 [-2.4 to 1.7]                             | (t(14871)=-25.6)                      |
| Full composite              | Mean -.21 (s.d. .69)                                   | Mean .05 (s.d. .58)                                  | <.001                                 |
|                             | Median -.14 [-2.5 to 1.3]                              | Median .13 [-2.3 to 1.3]                             | (t(14265)=-25.7)                      |

<sup>1</sup>Participants with a CES-D8 score of 4 or higher at any observation.

<sup>2</sup> Comparison of characteristics of excluded (not shown) vs included participants with depression at any observation.

<sup>3</sup>Dementia/memory disorder and CIDI-SF depression presumed absent if data were missing at every observation. For all other disorders, data completeness was 100%.

**Table 4.3:** Baseline characteristics of included participants with vs without PEDS

|                  | Included participants with no observed depression<br>N=13,011 | Included participants with PEDS<br>N=3,475   | p (PEDS vs no observed depression) |
|------------------|---------------------------------------------------------------|----------------------------------------------|------------------------------------|
| Ethnic group:    |                                                               |                                              | .358                               |
| White            | 78%                                                           | 79%                                          | ( $\chi^2(3)=3.23$ )               |
| Black            | 16%                                                           | 16%                                          |                                    |
| Other            | 6%                                                            | 5%                                           |                                    |
| Missing          | .2%                                                           | .1%                                          |                                    |
| Age (years)      | Mean 60.9 (s.d. 9.7)<br>Median 58 [45 to 92]                  | Mean 59.9 (s.d. 8.6)<br>Median 58 [45 to 88] | <.001<br>(t(16484)=5.48)           |
| Decade of birth: |                                                               |                                              | <.001                              |
| Pre-1920         | 9%                                                            | 5%                                           | ( $\chi^2(5)=345$ )                |
| 1920s            | 16%                                                           | 14%                                          |                                    |
| 1930s            | 26%                                                           | 33%                                          |                                    |
| 1940s            | 21%                                                           | 31%                                          |                                    |
| 1950s            | 25%                                                           | 16%                                          |                                    |
| 1960 or later    | 3%                                                            | 1%                                           |                                    |

|                               | Included participants<br>with no observed<br>depression | Included participants<br>with PEDS | p (PEDS vs no<br>observed<br>depression)<br><.001 |
|-------------------------------|---------------------------------------------------------|------------------------------------|---------------------------------------------------|
| Education (yrs):              |                                                         |                                    |                                                   |
| <9                            | 7%                                                      | 11%                                | ( $\chi^2(4)=170$ )                               |
| 9 to 11                       | 10%                                                     | 15%                                |                                                   |
| 12                            | 32%                                                     | 34%                                |                                                   |
| 13 to 15                      | 24%                                                     | 21%                                |                                                   |
| >15                           | 27%                                                     | 19%                                |                                                   |
| Body Mass Index (BMI)         | 27.3 (s.d. 5.1)                                         | 27.8 (s.d. 5.5)                    | <.001                                             |
|                               | Median 26.6 [9.7 to<br>60.5]                            | Median 27.0 [15.3 to<br>56.9]      | (t(16484)=-4.52)                                  |
| Smoking status:               |                                                         |                                    | <.001                                             |
| Current                       | 15%                                                     | 21%                                | ( $\chi^2(3)=66.5$ )                              |
| Past                          | 40%                                                     | 37%                                |                                                   |
| Never                         | 44%                                                     | 41%                                |                                                   |
| Missing                       | .6%                                                     | .9%                                |                                                   |
| Self-reported history of:     |                                                         |                                    |                                                   |
| High blood pressure           | 36%                                                     | 37%                                | .131<br>( $\chi^2(1)=2.28$ )                      |
| Diabetes                      | 10%                                                     | 10%                                | .958<br>( $\chi^2(1)=0.003$ )                     |
| Heart disease                 | 12%                                                     | 13%                                | .085<br>( $\chi^2(1)=3.00$ )                      |
| Stroke                        | 3.0%                                                    | 3.3%                               | .370<br>( $\chi^2(1)=0.802$ )                     |
| Psychiatric disorder          | excluded                                                | 11%                                | n/a                                               |
| CES-D8 depressive<br>symptoms | .4 (s.d. .6)<br>Median 0 [0 to 3]                       | .6 (s.d. .7)<br>Median 0 [0 to 3]  | <.001<br>(t(16484)=-17.6)                         |

|                                | Included participants<br>with no observed<br>depression | Included participants<br>with PEDS | p (PEDS vs no<br>observed<br>depression) |
|--------------------------------|---------------------------------------------------------|------------------------------------|------------------------------------------|
| Cognitive composite<br>scores: |                                                         |                                    |                                          |
| Two-component composite        | .09 (s.d. .68)                                          | .07 (s.d. .69)                     | .154                                     |
|                                | Median .17 [-2.38 to<br>1.71]                           | Median .16 [-2.38 to 1.71]         | (t(16484)=1.42)                          |
| Full composite                 | .08 (s.d. .56)                                          | .04 (s.d. .59)                     | <.001                                    |
|                                | Median .16 [-2.36 to<br>1.31]                           | Median .13 [-2.27 to 1.31]         | (t(15576)=3.94)                          |

### *Results of the multilevel regression analyses*

In most age groups, after adjustment for age, cognition was poorer amongst participants who had recovered from a PEDS than amongst participants prior to a PEDS (Table 4.4). The post-hoc contrast analysis indicated that the age-adjusted episodic and working memory composite was significantly poorer during PEDS ( $p < .001$ ) and after PEDS ( $P < .001$ ) than before PEDS (Table 4.5). The pattern of results (Table 4.4) illustrates that this was driven by differences amongst participants aged over 55 which were not evident amongst younger participants. At age 65 and over, when the full three-component cognitive composite measure was available, the full composite was also poorer during PEDS ( $p = .009$ ) and after PEDS ( $p < .001$ ) than before PEDS (Table 4.5). Results of the fully adjusted model did not differ from results adjusted only for age, sex and education (Table 4.6), suggesting that residual confounding due to these covariates was likely to be small.

Marginal values of cognition at the midpoint of each ten-year age group are also presented in Table 4.4. By comparison, the differences between pre- and post-PEDS cognition range from approximately 20% to 40% of the differences associated with ten additional years of age. Compared with the effect of education (also presented in Table 4.4), the post-PEDS deficit is equivalent to the difference associated with .6 to 1.5 fewer years of education.

In sensitivity analyses, in most age groups the results did not appear to be attenuated when restricted to participants before 1950 (Table 4.7) and to participants who reported no history of psychiatric disorder (Table 4.8).

**Table 4.4:** Associations of cognitive performance with age and depression status

|                                                         |                        | Two-component composite<br>(n=16,486 including 3,475 with<br>depression) | Full cognitive composite<br>(n=14,712 including 2,425 with<br>depression) |
|---------------------------------------------------------|------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Mean difference from the pre-PEDS reference group:      |                        |                                                                          |                                                                           |
| Age 45 to 54                                            | No observed depression | -.024 (-.055 to .008)                                                    | -.085 (-.131 to -.039) <sup>c</sup>                                       |
|                                                         | During PEDS            | -.032 (-.078 to .015)                                                    |                                                                           |
|                                                         | Post-PEDS              | .013 (-.058 to .083)                                                     |                                                                           |
| Age 55 to 64                                            | No observed depression | .000 (-.023 to .023)                                                     | -.009 (-.040 to .022)                                                     |
|                                                         | During PEDS            | -.079 (-.103 to -.055) <sup>c</sup>                                      |                                                                           |
|                                                         | Post-PEDS              | -.070 (-.095 to -.044) <sup>c</sup>                                      |                                                                           |
| Age 65 to 74                                            | No observed depression | .002 (-.024 to .028)                                                     | -.008 (-.031 to .016)                                                     |
|                                                         | During PEDS            | -.072 (-.099 to -.045) <sup>c</sup>                                      | -.054 (-.079 to -.030) <sup>c</sup>                                       |
|                                                         | Post-PEDS              | -.063 (-.088 to -.038) <sup>c</sup>                                      | -.073 (-.096 to -.050) <sup>c</sup>                                       |
| Age 75 to 84                                            | No observed depression | -.004 (-.042 to .033)                                                    | -.022 (-.054 to .011)                                                     |
|                                                         | During PEDS            | -.048 (-.088 to -.009) <sup>a</sup>                                      | -.052 (-.085 to -.018) <sup>b</sup>                                       |
|                                                         | Post-PEDS              | -.090 (-.126 to -.053) <sup>c</sup>                                      | -.105 (-.136 to -.074) <sup>c</sup>                                       |
| Age 85 to 94                                            | No observed depression | -.070 (-.176 to .036)                                                    | -.089 (-.179 to .001)                                                     |
|                                                         | During PEDS            | -.030 (-.143 to .082)                                                    | -.049 (-.145 to .046)                                                     |
|                                                         | Post-PEDS              | -.125 (-.230 to -.020) <sup>a</sup>                                      | -.146 (-.235 to -.057) <sup>c</sup>                                       |
| Sex                                                     | Female, vs male        | .076 (.061 to .091) <sup>***</sup>                                       | .060 (.045 to .074) <sup>***</sup>                                        |
| Education                                               | per year               | .081 (.079 to .084) <sup>***</sup>                                       | .072 (.070 to .075) <sup>***</sup>                                        |
| Marginal values in the pre-PEDS reference group at age: |                        |                                                                          |                                                                           |
|                                                         | 50                     | .192 (.164 to .222)                                                      | .214 (.169 to .259)                                                       |
|                                                         | 60                     | .144 (.123 to .165)                                                      | .132 (.104 to .159)                                                       |
|                                                         | 70                     | -.031 (-.056 to -.007)                                                   | .016 (.005 to .038)                                                       |
|                                                         | 80                     | -.350 (-.386 to -.313)                                                   | -.267 (-.298 to -.235)                                                    |
|                                                         | 90                     | -.788 (-.894 to -.681)                                                   | -.727 (-.818 to -.636)                                                    |
|                                                         | 94                     | -1.012 (-1.125 to -.899)                                                 | -.970 (-1.066 to -.874)                                                   |

\*\*\*p&lt;.001

p-values of age-stratified results are not corrected for multiple testing but are presented for descriptive purposes: <sup>a</sup>uncorrected p<.05    <sup>b</sup>uncorrected p<.01    <sup>c</sup>uncorrected p<.001

Also adjusted for baseline smoking status, BMI, and histories of high blood pressure, diabetes, heart disease and stroke.

**Table 4.5:** Contrasts of marginal values of cognitive function during, after and without PEDS, with cognitive function before PEDS.

|                                    | Average (and 95% CI) contrast with pre-PEDS value | p     |
|------------------------------------|---------------------------------------------------|-------|
| Two-component cognitive composite: |                                                   |       |
| no observed PEDS                   | -.019 (-.048 to .009)                             | .186  |
| during PEDS                        | -.052 (-.079 to -.026)                            | <.001 |
| after PEDS                         | -.067 (-.095 to -.039)                            | <.001 |
| Full cognitive composite:          |                                                   |       |
| no observed PEDS                   | -.04 (-.079 to -.002)                             | .040  |
| during PEDS                        | -.048 (-.083 to -.012)                            | .009  |
| after PEDS                         | -.099 (-.134 to -.064)                            | <.001 |

**Table 4.6:** Comparison of the results of regression analysis with and without adjustment for covariates related to vascular health

|           | Cognitive performance <sup>1</sup> post-PEDS, vs pre-PEDS |                                     |
|-----------|-----------------------------------------------------------|-------------------------------------|
| Age group | Basic model <sup>2</sup>                                  | Fully adjusted model <sup>3</sup>   |
| 45 to 54  | .013 (-.058 to .083)                                      | .015 (-.055 to .086)                |
| 55 to 64  | -.070 (-.095 to -.044) <sup>c</sup>                       | -.069 (-.094 to -.044) <sup>c</sup> |
| 65 to 74  | -.063 (-.088 to -.038) <sup>c</sup>                       | -.066 (-.092 to -.041) <sup>c</sup> |
| 75 to 84  | -.090 (-.126 to -.053) <sup>c</sup>                       | -.092 (-.128 to -.055) <sup>c</sup> |
| 85 to 94  | -.125 (-.230 to -.020) <sup>a</sup>                       | -.13 (-.235 to -.025) <sup>a</sup>  |

<sup>1</sup>Two-component cognitive composite

<sup>2</sup>Adjusted for age, sex and education

<sup>3</sup> Also adjusted for baseline BMI, smoking status and histories of high blood pressure, diabetes, heart disease and stroke.

p-values of age-stratified results are not corrected for multiple testing but are presented for descriptive purposes: <sup>a</sup>uncorrected p<.05    <sup>c</sup>uncorrected p<.001

**Table 4.7:** Mean differences between pre-PEDS and post-PEDS cognition amongst participants born before 1950

| Age group | Mean difference in cognition post-PEDS, ref pre-PEDS |                                     |
|-----------|------------------------------------------------------|-------------------------------------|
|           | Full sample (from Table 4.4)                         | Born before 1950 <sup>1</sup>       |
| 45 to 54  | .013 (-.058 to .083)                                 | .026 (-.127 to .179)                |
| 55 to 64  | -.070 (-.095 to -.044) <sup>c</sup>                  | -.057 (-.087 to -.027) <sup>c</sup> |
| 65 to 74  | -.063 (-.088 to -.038) <sup>c</sup>                  | -.056 (-.082 to -.031) <sup>c</sup> |
| 65 to 84  | -.090 (-.126 to -.053) <sup>c</sup>                  | -.086 (-.123 to -.05) <sup>c</sup>  |
| 85 to 94  | -.125 (-.230 to -.020) <sup>a</sup>                  | -.124 (-.23 to -.019) <sup>a</sup>  |

Two-component cognitive composite.

<sup>1</sup>n=12,197 including 2,879 with PEDS.

p-values (uncorrected for multiple testing), presented for descriptive purposes. <sup>a</sup>uncorrected p<.05

<sup>c</sup>uncorrected p<.001

**Table 4.8:** Mean differences between pre-PEDS and post-PEDS cognition amongst participants with no reported psychiatric history

| Age group | Mean difference in cognition post-PEDS, ref pre-PEDS |                                     |
|-----------|------------------------------------------------------|-------------------------------------|
|           | Full sample (from Table 4.4)                         | No psychiatric history <sup>1</sup> |
| 45 to 54  | .013 (-.058 to .083)                                 | .012 (-.071 to .095)                |
| 55 to 64  | -.070 (-.095 to -.044) <sup>c</sup>                  | -.072 (-.102 to -.042) <sup>c</sup> |
| 65 to 74  | -.063 (-.088 to -.038) <sup>c</sup>                  | -.066 (-.094 to -.037) <sup>c</sup> |
| 65 to 84  | -.090 (-.126 to -.053) <sup>c</sup>                  | -.056 (-.097 to -.015) <sup>b</sup> |
| 85 to 94  | -.125 (-.230 to -.020) <sup>a</sup>                  | -.130 (-.245 to -.015) <sup>a</sup> |

Two-component cognitive composite.

<sup>1</sup>n=15,555 including 2,544 with PEDS.

p-values (uncorrected for multiple testing), presented for descriptive purposes. <sup>a</sup>uncorrected p<.05

<sup>b</sup>uncorrected p<.01 <sup>c</sup>uncorrected p<.001

## 4.2 Cognitive trajectories before, during, after and without PEDS

Further to the analyses comparing average levels of cognitive function before and after PEDS, analyses were also conducted to compare rates of change in cognition before and after PEDS.

To facilitate this comparison, the association of cognition with time (i.e. ageing) was modelled as linear. Linear modelling of cognition over time could introduce confounding. If cognitive decline accelerates with age, the rate of decline after a PEDS is expected to be faster than the rate before the PEDS, even if the PEDS has no effect on the rate. To evaluate the impact of this simplification, a sensitivity analysis was conducted in which the duration of the follow-up period was restricted.

### Method

Inclusion and exclusion criteria and all variables were as described in the previous analysis (section 4.1). For this analysis, time (in years) was also included.

### Statistical analyses

To compare rate of change in cognition per year before PEDS with rate of change during and after PEDS and amongst individuals with no depression, a multilevel linear regression model was fitted, with cognitive function as outcome and participant identifier as the class variable.

The depression status of each observation was classified as no observed depression, pre-, during or post-PEDS, with pre-PEDS as the reference value. To evaluate how rates of change in cognition differed by depression status, a baseline was defined (described below), and the simple interaction between time (in years) since baseline and depression status was included in the model (thus modelling time since baseline as a continuous linear variable).

In addition, to compare levels of cognition at baseline, each participant was classified either as a participant with no observed depression or as a participant with PEDS. This binary classification was included as a covariate in the analysis, without interaction with time (or any other variable).

The nonlinear association of cognition with age was accounted for at baseline, by adjusting for the participant's ten-year age group at baseline (specified as a factor variable) and its interaction with year within the age group (specified as a continuous variable ranging from 0 to 9).

Baseline was defined as follows. For participants with PEDS, the baseline was the first observation in the pre-PEDS period. For those with multiple PEDS, a new baseline was specified for each PEDS.

For those with no observed depression, the baseline was initially specified as the first nondepressed observation. However, the linear modelling of cognition over time was expected to become increasingly inaccurate over longer durations of follow up. Amongst participants with no observed depression, this was addressed by setting a new baseline every ten years. Amongst those with PEDS, this was instead addressed with a sensitivity analysis, restricted to PEDS lasting less than three years and using observations no more than six years before or after the PEDS. In the sensitivity analysis, baseline was the first observation within this period, and PEDS were included only if both pre- and post-PEDS cognitive measures were available within the restricted period.

Adjustment for other covariates is addressed by including sex, education, and baseline BMI, smoking status, and histories of high blood pressure, diabetes, heart disease and stroke.

## Results

### *Characteristics of included participants*

The participants included in this analysis were the same as for the previous analysis, and their characteristics at study entry and (first) baseline are presented there (section 4.1).

### *Results of the multilevel regression analysis*

At baseline, cognition amongst participants who subsequently developed PEDS did not differ from cognition in the nondepressed group. Rates of cognitive decline

during and after PEDS were faster than the rate before the onset of the PEDS (Table 4.9).

Amongst PEDS, 1,570 (41%) had pre-PEDS or post-PEDS periods lasting more than six years. After excluding observations more than six years before the start or after the end of the PEDS and restricting the analysis to PEDS lasting less than three years, the results did not appear to be attenuated. This suggests that the contribution of confounding due to the nonlinear effect of ageing is likely to be small.

**Table 4.9:** Average rates of change in cognition<sup>1</sup> before, during and after PEDS, after linear adjustment for ageing

|                                                                             | Primary analysis<br>n=16,486          | Sensitivity analysis <sup>2</sup><br>n=15,789 |
|-----------------------------------------------------------------------------|---------------------------------------|-----------------------------------------------|
| Baseline pre-PEDS cognition (ref participants with no observed depression): |                                       |                                               |
|                                                                             | -.010 (-.029 to .010)                 | -.015 (-.037 to .008)                         |
| Rate of change per year, by depression status (ref pre-PEDS):               |                                       |                                               |
| No observed depression                                                      | -.002 (-.005 to .001)                 | -.007 (-.015 to .000)                         |
| Pre-PEDS                                                                    | Reference                             | Reference                                     |
| During PEDS                                                                 | -.006 (-.009 to -.004) <sup>c</sup>   | -.012 (-.019 to -.005) <sup>c</sup>           |
| Post-PEDS                                                                   | -.006 (-.008 to -.003) <sup>***</sup> | -.011 (-.017 to -.004) <sup>**</sup>          |

Significant differences from reference group: \*\*p<.01 \*\*\*p≤.001

p-values of secondary/exploratory analyses (not corrected for multiple testing, presented for descriptive purposes): <sup>c</sup>uncorrected p<.001

Adjusted for the nonlinear effect of baseline age. Also adjusted for sex, years of education, baseline BMI, smoking status, and histories of high blood pressure, diabetes, heart disease and stroke.

<sup>1</sup>Two component cognitive composite (mean of episodic and working memory z-scores)

<sup>2</sup>Based on PEDS which lasted less than three years, with observations restricted to a maximum of six years before the start or after the end of the PEDS.

### 4.3 Sensitivity analyses to exclude prodromal symptoms of dementia

#### Method

To investigate associations amongst individuals who are not in the prodromal stages of dementia, a prodromal period prior to dementia diagnosis was defined, based on the length of time from the onset of each PEDS to the latest observation at which the participant stated that they had never received a diagnosis of dementia. If this period was more than twelve years (i.e. if absence of a dementia diagnosis was documented twelve or more years later after the onset of the PEDS), the PEDS was classified as non-prodromal. If the participant reported dementia within twelve years of the start of the PEDS, the PEDS was classified as falling within the prodromal period, and all of the pre-, during and post-PEDS observations were excluded from the analysis. For participants with no observed depression who develop dementia, observations twelve or fewer years prior to the development of dementia were classified as falling within the prodromal period, and excluded from the sensitivity analyses.

Where data were unavailable more than twelve years after the onset of a PEDS (either because the participant was not followed up for a further twelve years, or because the self-report of dementia status was missing at follow-up), it was not possible to determine whether the PEDS fell within a prodromal period. The prodromal status of these PEDS was classified as indeterminate. Each sensitivity analysis was conducted firstly including, and then excluding, these indeterminate PEDS.

#### Statistical analyses

The above exclusions were applied to the analyses of levels of cognitive function (described in section 4.1) and cognitive trajectories (section 4.2), using the two-component cognitive measure as the outcome.

#### Results

##### *Inclusions and exclusions*

In total, 322 of the 3,873 PEDS were excluded from all sensitivity analyses. In 45 of these PEDS, the participant had already developed dementia between the beginning of the pre-PEDS period and the onset of the PEDS. The remaining 277 PEDS fell in

the prodromal period of a subsequent dementia diagnosis. Exclusion of these 322 PEDS resulted in 283 participants being excluded from the analyses.

In 2,104 PEDS, no dementia was documented but there was insufficient follow-up data to eliminate the possibility of dementia within twelve years of PEDS onset. These indeterminate PEDS were included in the first sensitivity analysis and excluded from the more stringent analysis. In the remaining 1,447 PEDS, the participant was non-prodromal at PEDS onset. These episodes were included in all analyses. In total, 3,551 PEDS (in 3,192 participants) were included in the first sensitivity analysis, and 1,447 PEDS (in 1,375 participants) were included in the more stringent sensitivity analysis.

Amongst participants with no observed depression, 857 developed dementia. Of these, 423 were excluded from the sensitivity analyses. The remainder had observations more than twelve years before dementia diagnosis, and these observations were included in the analyses. In total, 12,588 participants with no observed depression were included in the sensitivity analyses.

#### *Levels of cognition before and after PEDS*

When known cases of prodromal dementia were excluded, cognition remained poorer after PEDS than before them (Tables 4.10 and 4.12). When restricted to participants who confirmed the absence of a dementia diagnosis at follow-up twelve years later, no pre-PEDS observations were available for participants aged over 85. Amongst under-85s, cognition was also poorer after PEDS than before them (Table 4.12), primarily amongst participants aged over 75 (Table 4.11).

#### *Cognitive trajectories before and after depressive episodes*

After excluding known cases of prodromal dementia, the average rate of cognitive decline after a PEDS remained faster than the rate before the PEDS (Table 4.13). Amongst participants who confirmed the absence of a diagnosis twelve years later, the difference did not reach statistical significance but was not attenuated in magnitude (Table 4.14).

**Table 4.10:** Associations of cognitive performance with age and depression status after excluding known cases of prodromal dementia

|                                                    |                        | Full sample (from Table 4.4)        | Excluding known cases of prodromal dementia <sup>1</sup> |
|----------------------------------------------------|------------------------|-------------------------------------|----------------------------------------------------------|
| Mean difference from the pre-PEDS reference group: |                        |                                     |                                                          |
| Age 45 to 54                                       | No observed depression | -.024 (-.055 to .008)               | -.024 (-.056 to .007)                                    |
|                                                    | During PEDS            | -.032 (-.078 to .015)               | -.030 (-.077 to .016)                                    |
|                                                    | Post-PEDS              | .013 (-.058 to .083)                | .020 (-.05 to .091)                                      |
| Age 55 to 64                                       | No observed depression | .000 (-.023 to .023)                | -.005 (-.028 to .019)                                    |
|                                                    | During PEDS            | -.079 (-.103 to -.055) <sup>c</sup> | -.077 (-.101 to -.053) <sup>c</sup>                      |
|                                                    | Post-PEDS              | -.070 (-.095 to -.044) <sup>c</sup> | -.068 (-.094 to -.043) <sup>c</sup>                      |
| Age 65 to 74                                       | No observed depression | .002 (-.024 to .028)                | 0 (-.028 to .027)                                        |
|                                                    | During PEDS            | -.072 (-.099 to -.045) <sup>c</sup> | -.067 (-.095 to -.039) <sup>c</sup>                      |
|                                                    | Post-PEDS              | -.063 (-.088 to -.038) <sup>c</sup> | -.057 (-.083 to -.031) <sup>c</sup>                      |
| Age 75 to 84                                       | No observed depression | -.004 (-.042 to .033)               | .002 (-.039 to .044)                                     |
|                                                    | During PEDS            | -.048 (-.088 to -.009) <sup>a</sup> | -.037 (-.08 to .006)                                     |
|                                                    | Post-PEDS              | -.090 (-.126 to -.053) <sup>c</sup> | -.078 (-.118 to -.038) <sup>c</sup>                      |
| Age 85 to 94                                       | No observed depression | -.070 (-.176 to .036)               | -.061 (-.177 to .055)                                    |
|                                                    | During PEDS            | -.030 (-.143 to .082)               | -.041 (-.164 to .082)                                    |
|                                                    | Post-PEDS              | -.125 (-.230 to -.020) <sup>a</sup> | -.128 (-.243 to -.013) <sup>a</sup>                      |

Two-component cognitive composite

<sup>1</sup>n=15,780 including 3,192 with PEDS

p-values of age-stratified results (not corrected for multiple testing, presented for descriptive purposes): <sup>a</sup>uncorrected p<.05      <sup>c</sup>uncorrected p<.001

**Table 4.11:** Associations of cognitive performance with age and depression status, restricted to participants who confirmed absence of dementia diagnosis twelve years later

|                                                    |                        | Full sample (from Table 4.4)        | Participants with 12 further years dementia-free follow-up <sup>1</sup> |
|----------------------------------------------------|------------------------|-------------------------------------|-------------------------------------------------------------------------|
| Mean difference from the pre-PEDS reference group: |                        |                                     |                                                                         |
| Age 45 to 54                                       | No observed depression | -.024 (-.055 to .008)               | -.079 (-.124 to -.034) <sup>c</sup>                                     |
|                                                    | During PEDS            | -.032 (-.078 to .015)               | -.031 (-.093 to .032)                                                   |
|                                                    | Post-PEDS              | .013 (-.058 to .083)                | .016 (-.077 to .110)                                                    |
| Age 55 to 64                                       | No observed depression | .000 (-.023 to .023)                | -.025 (-.059 to .009)                                                   |
|                                                    | During PEDS            | -.079 (-.103 to -.055) <sup>c</sup> | -.070 (-.104 to -.036) <sup>c</sup>                                     |
|                                                    | Post-PEDS              | -.070 (-.095 to -.044) <sup>c</sup> | -.052 (-.089 to -.016) <sup>b</sup>                                     |
| Age 65 to 74                                       | No observed depression | .002 (-.024 to .028)                | -.004 (-.052 to .044)                                                   |
|                                                    | During PEDS            | -.072 (-.099 to -.045) <sup>c</sup> | -.042 (-.091 to .007)                                                   |
|                                                    | Post-PEDS              | -.063 (-.088 to -.038) <sup>c</sup> | -.041 (-.088 to .005)                                                   |
| Age 75 to 84                                       | No observed depression | -.004 (-.042 to .033)               | -.093 (-.203 to .016)                                                   |
|                                                    | During PEDS            | -.048 (-.088 to -.009) <sup>a</sup> | -.09 (-.203 to .022)                                                    |
|                                                    | Post-PEDS              | -.090 (-.126 to -.053) <sup>c</sup> | -.125 (-.233 to -.017)                                                  |
| Age 85 to 94                                       | No observed depression | -.070 (-.176 to .036)               | n/a <sup>2</sup>                                                        |
|                                                    | During PEDS            | -.030 (-.143 to .082)               |                                                                         |
|                                                    | Post-PEDS              | -.125 (-.230 to -.020) <sup>a</sup> |                                                                         |

<sup>1</sup>n=13,963 including 1,447 with PEDS

<sup>2</sup>No reference (pre-PEDS) observations available over the age of 85

p-values of age-stratified results (not corrected for multiple testing, presented for descriptive purposes): <sup>a</sup>uncorrected p<.05    <sup>b</sup>uncorrected p<.01    <sup>c</sup>uncorrected p<.001

**Table 4.12:** Contrasts of marginal values of cognitive function during, after and without PEDS, with cognitive function before PEDS, after exclusion of prodromal dementia.

|                                                                                    | Average (and 95% CI) contrast with pre-PEDS value | p     |
|------------------------------------------------------------------------------------|---------------------------------------------------|-------|
| Excluding known cases of dementia:                                                 |                                                   |       |
| no observed PEDS                                                                   | -.018 (-.048 to .013)                             | .264  |
| during PEDS                                                                        | -.051 (-.079 to -.022)                            | .001  |
| after PEDS                                                                         | -.062 (-.092 to -.032)                            | <.001 |
| Restricted to participants under 85 with 12 further years dementia-free follow-up: |                                                   |       |
| no observed PEDS                                                                   | -.052 (-.095 to -.010)                            | .016  |
| during PEDS                                                                        | -.058 (-.098 to -.018)                            | .004  |
| after PEDS                                                                         | -.052 (-.095 to -.009)                            | .018  |

**Table 4.13:** Average rates of change in cognition<sup>1</sup> before, during and after PEDS, excluding known cases of prodromal dementia

|                                                                             | Full sample (from Table 4.9)          | Excluding known cases of prodromal dementia <sup>2</sup> |
|-----------------------------------------------------------------------------|---------------------------------------|----------------------------------------------------------|
| Baseline pre-PEDS cognition (ref participants with no observed depression): |                                       |                                                          |
|                                                                             | -.010 (-.029 to .010)                 | -.004 (-.024 to .016)                                    |
| Rate of change per year, by depression status (ref pre-PEDS):               |                                       |                                                          |
| No observed depression                                                      | -.002 (-.005 to .001)                 | -.001 (-.004 to .002)                                    |
| Pre-PEDS                                                                    | Reference                             | Reference                                                |
| During PEDS                                                                 | -.006 (-.009 to -.004) <sup>°</sup>   | -.006 (-.009 to -.003) <sup>°</sup>                      |
| Post-PEDS                                                                   | -.006 (-.008 to -.003) <sup>***</sup> | -.005 (-.008 to -.002) <sup>***</sup>                    |

Significant differences from reference group: \*\*\*p≤.001

p-values of secondary/exploratory analyses (not corrected for multiple testing, presented for descriptive purposes): <sup>°</sup>uncorrected p<.001

Adjusted for the nonlinear effect of baseline age. Also adjusted for sex, years of education, baseline BMI, smoking status, and histories of high blood pressure, diabetes, heart disease and stroke.

<sup>1</sup>Two component cognitive composite (mean of episodic and working memory z-scores)

<sup>2</sup>n=15,780 including 3,192 with PEDS.

**Table 4.14:** Average rates of change in cognition<sup>1</sup> before, during and after PEDS, restricted to participants who confirmed absence of dementia diagnosis twelve years later

|                                                                             | Full sample (from Table 4.9)          | Participants with 12 further years dementia-free follow-up <sup>2</sup> |
|-----------------------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------|
| Baseline pre-PEDS cognition (ref participants with no observed depression): |                                       |                                                                         |
|                                                                             | -.010 (-.029 to .010)                 | .023 (-.006 to .052)                                                    |
| Rate of change per year, by depression status (ref pre-PEDS):               |                                       |                                                                         |
| No observed depression                                                      | -.002 (-.005 to .001)                 | -.003 (-.011 to .005)                                                   |
| Pre-PEDS                                                                    | Reference                             | Reference                                                               |
| During PEDS                                                                 | -.006 (-.009 to -.004) <sup>c</sup>   | -.008 (-.015 to -.001) <sup>a</sup>                                     |
| Post-PEDS                                                                   | -.006 (-.008 to -.003) <sup>***</sup> | -.006 (-.014 to .001)                                                   |

Significant differences from reference group: \*p<.05 \*\*p<.01 \*\*\*p≤.001

p-values of secondary/exploratory analyses (not corrected for multiple testing, presented for descriptive purposes): <sup>a</sup>uncorrected p<.05 <sup>c</sup>uncorrected p<.001

Adjusted for the nonlinear effect of baseline age. Also adjusted for sex, years of education, baseline BMI, smoking status, and histories of high blood pressure, diabetes, heart disease and stroke.

<sup>1</sup>Two component cognitive composite (mean of episodic and working memory z-scores)

<sup>2</sup>n=13,963 including 1,375 with PEDS.

#### **4.4 Sensitivity analyses to exclude subclinical depressive symptoms**

##### Method

To exclude the effect of subclinical depressive symptoms on post-PEDS cognition, the individual CES-D8 items significantly associated with cognition were identified, and the PEDS included in the analyses were restricted to those for which none of these symptoms was present in the post-PEDS phase. In exploratory analyses (section 3.4), the relevant CES-D8 items were identified as 'I felt depressed', 'everything was an effort', 'I felt lonely' and 'I could not get going'.

##### Statistical analyses

The above exclusion was applied to the analyses of levels of cognitive function (described in section 4.1) and cognitive trajectories (section 4.2), using the two-component cognitive measure as the outcome.

##### Results

Of the 3,873 PEDS in the original analysis, 1,747 (45%) had none of the four CES-D8 items in the post-PEDS phase. These PEDS were included in the sensitivity analysis. Post-PEDS deficits in average levels of cognitive performance remained evident (Tables 4.15 and 4.16).

Cognitive decline was more rapid during PEDS ( $p < .001$ ) and after PEDS ( $p < .05$ ) than before PEDS (Table 4.17).

**Table 4.15:** Associations of cognitive performance with age and depression status, after excluding subclinical symptoms associated with poorer cognition

|                                                    |                        | Full sample (from Table 4.4)        | Excluding PEDS with relevant post-PEDS subclinical symptoms |
|----------------------------------------------------|------------------------|-------------------------------------|-------------------------------------------------------------|
| Mean difference from the pre-PEDS reference group: |                        |                                     |                                                             |
| Age 45 to 54                                       | No observed depression | -.024 (-.055 to .008)               | -.035 (-.077 to .006)                                       |
|                                                    | During PEDS            | -.032 (-.078 to .015)               | -.013 (-.078 to .053)                                       |
|                                                    | Post-PEDS              | .013 (-.058 to .083)                | .063 (-.04 to .165)                                         |
| Age 55 to 64                                       | No observed depression | .000 (-.023 to .023)                | -.025 (-.057 to .007)                                       |
|                                                    | During PEDS            | -.079 (-.103 to -.055) <sup>c</sup> | -.095 (-.13 to -.06) <sup>c</sup>                           |
|                                                    | Post-PEDS              | -.070 (-.095 to -.044) <sup>c</sup> | -.064 (-.101 to -.027) <sup>c</sup>                         |
| Age 65 to 74                                       | No observed depression | .002 (-.024 to .028)                | -.018 (-.055 to .019)                                       |
|                                                    | During PEDS            | -.072 (-.099 to -.045) <sup>c</sup> | -.082 (-.123 to -.042) <sup>c</sup>                         |
|                                                    | Post-PEDS              | -.063 (-.088 to -.038) <sup>c</sup> | -.056 (-.095 to -.017) <sup>b</sup>                         |
| Age 75 to 84                                       | No observed depression | -.004 (-.042 to .033)               | -.03 (-.088 to .028)                                        |
|                                                    | During PEDS            | -.048 (-.088 to -.009) <sup>a</sup> | -.054 (-.117 to .008)                                       |
|                                                    | Post-PEDS              | -.090 (-.126 to -.053) <sup>c</sup> | -.103 (-.163 to -.044) <sup>c</sup>                         |
| Age 85 to 94                                       | No observed depression | -.070 (-.176 to .036)               | -.131 (-.279 to .017)                                       |
|                                                    | During PEDS            | -.030 (-.143 to .082)               | -.108 (-.267 to .051)                                       |
|                                                    | Post-PEDS              | -.125 (-.230 to -.020) <sup>a</sup> | -.204 (-.353 to -.054) <sup>b</sup>                         |

p-values of age-stratified results (not corrected for multiple testing, presented for descriptive purposes): <sup>a</sup>uncorrected  $p < .05$     <sup>b</sup>uncorrected  $p < .01$     <sup>c</sup>uncorrected  $p < .001$

**Table 4.16:** Contrasts of marginal values of cognitive function during, after and without PEDS, with cognitive function before PEDS, after excluding subclinical symptoms associated with poorer cognition.

|                  | Average (and 95% CI) contrast with pre-PEDS value | p     |
|------------------|---------------------------------------------------|-------|
| no observed PEDS | -.048 (-.088 to -.008)                            | .020  |
| during PEDS      | -.071 (-.109 to -.032)                            | <.001 |
| after PEDS       | -.073 (-.113 to -.032)                            | <.001 |

**Table 4.17:** Average rates of change in cognition<sup>1</sup> before, during and after PEDS, after excluding PEDS with post-PEDS subclinical symptoms associated with poorer cognition

|                                                                             | Primary analysis<br>(from Table 4.9)  | Excluding PEDS with<br>relevant post-PEDS<br>subclinical symptoms <sup>2</sup> |
|-----------------------------------------------------------------------------|---------------------------------------|--------------------------------------------------------------------------------|
| Baseline pre-PEDS cognition (ref participants with no observed depression): |                                       |                                                                                |
|                                                                             | -.010 (-.029 to .010)                 | .008 (-.019 to .035)                                                           |
| Rate of change per year, by depression status (ref pre-PEDS):               |                                       |                                                                                |
| No<br>observed depression                                                   | -.002 (-.005 to .001)                 | -.002 (-.006 to .002)                                                          |
| During PEDS                                                                 | -.006 (-.009 to -.004) <sup>c</sup>   | -.007 (-.011 to -.003) <sup>c</sup>                                            |
| Post-PEDS                                                                   | -.006 (-.008 to -.003) <sup>***</sup> | -.005 (-.008 to -.001) <sup>*</sup>                                            |

Significant differences from reference group: \*p<.05 \*\*\*p≤.001

p-values of secondary/exploratory analyses (not corrected for multiple testing, presented for descriptive purposes): <sup>c</sup>uncorrected p<.001

Adjusted for the nonlinear effect of baseline age. Also adjusted for sex, years of education, baseline BMI, smoking status, and histories of high blood pressure, diabetes, heart disease and stroke.

<sup>1</sup>Two component cognitive composite

<sup>2</sup>n=14,626 including 1,615 with depression

#### **4.5. Analyses of cognitive trajectories stratified by age of onset of PEDS**

Some cases of late-life depression have aetiologies which are rare at younger ages. This could explain some cases of late onset depression, where a previously nondepressed individual develops a depressive episode for the first time in late life. The cognitive features of depressive episodes may therefore vary according to the age of onset of the episode. To address these possibilities, analyses were stratified by age of onset of the PEDS, followed by sensitivity analyses excluding, and then restricted to, participants with prior psychiatric history.

##### *Analysis stratified by age of onset of the PEDS*

###### Method

Five successive analyses were conducted, one for each ten-year age group. Each analysis included all PEDS which began in the age group. The pre- and post-PEDS observations of the included PEDS were also included. To obtain a comparable nondepressed group for each stratum of depressed participants, the age ranges at the start and end of their follow-up periods were matched, as follows. Amongst the depressed participants in each stratum, the distribution of baseline ages was examined, and the 5th and 95th percentiles of this distribution were obtained. Non-depressed participants were then eligible for inclusion in the analysis if their age at first observation fell within this age range. The same procedure was applied to the age at participants' final observation, and nondepressed participants were included if both their first observation and their final observation fell within the required age ranges.

Baseline cognition in participants with PEDS was compared with baseline cognition amongst those with no observed depression, and the rate of change of cognition before PEDS was compared with the rate of change after PEDS.

###### Statistical analyses

The analyses used the multilevel regression model described in section 4.2. Specifically, to compare levels of cognition at baseline, each participant was

classified either as a participant with no observed depression or as a participant with PEDS. This binary classification was included as a covariate in the analysis. To evaluate how rates of change in cognition differed by depression status, the interaction between time since baseline and depression status was included in the model, with pre-PEDS specified as the reference value of depression status.

## Results

Amongst PEDS beginning between the ages of 55 and 74, baseline cognition was poorer amongst the depressed group (in the pre-PEDS period) than amongst those with no observed depression (Table 4.18). This difference was not found in other age groups.

Amongst PEDS starting after the age of 65, cognitive decline was significantly faster after the PEDS than before the PEDS, whereas this was not found for PEDS starting at younger ages (Table 4.18).

Thus in general, younger onsets were preceded by cognitive deficits before the start of the PEDS, whilst older onsets were followed by accelerated cognitive decline after the end of the PEDS.

**Table 4.18:** Pre-PEDS baselines and post-PEDS trajectories of cognition, stratified by age at the start of the PEDS

| Age at start of PEDS                  | Difference at baseline (pre-PEDS vs no depression) | Rate of change in cognition (post-PEDS vs pre-PEDS) |
|---------------------------------------|----------------------------------------------------|-----------------------------------------------------|
| 45 to 54<br>(n=2,379; 389 with PEDS)  | -.040 (-.096 to .017)                              | -.024 (-.048 to .001)                               |
| 55 to 64<br>n=5,892 (1,486 with PEDS) | -.060 (-.090 to -.029) <sup>c</sup>                | -.003 (-.009 to .003)                               |
| 65 to 74<br>n=5,218 (1,102 with PEDS) | -.058 (-.093 to -.023) <sup>c</sup>                | -.005 (-.009 to -.001) <sup>a</sup>                 |
| 75 to 84<br>n=3,678 (642 with PEDS)   | -.020 (-.065 to .025)                              | -.008 (-.013 to -.003) <sup>c</sup>                 |
| 85 to 94<br>n=1,415 (122 with PEDS)   | -.035 (-.132 to .062)                              | -.013 (-.023 to -.003) <sup>b</sup>                 |

Significant differences from the pre-PEDS rate of change (not corrected for multiple testing): <sup>a</sup>uncorrected p<.05    <sup>b</sup>uncorrected p<.01    <sup>c</sup>uncorrected p<.001

## *Analyses of late-onset depression vs PEDS in participants with pre-existing disorder*

### Method

For these analyses, PEDS were included if they began after the age of 65. Amongst all participants with such PEDS, the distributions of ages at first and final observation were examined, and participants without depression were selected for inclusion if their first and final observations fell between the 5<sup>th</sup> and 95<sup>th</sup> percentiles of these age ranges.

PEDS beginning after the age of 65 were classified into those with, and those without, prior psychiatric history (including but not limited to depression).

To define psychiatric history, three variables were used: the CES-D8 depression score (taking scores of 4 or higher to indicate depression), the CIDI-SF depression diagnostic checklist, and the self-report of history of psychiatric disorder.

Participants were presumed to remain free of psychiatric disorder at every observation until disorder was indicated on one of these three variables. For each participant, their age at their final disorder-free observation was obtained. If this age was 65 or over, the participant was classified as having no psychiatric history before the age of 65.

Baseline cognition in participants with depressive episodes was compared with baseline cognition amongst those with no observed depression, and the rate of change of cognition before PEDS was compared with the rate of change after PEDS.

### Statistical analyses

The analyses again followed the procedure described in section 4.2, using a binary variable to compare baseline cognition in participants with vs without PEDS, and the interaction between time since baseline and depression status to compare rates of change before vs after PEDS.

The comparisons were first conducted in the aggregated sample of all participants whose PEDS began at or over the age of 65 and the age-matched nondepressed

participants. Two sensitivity analyses were then conducted in which the participants with PEDS were restricted to those firstly with, and then without, psychiatric history.

## Results

Amongst participants with PEDS starting at or over the age of 65, patterns of association with the two-component cognitive composite differed by psychiatric history (Table 4.19a). Amongst those with psychiatric history (but not amongst those without), baseline cognition was significantly poorer than amongst nondepressives. Amongst those with no psychiatric history (but not amongst those with), cognitive decline was significantly faster after PEDS than before PEDS.

Using the full cognitive composite (including measures of orientation and naming: Table 4.19b), a pre-PEDS deficit in baseline cognition was again present in those with psychiatric history and absent in those without, and in both groups cognitive decline was significantly faster after PEDS than before PEDS.

**Table 4.19 a & b:** Pre-PEDS baselines and post-PEDS trajectories of cognition, including and excluding cases with no prior psychiatric history

(a) two-component cognitive composite

| PEDS included in the analysis <sup>1</sup>                       | Difference at baseline (pre-PEDS vs no depression) | Rate of change in cognition (post-PEDS vs pre-PEDS) |
|------------------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------|
| All PEDS with onset 65 or over (n=1,779)                         | -.039 (-.067 to -.010) <sup>b</sup>                | -.007 (-.010 to -.004) <sup>c</sup>                 |
| PEDS in participants with prior psychiatric history (n=539)      | -.137 (-.184 to -.090) <sup>c</sup>                | -.003 (-.008 to .003)                               |
| PEDS in participants with no prior psychiatric history (n=1,240) | .002 (-.030 to .034)                               | -.008 (-.012 to -.005) <sup>c</sup>                 |

<sup>1</sup>Participants with no observed depression also included: n=5,794

descriptive p-values (not corrected for multiple testing): <sup>b</sup>uncorrected p<.01    <sup>c</sup>uncorrected p<.001

(b) Full cognitive composite

| PEDS included in the analysis <sup>1</sup>                       | Difference at baseline (pre-episode vs no depression) | Rate of change in cognition (post-episode vs pre-episode) |
|------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------|
| All PEDS with onset 65 or over (n=1,663)                         | -.015 (-.040 to .011)                                 | -.010 (-.012 to -.007) <sup>c</sup>                       |
| PEDS in participants with prior psychiatric history (n=446)      | -.127 (-.174 to -.081) <sup>c</sup>                   | -.010 (-.016 to -.004) <sup>b</sup>                       |
| PEDS in participants with no prior psychiatric history (n=1,217) | -.021 (-.008 to .049)                                 | -.010 (-.013 to -.007) <sup>c</sup>                       |

<sup>1</sup>Participants with no observed depression also included: n=5,790

descriptive p-values (not corrected for multiple testing): <sup>b</sup>uncorrected p<.01    <sup>c</sup>uncorrected p<.001

#### **4.6 Summary of the results of the longitudinal analyses**

Amongst participants with episodes included in the longitudinal analyses (who were, on average, healthier and more highly educated than those the general population as represented by the full HRS sample), cognitive performance (adjusted for age) was poorer after the PEDS than before them. The difference was evident in every age group from 55 upwards, and was approximately 20% to 40% of the difference between levels of cognition at successive decades, thus approximately equivalent to the effect of two to four years of ageing.

In addition, the rate of cognitive decline was found to be more rapid after the end of PEDS than before the start of PEDS.

The post-PEDS cognitive deficit and faster cognitive decline remained evident after excluding PEDS which started within twelve years of a subsequent diagnosis of dementia, and also after excluding those with persistent subclinical depressive symptoms after the end of the PEDS.

In age-stratified analyses, amongst PEDS which began between the ages of 55 and 74 (but not at other ages), cognitive function before the start of the PEDS was poorer than cognitive function amongst individuals who did not develop depression. The faster cognitive decline after the end of the PEDS (compared with the rate before the PEDS) appeared to be more prominent at older ages of PEDS onset.

Amongst PEDS beginning over the age of 65, participants with prior psychiatric history had poorer cognition before the start of PEDS than participants with no psychiatric history or depressive PEDS. Rate of decline post-PEDS was faster than pre-PEDS on one measure of cognition but not on another. Amongst those with no prior psychiatric history, cognition before the start of PEDS did not differ from cognition amongst nondepressed participants, and cognitive decline was faster post-episode than pre-episode.

## Chapter 5: Discussion

### 5.1 Summary of the findings

This thesis set out to evaluate whether cognitive function is poorer after recovery from periods of elevated depressive symptoms (PEDS) than before their onset. Data were obtained from HRS, a large population-based longitudinal cohort study of US household residents aged over 50 and their cohabiting partners followed up every two years since 1992, with further recruitment every six years. Of 37,662 individuals who participated in HRS between 1996 and 2016, 16,486 were included in longitudinal analyses with an average of 6.5 (s.d. 2.9) included observations and a mean follow-up period of 12.3 (s.d. 6.0) years.

Cognitive function, adjusted for the non-linear effect of age on cognition, was found to be poorer after a PEDS than before the start of the PEDS. The difference was evident amongst participants aged over 55. The difference was approximately 20% to 40% of the difference between levels of cognition at successive decades, thus approximately equivalent to the effect of two to four years of ageing.

The result was similar whether vascular risk factors (BMI, smoking, high blood pressure, diabetes, heart disease and stroke) were included or omitted as covariates, suggesting that further residual confounding due to these factors was small. A sensitivity analysis suggested that the result was not confounded by use of psychiatric medication, as it was also found amongst participants who reported no psychiatric history and who were therefore unlikely to have received such medication.

In addition, the rate of cognitive decline was found to be more rapid after the end of PEDS than before the start of PEDS. A sensitivity analysis suggested that this was not likely to be confounded by the effects of ageing.

The potential contribution of prodromal symptoms of dementia was considered. In exploratory analyses, elevated depressive symptoms and declining cognition were observed amongst participants who later developed dementia. This observation was consistent with the possibility that the depressive episodes (or PEDS) and cognitive decline could both be prodromal symptoms of dementia. However, in sensitivity

analyses, the post-PEDS cognitive deficit and decline remained evident after excluding participants who subsequently developed dementia.

Further analyses considered the possibility that, if depressive symptoms had not fully resolved after the end of PEDS, then residual subclinical depressive symptoms could account for the post-PEDS cognitive deficits. Exploratory analyses confirmed the presence of an incremental negative association of cognition with depressive symptoms, throughout the full range from subclinical to higher levels. Individual symptoms most strongly associated with poorer cognition were identified.

Nevertheless, in sensitivity analyses, the deficits and decline remained evident after excluding PEDS which were followed by the persistence of these symptoms.

In age-stratified analyses, amongst participants aged over 55 the relative rate of post-PEDS cognitive decline appeared to be more pronounced at older ages of onset. Conversely, in comparison with participants with no depression, cognition before the start of the PEDS was significantly poorer amongst participants aged 55 to 74, whereas this difference was attenuated and nonsignificant amongst older participants.

PEDS beginning over the age of 65 were further investigated with respect to the presence or absence of prior psychiatric history. Amongst those with prior psychiatric history, cognition before the start of PEDS was poorer than cognition amongst nondepressed participants. Findings regarding post-PEDS decline in this group differed according to the cognitive measure used. Amongst those with no prior psychiatric history, cognition before the start of PEDS did not differ from cognition amongst nondepressed participants, and cognitive decline was faster post-PEDS than pre-PEDS.

## **5.2 Strengths and limitations of the study**

A strength of the study was the use of the HRS data source, which included the repeated, concurrent administration of measures of cognition and depression in a large sample over an extended follow-up period. The duration of follow-up facilitated the comparison of trajectories of cognitive change before and after PEDS.

The two-year interval between observations is longer than the typical duration of a depressive episode. This is a limitation because PEDS may have occurred between observations and gone undetected. In the group with no observed depression, the consistency of their non-depressed status at all observations (including CIDI-SF retrospective evaluations of the year prior to the observation), together with their absence of prior psychiatric history, provides some confidence that they are likely to have remained non-depressed between observations. Furthermore, in this large group, the impact of occasional misclassifications on the findings due to unobserved PEDS is likely to be small. However, amongst those with observed PEDS in the longitudinal analysis, depression status was (by definition) observed to fluctuate, and thus more likely also to have fluctuated between observations. Furthermore, misclassifications in this smaller group will have greater impact on results. Potentially, cognitive decline during the supposedly nondepressed period after a PEDS could in fact be due to unobserved PEDS during that period. On the other hand, if this were a significant contributor to the results, it would be expected to have a similar impact in the pre-PEDS period. The results indicated that pre-PEDS cognitive decline did not differ from cognitive decline in participants without observed depression.

Because any observed PEDS and any observed cognitive change could have begun at any point since the last observation, the two-year interval between assessments also limits the evaluation of PEDS duration and the accurate tracking of the temporal relationship between changes in depressive symptoms and cognition.

Whilst the two-year interval between observations was too long to ensure detection of PEDS, it was also too short to ensure that the cognitive measure was free of practice effects, which have been reported to persist for up to five years in some circumstances (Calamia et al., 2012). It is possible that the findings could represent a depression-related decline in the ability to benefit from practice, rather than a decline in cognitive function. A loss of practice effect would still be of potential clinical concern, as the absence of practice effects may be associated with pathology and predict future cognitive functioning (Calamia et al., 2012). It is also possible that a higher number of repeat assessments could result in greater practice effects. If measures of cognitive function become increasingly inflated at successive assessments, the observed cognitive deficit after PEDS (relative to measures taken

before the PEDS) could be an underestimate. However, in this study, practice effects are likely to have been reduced, at least for the episodic memory component, by the use of alternate forms in the list learning test.

The cognitive assessment used in the analysis was a version of the TICS-M cognitive assessment. This test and its variants have been used widely, although this may be due primarily to its convenience of administration rather than its psychometric properties. A recent systematic review of psychometric properties of screening tools for MCI (Wen et al., 2025) found only one psychometric evaluation of TICS-M (Bentvelzen et al., 2019) and concluded that the test was not sufficiently reliable to be recommended as a screening instrument for this purpose. However, screening for MCI was not its purpose in this thesis. For the assessment of healthy older people for research purposes, TICS-M has been recommended on the basis of the distribution of its scores, which are normally distributed and free of the ceiling effect which limits the value of some other tests with this population (De Jager, Judge & Clarke, 2003). The total TICS-M score has also been reported to show moderate correlations with comprehensive neuropsychological assessment results (Van den Berg et al., 2012) Furthermore, as previously noted, cognitive deficits associated with depression are observed across a range of functions and are not domain specific (Kriesche et al., 2023). Findings were therefore not expected to be specific to the precise choice of cognitive test. There is a lack of information available to evaluate whether the use of the TICS-M could artifactually overestimate associations between cognitive function and depression. Some underestimation of true associations may be expected, given the somewhat modest associations of the TICS-M with more comprehensive measures of cognition.

TICS-M is commonly scored simply by summing all item scores. This results in a score which is heavily weighted towards episodic memory (as the word lists make up a high proportion of all test items). The study addressed this by creating composites giving equal weights to episodic memory, working memory, and (where available) the orientation and naming score, to derive a more balanced measure of general cognitive functioning. This procedure followed common practice in the construction of composite cognitive measures (Harrison et al., 2007), but other procedures could have been considered. Factor analysis (FA) and principal components analysis (PCA) are analytical procedures commonly applied to cognitive data (Santos et al.,

2015). FA hypothesises underlying “latent” variables (such as the g factor) which contribute to cognitive test performance, whereas PCA is a pragmatic data reduction method which does not presume or draw on the concept of latent variables. Cognitive/psychometric theory is often based on the latent variable assumption and evaluated using FA (Carroll, 1993), and whilst PCA is also commonly used in cognition research (e.g. Lyall et al., 2016), the appropriateness of this usage is debated (Santos et al., 2015).

FA and PCA of cognitive test scores typically yield multiple-factor/multiple-component solutions, representing different cognitive functions or domains as separate constructs. In a sample of 243 cognitively unimpaired older people, Van den Berg et al., (2012) extracted four factors from a version of the TICS-M. For the purposes of the current thesis, it is not clear whether decomposing cognition into multiple components would have been desirable, given that the cognitive deficits associated with depression have been found not to be specific to particular cognitive domains. Truong et al.(2023) analysed a version of the TICS-M using Rasch analysis, a procedure which yields a unidimensional model and facilitates transformation of (ordinal) raw cognitive test scores into an interval variable. They argue that the use of a transformed interval variable reduces measurement error and may thus improve the statistical power of analyses. In the current thesis, it is possible that the use of a suboptimal method of defining a composite cognitive test score could have resulted in true associations being overlooked.

With regard to the measurement of depression, the CES-D8 data (collected at 94% of a total of over 200,000 observations) were used in preference to the less frequently administered CIDI-SF measure. Exploratory analyses suggested that the CES-D8 was also more closely related than the CIDI-SF to cognitive function. However, scores on the CES-D8 scale are not direct indicators of the presence or absence of depressive episodes. To address the research question, it was necessary to construct an analogue of depressive episode, namely PEDS based on CES-D8 scores. This definition used a recommended cut point for identifying cases of depression, combined with a longitudinal change criterion to mitigate against the possibility of excessively frequent reclassification due to trivial fluctuations in the

score. The relatively high numbers of these PEDS (relative to the lower numbers of episodes identified by the CIDI-SF where concurrent, and to population estimates of the prevalence of depressive disorder) suggests that includes instances of subclinical depressive symptoms which fall short of a diagnostic threshold. Thus, PEDS are not equivalent to depressive episodes and may in some cases be milder expressions of depression. Cognitive effects associated with depressive episodes could potentially be stronger than those associated with PEDS in the current analyses, but this cannot be assumed, as associations of cognition with depressive episodes could be qualitatively different from those with PEDS. (For example, depressive episodes could be more strongly associated with poorer pre-episode cognitive function and less with cognitive decline during the episode.)

The definition of PEDS used in this thesis could be vulnerable to contamination if some CES-D8 items are more closely related to cognitive function than to depression. In particular, the item “everything was an effort” was strongly related to cognition but does not correspond directly to any of the diagnostic criteria for depressive disorder. If this item is a subjective marker of cognitive decline and not a symptom of depression, the associations presented in this thesis may have been artifactually inflated.

The design of the study introduced significant selection bias. Specifically, its requirements resulted in the exclusion of severe and chronic cases of depression. Individuals with poorer baseline cognition or higher baseline levels of depression were less likely to participate in sufficient follow-up visits to be included in the longitudinal analysis. Furthermore, in order to be included, those who participated in follow-up were required to develop and recover from a PEDS during the observation period. Therefore, chronically depressed individuals were systematically excluded. This is likely to have reduced variance in trait phenomena within the sample. In contrast to the full HRS sample, in which participants with PEDS had lower than average levels of education, depressed participants in the longitudinal analysis were educationally similar to the HRS average. Thus the observed baseline characteristics of participants with PEDS, and comparisons with those without, are peculiar to this sample and not generalisable to populations. The finding that cognition is poorer after PEDS than before them is likely to reflect a true difference amongst individuals who experience depression relatively briefly and mildly, whereas

different patterns remain possible amongst those with more severe or chronic presentations. For example, more severe and chronic cases could be associated primarily with poor premorbid cognitive function rather than with cognitive decline during the period of depression.

Bias could also have been introduced by the decision to use complete-case analysis (CCA, i.e. excluding participants with missing data) instead of imputing missing data. As well as reducing sample size and thus statistical power, CCA may result in either over- or underestimation of effect sizes, depending on the pattern of associations of missingness with exposure and outcome variables (Knol et al., 2010). Such associations are likely in the current study as, given its reliance on self-report, it is plausible that participants with higher depression or poorer cognition could be less likely to provide complete data. The decision to use CCA was based on the high rates of data completeness in the full sample, with depression data available at 94% of all observations, the components of the two-component cognitive composite (episodic and working memory) available at 90% of all observations, and baseline values of each covariate available for over 99% of participants. Thus few participants were excluded due to missing data and the consequent loss of statistical power is therefore modest. The high rates of data completeness are likely to have limited but not eliminated the extent of bias (including the possibility that the reported effect sizes are overestimates). In simulations presented by Knol et al., (2010), whilst the extent of bias increased with higher rates of missing data, a small bias remained evident even when the rate of missingness for a confounder was below 5%. Conversely, the study may address a gap in the literature by reporting on a population with low levels of depression which are likely to be absent from studies of clinical samples. One advantage of this is the opportunity to evaluate associations amongst individuals who have not received treatment for depression, thus avoiding the potential for associations to be confounded by the effects of treatment.

A further strength of HRS was the availability of data on a wide range of relevant covariates and potential confounders, although the reliance on self-report is a limitation. In particular, the reliance on self-report of dementia will almost certainly have failed to identify many cases, as the majority of individuals with dementia are

likely to be undiagnosed or unaware of their diagnosis (Amjad et al., 2018). Although the exclusion of known cases of eventual dementia from sensitivity analyses had limited impact on the pattern of results, it remains possible that the findings could be attributable to depressive symptoms arising in the prodromal period prior to the development of dementia.

A limitation of the study was the absence of younger participants, with under-50s restricted to the small group of younger partners of older participants. The intended remit of the study was not restricted to late-life depression, but in the absence of younger participants it is not possible to evaluate whether the results represent a feature of late-life depression as distinct from depression in general. Age-stratified analyses are suggestive of this possibility, as the observed effects appeared to be more prominent at older ages. Reviews of cohort studies of younger participants revealed that cognitive function is less commonly assessed in younger cohorts, and where such assessments exist, they are repeated insufficiently frequently for the purposes of the study.

### **5.3 Relationship and contribution of the results to the knowledge base**

The results are consistent with the conclusions of multiple reviews that cognitive deficits persist after the resolution of a depressive episode (Hammar & Årdal, 2009; Douglas & Porter, 2009; Hasselbalch, Knorr & Kessing, 2011; Bora et al., 2013; Roca et al., 2015; Kriesche et al., 2023). The thesis adds the novel demonstration that deficits are at least partly acquired at or around the time of a PEDS.

The observation of accelerated cognitive decline after the end of PEDS is not straightforward to reconcile with prior literature. In smaller studies, accelerated decline during or after a depressive episode has been reported to be absent (Olaya et al., 2019; Köhler et al., 2010), or present only in subgroups (Geerlings et al., 2000). Formánek et al. (2020) analysed data from over 69,000 participants aged over 50. They found that cognitive decline was no faster amongst individuals whose depressive symptoms decreased (from broadly clinical to broadly nonclinical levels) than amongst participants with consistently low levels. In that study, cognitive trajectories represented the average rate of change over the full period of declining depressive symptoms, not the rate of change within the non-depressed period after

an episode. Potentially, a cognitive improvement associated with the decline in depressive symptoms could have offset and masked ongoing cognitive decline in the absence of symptoms. The current thesis also included longer duration of follow-up and more observations per participant than Formánek et al. (2020). Nonetheless, the finding is novel and warrants further investigation.

#### **5.4 Compatibility of the results with causal hypotheses**

The temporal sequence of PEDS and their associated changes in cognition is compatible with various directions and mechanisms of causality. The observed associations could arise if depression causes cognitive decline (for example, via biological mechanisms proposed by Byers and Yaffe (2011)), or if the onset of cognitive decline causes depression (perhaps as a psychological reaction to awareness of decline, or as a consequence of deteriorating ability to cope with stressors), or if a third (confounding) factor causes both. If the latter, the finding that periods of depression coincide with the onset of cognitive decline would be difficult to explain in terms of distal or long-term factors (such as low education) and suggests that temporally proximal factors may be involved. If such factors are potentially treatable or preventable, periods of depression could signal a window of opportunity to intervene to prevent cognitive decline.

#### **5.5 Potential implications for intervention**

The growing recognition of cognitive sequelae of depressive episodes has prompted calls to make the recovery of cognitive function an explicit target in the treatment of depression (Bortolato et al., 2016; Kaser, Zaman & Sahakian, 2017). Preliminary small-scale studies have explored cognitive remediation therapy or cognitive training (Therond et al, 2021; Naismith et al., 2010) as direct approaches to targeting cognitive dysfunction in depressive disorder, but these approaches are not yet well evidenced. Transcranial magnetic stimulation (Begemann et al., 2020) and physical exercise (Dauwan et al., 2021) have been reported to improve cognitive function in neurological and psychiatric disorders including depression. With regard to pharmaceutical interventions, vortioxetine is a novel antidepressant noted for its procognitive effects (Frampton, 2016) including in older adults (Bishop et al., 2021).

It has been reported to exert an independent effect on cognition (McIntyre, Lophaven & Olsen, 2014) over and above the indirect cognitive improvements associated with reduction in depressive symptoms which may be common to a range of antidepressant medications (Ainsworth et al., 2024). In older adults this independent effect may be restricted to depression of late (i.e. more recent) first onset (Xue et al., 2024).

The research question of the current thesis was predicated on the concept of depression as an episodic disorder. In clinical practice, intervention for depression is generally considered to have been successful if the individual is no longer in a depressive episode (or if recurrences are prevented), and individuals whose episodes resolve spontaneously are not considered to require intervention. By contrast, chronic health conditions such as diabetes and asthma are not presumed to be temporarily cured or optimally managed in the intervals between symptomatic episodes. The harms associated with diabetes do not arise solely during symptomatic episodes, but continue to accrue during asymptomatic periods and may be at least partly attenuated by enhanced glucose control over and above what is required to prevent episodes (Callaghan et al., 2012). In the case of depression, whilst the results of the current thesis are consistent with the hypothesis that cognitive decline is associated with depressive episodes, the observation of continuing cognitive decline after the end of a PEDS (at least in older people) provides a rationale for ongoing management of cognitive risk outside symptomatic episodes.

The characteristics of the full HRS sample, and the body of literature on the topic, indicate that cognition prior to the development of depression is likely to be poorer, on average, than cognition in the general population. This poses difficulties for defining the goal of 'restoring' cognitive function in patients whose level of premorbid function was not measured. By contrast, the rate of ongoing cognitive decline amongst individuals who have recovered from an episode of depression is directly measurable. This provides opportunities for the investigation of possible pathologies and the evaluation of treatments.

Regarding pathologies or markers of cognitive decline, emerging new technologies now facilitate the rapid measurement of many thousands of proteins and fluid

biomarkers in small volumes of serum or plasma, and are transforming research into biomarkers of age-related neurodegenerative disorders (Durcan et al., 2025) and cognitive function (Tin et al., 2023). These technologies may be particularly valuable in the detection of silent pathologies and biological pathways underpinning aetiological mechanisms at pre-symptomatic disease stages. In the context of depressive disorder, biomarker identification is already an active focus of research in relation to symptomatic presentations and the outcomes of symptomatic treatment (Mora, Zonca, Riva & Cattaneo, 2018). On the basis of the current results, it may be hypothesised that biomarker evaluation could also be informative in the asymptomatic period after recovery from a depressive episode, to investigate factors associated with cognitive decline in this period.

With regard to the evaluation of treatments, individuals who have reached remission from a depressive episode could be randomised to a treatment intended to maintain cognitive function, and their subsequent cognitive trajectories compared with a control group. A recent study (Rajji et al., 2025) used this design to evaluate the effectiveness of cognitive remediation in combination with transcranial direct current stimulation (tDCS) in older people with remitted MDD. Over a mean follow-up period of four years, with five-day booster treatments every six months, cognitive decline in the treatment group was significantly slower than in the control group. In principle, this design could be used to evaluate other interventions. For example, lifestyle interventions to prevent cognitive decline in older people at risk of dementia (such as FINGER: Ngandu et al., 2015) already contain many components of behavioural interventions for depression. If applied or continued after remission from a depressive episode, it would be possible to investigate whether they could fulfil an enhanced or dual function, serving not only to prevent the recurrence of depressive symptoms but also to prevent cognitive decline whilst asymptomatic.

Nevertheless, it is not necessary to presume that the affective and cognitive elements of depression will be optimally addressed by developing a single intervention with dual effects. Whilst a depressive episode may contribute to the development of cognitive dysfunction (and hence, potentially, the prevention of depression could help to prevent cognitive decline), subsequent management of the associated cognitive dysfunction could be considered quite separately from the treatment and resolution of the depressive episode. As a goal of treatment, delaying

decline over the longer term is likely to amount to a more impactful clinical outcome than a short-term target of restoring cognitive function immediately following a depressive episode.

## **5.6 Conclusions and implications**

Based on a sample of US residents aged over 45 drawn from a general population sample, this study found that those who developed and recovered from a period of depressive symptoms had poorer cognition after the episodes than before them. This result is consistent with the balance of the existing evidence, and contributes the novel finding that post-depressive cognitive deficits were acquired at or around the time of the depressive symptoms.

After recovery from depressive symptoms, cognition was found not only to remain poorer than before the depressive symptoms, but to continue to decline. Attempts to exclude individuals in the preclinical stages of an incipient dementia yielded inconclusive results: after these exclusions the magnitude of the effect size was not attenuated, but the difference was no longer statistically significant. Further research, monitoring the trajectories of cognitive function amongst older people who have recovered from a depressive episode, is required in order to evaluate their risk of cognitive decline. If so, emerging new research technologies and intervention strategies could facilitate the investigation and development of interventions to prevent further cognitive decline in this group.

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