Depression prodromal to dementia mechanisms, biomarkers and potential drug targets

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Depression prodromal to dementia: mechanisms, biomarkers and potential drug targets

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Contents

Abstract

Background

The association between depression occurring in late life (in individuals aged 60-65 and above) and subsequent onset of dementia has been demonstrated consistently in a number of cohort studies and meta-analyses. However, much remains unknown at the moment about the determinants of this association. In particular, it is debated whether depression in late life represents a prodrome or risk factor for dementia, or a reaction to emerging cognitive deficits, and whether depression with an onset in later life (LOD) is a stronger predictor of future dementia compared to early- and midlife-onset depression (EOD) with recurring episodes in later life. Furthermore, little is known about the specific factors of a late-life depressive episode – especially biological markers - that might predict progression to dementia.

Methods

The present thesis investigates the relationship between depression in later life and dementia or cognitive decline by means of two systematic reviews and the analysis of three longitudinal cohorts. Using a retrospective cohort derived from the Clinical Record Interactive Search (CRIS) dataset and linked datasets, the clinical phenotypes and specific symptoms of late-life depression predicting future progression to dementia were explored. Second, the longitudinal associations between the trajectories of depressive symptoms, anxiety symptoms, and four cognitive domains were explored in a longitudinal prospective internet-based population sample (the PROTECT study). Finally, the role of an array of plasma inflammatory markers in late-life depression and subsequent progression to dementia was examined using a clinical inpatient sample of elderly depressed patients (PRODE) and a control group of non-depressed cognitively intact elderly individuals (COGNORM).

Results

The two cohorts with diagnosis of dementia as an outcome measure demonstrated a rate of progression to dementia of around 26%. In neither cohort substantial evidence was found to support the hypothesis that late-onset depression is associated with higher risk of conversion to dementia than earlier onset. Clinical symptoms of depression most strongly associated with subsequent onset of dementia were hallucinations and irritability. A number of plasma inflammatory markers were higher in participants with late-life depression compared to

controls; however, none of these markers were predictive of progression from late-life depression to dementia during 3 years of follow-up.

The study exploring longitudinal associations between the trajectories of PHQ-9 scores, GAD-7 scores, and four cognitive domains found that depressive symptoms were predictive of worse performance on verbal working memory and episodic memory tests, while anxiety was negatively associated with performance on spatial working memory (SWM) tests. Stratification into participants with and without a history of depression demonstrated substantial differences, namely depressive symptoms only predicted poorer scores on verbal memory tests in never-depressed participants, similarly for the relationship between anxiety and SWM; however, the associations between both depression and anxiety and measures of general intelligence were much stronger in the group of participants reporting a history of depression.

Conclusions

This thesis confirms a substantial increase in dementia risk in patients with late-life depression. The likelihood of progression to dementia was not significantly higher in late-onset depression compared to early-onset depression, although mechanisms may be different. Future research should strive to differentiate between the phenotypes of late-life depression and early dementia with more precision. Although no evidence of the role of plasma inflammatory factors as predictors of progression from depression to dementia was found, patients with late-life depression had higher levels of several inflammatory markers compared to control subjects. Future research should continue to examine whether both inflammatory and non-inflammatory, biomarkers can predict progression from late-life depression to dementia.

Statement of contribution

All aspects of the four cohort studies (including three longitudinal cohorts and one cohort of control subjects, COGNORM) were designed by the principal investigators and co-investigators.

The Clinical Record Interactive Search (CRIS) system was developed for use within the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC). The principal investigator is Professor Robert Stewart; access to data and data retrieval were achieved with the assistance of Dr Gayan Perera and Dr Christoph Mueller. Chapter 5 represents independent research conducted on the platform of National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

The PROTECT cohort was developed under the leadership of Professor Clive Ballard while he was Professor at King's College London; at present Prof Ballard is the Pro-Vice Chancellor and Executive Dean at University of Exeter Medical School. The principal investigator of the study is Dr Anne Corbett, Senior Lecturer in Dementia Research at University of Exeter Medical School, who also previously worked at IoPPN, KCL.

The PRODE cohort was developed by Dr Tom Borza, a geriatric psychiatrist working at the Institute of Clinical Medicine, Faculty of Medicine at University of Oslo, during his PhD. The project was supervised by Professor Knut Engedal and Pprofessor Geir Selbæk. The COGNORM is a cohort of non-depressed cognitively healthy Norwegian adults aged 65 and above, designed by Dr Leiv Otto Watne, a postdoctoral researcher at the Department of Geriatric Medicine, University of Oslo.

This thesis uses data retrieved from the CRIS cohort and matched datasets (Hospital Episode Statistics and Office for National Statistics mortality data) for the period between January 1st, 2008 and March 31st, 2017; data from the PROTECT cohort collected between November 2015 and August 2019; data from the PRODE cohort collected between December 1st, 2009 and January 1st, 2013, and control data from the COGNRM study collected between 2012 and 2013.

I started the PhD in October 2017 by writing the protocol for and then conducting the systematic review of biomarkers predicting the conversion from late-life depression to dementia (Chapter 3; review was updated in March 2021). Next, I formulated the hypotheses and requested and received approval for access to the four cohorts mentioned above. Initially, data was also requested from the Dementia Disease Initiation (DDI) cohort (Principal Investigator Professor Tormod Fladby, Akershus University Hospital), and data analysis was performed, and results reported in a research meeting, however this section was not included in the final thesis due to the absence of clinically significant depressive symptoms among participants.

I was responsible for all hypothesis formulation, data management, statistical analysis and interpretation of findings throughout the course of the PhD, with statistical guidance from the Department of Biostatistics and Health Informatics, IoPPN, King's College London. My supervisors, Professor Dag Årsland and Professor Allan Young, advised me on each step. I completed a postgraduate certificate programme (PgCert) in Applied Statistical Modelling and Health Informatics at the Department of Biostatistics and Health Informatics, IoPPN, KCL, and have extended it to a part-time MSc which is currently underway. For example, Chapter 6 was completed using the knowledge and skills obtained in the "Structured Equation Modelling" module of the PgCert. Dr Christoph Müller advised me on the initial statistical analysis plan for Chapter 5; Dr Roopal Desai and Dr Amber John from the ADAPT Lab at University College London (UCL) have advised on statistical analysis plan for Chapter 6.

All manuscripts presented have been written by me and edited in response to my supervisors' comments, as well as comments from the following collaborators: Dr Christoph Mueller (Chapter 5), Dr Byron Creese, Dr Roopal Desai and Dr Amber John (Chapter 6), and Dr Tom Borza (Chapter 7, parts A and B).

Chapter 1. Introduction

1.1 DEPRESSION

1.1.1 Definition and healthcare implications of depression

Major depressive disorder (MDD) is a common medical condition characterised by low mood, anhedonia, alteration of levels of energy or aversion to activity. In accordance with the latest edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a diagnosis of MDD can be made if the person presents with at least one of two core symptoms (depressed mood and lack of interest) along with four or more of the following symptoms for at least 2 weeks: feelings of worthlessness or inappropriate guilt; diminished ability to concentrate or make decisions; fatigue; psychomotor agitation or retardation; insomnia or hypersomnia; significant decrease or increase in weight or appetite; and recurrent thoughts of death or suicidal ideation (American Psychiatric Association, 2013).

While DSM-5 does not distinguish between mild and moderate/severe depression on the basis of the number of symptoms (rather on the severity of the symptoms and functional impairment), ICD-10 requires that a different number of core and additional criteria from the following list be satisfied for mild, moderate and severe depression:

A. The general criteria for depressive episode (F32) must be met.

B.

(1) depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and

almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks.

(2) loss of interest or pleasure in activities that are normally pleasurable.

(3) decreased energy or increased fatiguability.

C.

(1) loss of confidence and self-esteem.

(2) unreasonable feelings of self-reproach or excessive and inappropriate guilt.

(3) recurrent thoughts of death or suicide, or any suicidal behaviour.

(4) complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation.

(5) change in psychomotor activity, with agitation or retardation (either subjective or objective);

(6) sleep disturbance of any type.

(7) change in appetite (decrease or increase) with corresponding weight change).

For a diagnosis of mild depression, a patient's condition must satisfy at least 2 criteria from (B) and at least 1 criterion from (C), such that at least 4 symptoms in total are present. For a diagnosis of mild depression, a patient's condition must satisfy at least 2 criteria from (B) and at least 3 criteria from (C), such that at least 6 symptoms in total are present. Finally, for depression to be classified as severe, all 3 criteria from (B) and at least 5 criteria from (C) must be satisfied, summing up to at least 8. Additional specifications exist for a diagnosis of severe depression with psychotic features (World Health Organisation, 2004).

According to the recent WHO report, more than 264 million people worldwide are affected by depression, and the estimated annual costs associated with depression in the UK is £7.5 billion, although as mentioned in the Department of Health strategy on mental health, the impact of decreased productivity and human costs might increase this economic burden up to £20.2–23.8 billion a year (GBD 2017 Collaborators, 2018; Department of Health, 2011). In February 2017, the WHO report named depression as the leading cause of disability worldwide (World Health Organisation, 2017).

1.1.2 Definition and epidemiology of late-life depression

The term "late-life depression", or "geriatric depression", refers to a depressive episode or "clinically significant depressive symptoms" occurring in patients aged 60 or above, although there is little consensus on the age threshold, and many authors consider 65 to be a more accurate cut-off (Fiske et al., 2009; Park et al., 2012; Ismail et al., 2013). The term 'clinically significant depressive symptoms" refers to depressive symptoms with severity above the threshold of commonly used psychometric scales, e.g. Geriatric Depression Scale (GDS-6 or GDS-15), Patient Health Questionnaire (PHQ-9), etc. Many studies operate definitions of depression based on psychometric scales as opposed to clinical diagnoses.

The estimates of the prevalence of clinically significant depressive symptoms or depressive episodes among older adults in the general population vary in a wide range, with varying definitions possibly contributing to the inconsistency in figures: from 2% to 23.6% according to various studies (Blazer et al., 1980; Murrell et al., 1983; Berkman et al., 1986; Ritchie et al., 2004; Fichter et al., 1995; Fontoulakis et al., 2003; Riedel-Heller et al., 2006). The proportion of people suffering from depressive symptoms increases with age (Chui et al., 2015). A more recent study using the Survey on Health, Ageing and Retirement showed a

prevalence of 29% among almost 29,000 elderly people residing in Europe in general, with the highest proportion (35%) observed in Southern Europe and the lowest (16%) in Scandinavia (Horackova et al., 2019). Another recent study reported a prevalence of 5.6% for subthreshold depressive symptoms in the population (Forlani et al., 2011). A meta-analysis focusing on incidence rates showed that the incidence rate of MD was 0.2–14.1/100 person-years, and incidence of clinically relevant depressive symptoms was 6.8/100 person-years (Buechtemann et al., 2012). Studies have highlighted the "enormous" burden of depression in old age for all sectors of the healthcare system (Bock et al., 2016).

1.1.3 The heterogeneity of late-life depression

Depression in general, and specifically late-life depression, is recognised as a heterogenous disorder. An important source of diversity in late-life depression is the difference in the age of onset. In the context of geriatric depression, the term "early-onset depression" (EOD) most often refers to depressive disorder with an onset at any time before the old age (i.e. may describe depression with an onset in adolescence, young age, midlife etc), and a recurrent episode after the age of 60-65, although definitions may vary based on the purpose of the study. Late-onset depression (LOD), in contrast, describes depression with the onset of the first episode after the age of 60 or 65.

Several studies have revealed clinical and phenomenological differences between EOD and LOD. EOD patients have been shown to have a higher rate of family history of mental illness, personality abnormalities and anxiety (Brodaty et al., 2001); while late-onset depression was linked to higher degree of loss of interest (Krishnan et al., 1995). However, the phenomenological differences have not been consistently replicated. The differences in vascular pathology, biological underpinnings and neurocognitive performance are discussed in further sections.

1.1.4 The current understanding of the neuropathological features of major depression

The present understanding of the neurobiological underpinnings of major depression spans across several areas of pathological changes: neuroanatomical, biochemical, immunological, etc.

Studies using voxel-based morphometry have demonstrated reduced volumes in ventromedial prefrontal cortex (VMPFC), lateral orbital prefrontal cortex (LOPFC),

dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), ventral striatum, the amygdala and the hippocampus (Maletic et al., 2007; Du et al., 2018). Besides structural abnormalities, multiple studies imply disrupted neuronal connectivity as one of the key features of depressive disorder (Li et al., 2018). Disruptions in neuronal connectivity refers to the dysfunctionality of the processing of information within neuronal networks, such as, for example, the default mode network (DMN) or the cortico-limbic network. The DMN is believed to be comprised of regions such as the ventromedial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC) and the precuneus, and altered activity and reduced stability of the DMN has been implicated in depression, and specifically depressive rumination (Kaiser et al., 2015; Bergman et al., 2014; Wise et al., 2017). The cortico-limbic network is the one linking the medial prefrontal cortex with limbic structures, and alterations in its functioning have also been associated with MDD (Klauser et al., 2015). Another type of neural network which has been described in association with major depression is the so-called affective network, encompassing the subgenual and the pregenual anterior cingulate cortex, the hypothalamus, the amygdala, and the nucleus accumbens (Helm et al., 2018).

The effect of depression on the dynamic relationship between neuroanatomical structures is illustrated by a graph adapted from Maletic et al. (2007; See Fig. 1)

One of the main factors influencing the activity of neural networks and neuronal density resulting in grey matter volume loss is synaptic plasticity, or the alteration in the efficacy of synaptic transmission between the neurons (Colicos et al., 2006). Synaptic plasticity is a fundamental function of the brain, responsible for processing and storing information and producing appropriate responses (Duman et al., 2016). Changes in synaptic plasticity, including synaptic loss, have been observed in patients with major depression (Duman et al., 2012). In rodent models, it has been demonstrated that stress can lead to the reduction in the density of glia and the dendritic atrophy of pyramidal neurons in the PFC (Li et al., 2008; Christoffel et al., 2011), and, in contrast, the increase in dendritic spine density in the amygdala (Vyas et al., 2006).

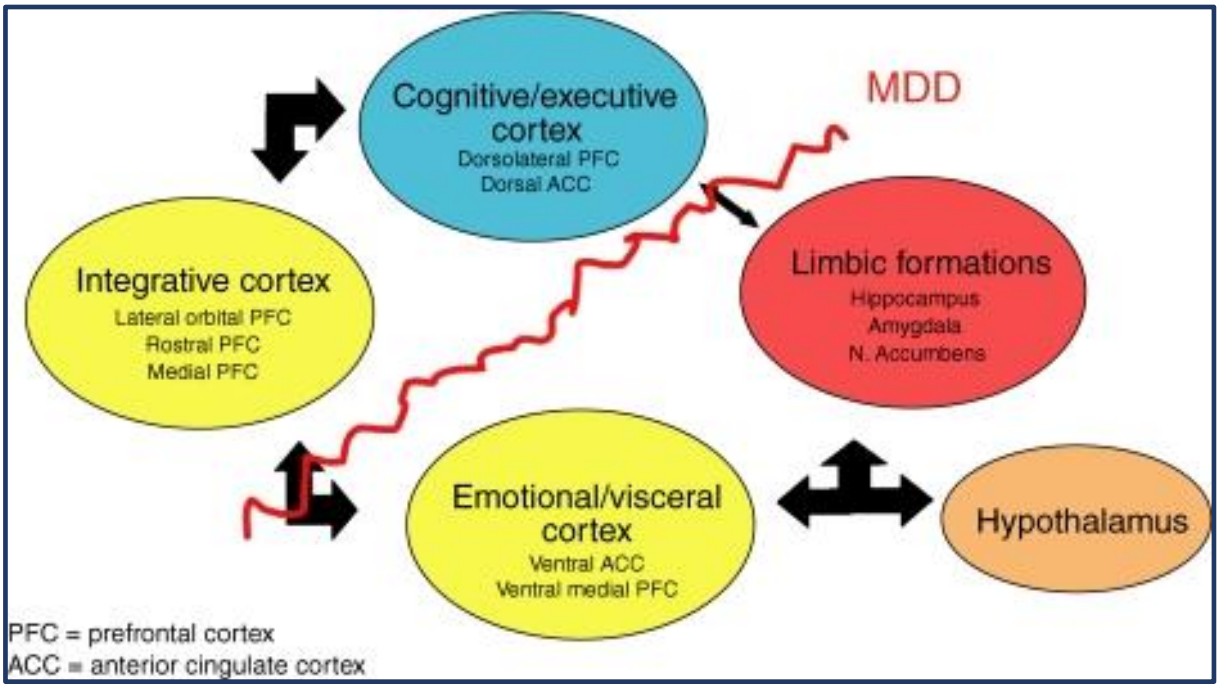


Fig. 1. A proposed scheme of the effect of major depression on the dynamic relationships between neuroanatomical structures (Adapted from Maletic et al., 2007)

Synaptic plasticity and grey volume loss may be tightly linked with the imbalances in neurotransmitter activity – the key element of the model of depression widely accepted today (Meyers et al., 2000). PET studies have demonstrated that in non-depressed people, the concentration of 5-HT(1A) receptors was positively associated with grey matter volumes, especially in the hippocampus, insula, orbital prefrontal cortex, and parietal lobe, although the correlation was not significant for MDD patients, suggesting a possible presynaptic 5-HT1A autoreceptor-mediated inhibition of neuroplasticity in MDD (Kraus et al., 2012; Zanderigo et al., 2018; Albert et al., 2019). Another PET study demonstrated that reduced serotoninergic transmission was correlated with the number of axons between the raphe nucleus and several cortical regions (Pillai et al., 2018). The administration of antidepressant medication, on the other hand, has been shown to improve synaptic plasticity through stimulating neurogenesis, increasing the expression of neurotrophic factors, and the regulation of synapse formation (Castren et al., 2013). Besides, recent studies have shown that an experimental antidepressant drug, NMDA-receptor antagonist ketamine, may rapidly increase hippocampal synaptogenesis (Ardalan et al., 2017).

Another mechanism largely contributing to synaptic loss and brain shrinkage, especially in the hippocampal area, is corticosteroid neurotoxicity (Tata et al., 2010). HPA

axis abnormalities have been long and consistently implicated in the pathophysiology of depression, although some authors argue this may not be relevant for all depression phenotypes (Juruena et al., 2018, Lamers et al., 2018). In rodent models, chronic exposure to high levels of corticosteroid hormones has been shown to result in neuronal atrophy, synaptic loss and reduction in synaptic activity in the PFC and hippocampus (Magarin et al., 1995; Liu et al., 2007). Besides direct neurotoxicity, chronic disruptions of the HPA-axis may affect grey matter volumes and synaptic plasticity via insufficient regulation of inflammatory immune response due to "glucocorticoid resistance", i.e., the resistance of glucocorticoid receptors (GR) (Silverman et al., 2012). A recent meta-analysis showed that glucocorticoid resistance in depressed patients is associated with increased levels of Il-6 and TNF-a (Perrin et al., 2019). Whatever the precise mechanisms, elevated levels of inflammation are a consistent finding in patients with late-life depression. **Table 1** summarises the findings of recent meta-analyses with regards to differences in plasma and CNF cytokines between patients with major depression and controls. Apart from inducing hippocampal damage (Dafsari et al., 2020; Tsopelas et al., 2011), inflammation is hypothesised to affect glial function in depressed patients and lead to exaggerated release of glutamate by glial cells (Haroon et al., 2017), although the reduction in glial density was only demonstrated in the amygdala (Bowley et al., 2002; Hamidi et al., 2004), and not in OFC, ACC or DLPFC for which volume loss has been consistently reported. Another proposed mechanism linking inflammation, glial function and late-life depression is through the enhanced expression of quinolinic acid by microglia and of kynurenic acid by astrocytes, which is known to interfere with neurotransmitter function and is proven to be a feature of depression.

A graph combining pooled estimates for a wide range of inflammatory factors, adapted from the latest meta-analysis by Osimo et al., is presented in **Fig. 2.**

Inflammatory marker	Author, year	N of studies included	Findings
IL6	Howren et al., 2009	61	d = 0.25 (0.18; 0.31), p<0.001
	Dowlati et al., 2010	16	WMD 1.78 (1.23; 2.33), p<0.001
	Liu et al., 2012	18	SMD = 0.68 (.443 - .916)
	Valkanova et al., 2013 (prospective)	3	Weighted mean ES 0.097 (-0.005 0.198), p = 0.06
	Haapakoski et al., 2015	31	d = 0.54 (0.399-0.685), p<0.001
	Koehler et al., 2017	42	g = 0.62 (0.49 – 0.76), p<0.001
	Wang et al., 2018	7	SMD 0.40 (0.17 - 0.63), p<0.05
	Osimo et al., 2020	62	g = 61(0.39-0.82), p<0.01
TNF-a	Dowlati et al., 2010	13	WMD 3.97 (2.24; 5.71), p<0.001
	Liu et al., 2012	15	SMD = 0.567 (.134 – .989), p = 0.01
	Haapakoski et al., 2015	31	d = 0.398 (0.148-0.647), p = 0.002
	Koehler et al., 2017	42	g = 0.68 (0.43 – 0.92), p<0.001
	Wang et al., 2018	3	SMD 0.26 (-0.10 - .63)
	Osimo et al., 2020	48	g = 0.54(0.32-0.76), p<0.01
IL-1ra	Howren et al., 2009	14	d = 0.35 (0.03, 0.67), p = 0.02
	Osimo et al., 2020	7	g = 0.53(0.18-0.89) p<0.01
IL-1beta	Dowlati et al., 2010	9	WMD -1.58 (-3.59; 0.43)
	Liu et al., 2012	10	SMD -0.525 (-1.364 – 0.315)
	Haapakoski et al., 2015	14	d = -.047 (-.057 – 0.476)
	Koehler et al., 2017	22	g = 0.03 (-0.29 – 0.35)
	Wang et al., 2018	2	SMD 0.27 (-0.21 – 0.75)
	Osimo et al., 2020	26	g = 0.51 (0.16-0.86), p<0.01
IL-4	Dowlati et al., 2010	5	WMD 7.86 (-11.03; 26.75)
	Liu et al., 2012	5	SMD = 0.648 pg/ml; p = 0.568
	Koehler et al., 2017	10	g = -0.46 (-0.97; 0.04)
	Osimo et al., 2020	10	g = -0.73(-1.16, -.030), p <0.01
IL-2	Dowlati et al., 2010	5	WMD − 5.75 (−100.45 - 88.96)
	Koehler et al., 2017	10	g = -0.11 (-0.90 – 0.68)
	Osimo et al., 2020	12	g = 0.58 (0.06 – 1.11), p = 0.03
sIL-2R	Liu et al., 2012	8	SMD = 0.555 (0.276 – 0.835), p<0.001

	Koehler et al., 2017	10	g = 0.74 (0.42 – 1.05), p<0.001
	Osimo et al., 2020	10	g = 0.71(0.44, 0.98), p<0.01
IL-8/CXCL8	Dowlati et al., 2010	4	WMD -0.39 (-2.13; 1.35)
	Liu et al., 2012	4	SMD = 0.543 pg/ml; p = 0.299
	Eyre et al., 2016	8	SMD −0.58 (−1.53 to 0.36)
	Koehler et al., 2017	7	g = 0.03 (-0.35; 0.41)
	Leighton et al., 2017	29	SMD 0.26 (0.05 – 0.46), p = 0.01
	Wang et al., 2018	2	SMD 0.57 (0.20 – 0.95), p = 0.003
	Osimo et al., 2020	9	g = 0.77 (0.29; 1.26), p<0.01
IL-10	Dowlati et al., 2010	6	WMD 1.13 (-0.37; 2.63)
	Liu et al., 2012	6	SMD = 0.387 pg/ml; n/s
	Koehler et al., 2017	17	g = 0.38 (0.01; 0.74), p = 0.045
	Osimo et al., 2020	19	g = 0.49(0.17-0.82), p <0.01
IL-18	Koehler et al., 2017	5	g = 1.72 (0.379–3.062), p = 0.012
	Osimo et al., 2020	6	g = 1.97 (1.00-2.95), p<0.01
CCL3/MIP-1a	Koehler et al., 2017	3	g = 1.97 (-0.23; 4.18)
	Leighton et al., 2017	5	SMD 0.48 (0.20 – 0.76), p<0.001
CCL2/MCP-1	Koehler et al., 2017	8	g = 1.72 (0.64 – 2.79), p = 0.002
	Leighton et al., 2017	17	SMD 0.26 (0.01 – 0.51), p = 0.04
	Eyre et al., 2016	8	SMD 36.43 (2.43 - 70.42), p = 0.036
IFN-γ	Dowlati et al., 2010	4	WMD -6.63 (-25.91; 12.65)
	Liu et al., 2012	4	SMD = 2.481 pg/ml; n/s
	Koehler et al., 2017	17	g = - 0.48 (-0.94; -0.02), p = 0.043
	Osimo et al., 2020	16	g = 0.13(-0.22; 0.48)
TGF- β	Koehler et al., 2017	3	g = -1.480 (-4.756–1.797)
	Osimo et al., 2020	5	g = 0.08(-0.51; 0.67)

Table 1. A summary of meta-analyses of the association between major depression and a range of inflammatory factors; significant findings in bold; p-values are presented for significant and marginally significant findings only.

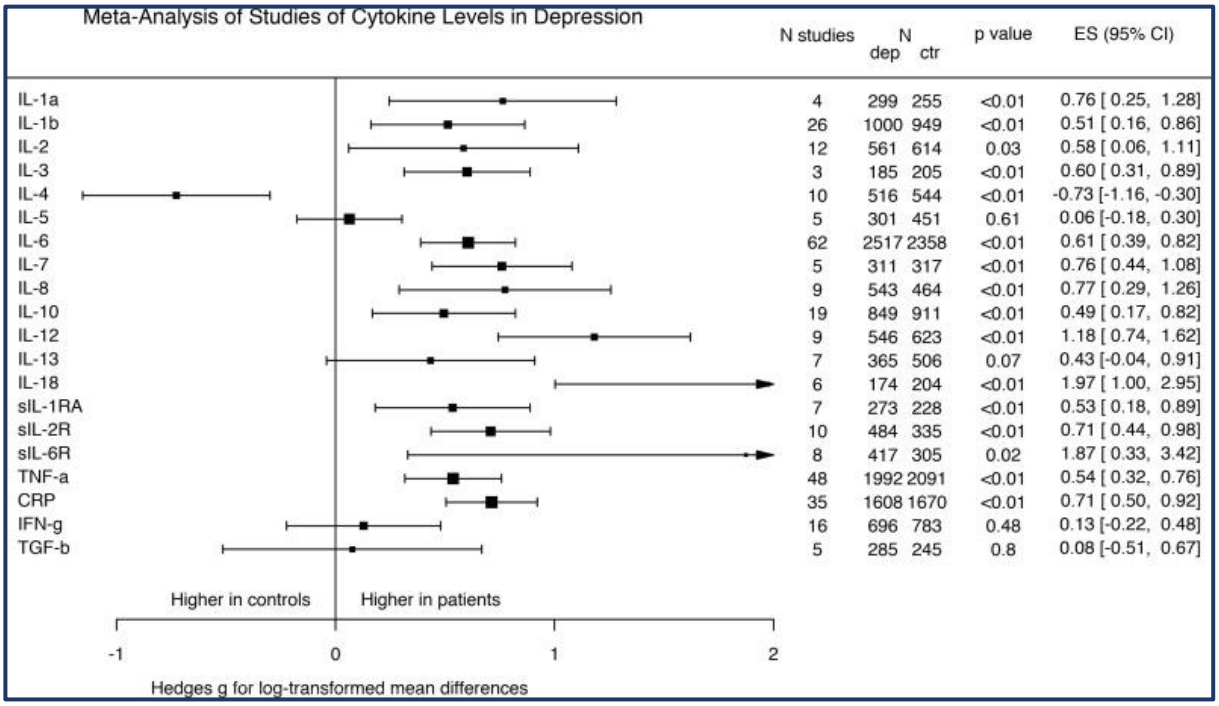


Fig. 2. A forest plot of the most recent and comprehensive meta-analysis of studies of cytokine levels in major depression (Adapted from Osimo et al., 2020).

1.1.5 Neuropathological features of MDD as observed specifically in late-life depression

All of the described pathological processes have been implicated in late-life depression as well.

A meta-analysis of 17 studies assessing whole-brain volumes, as well as the volumes of the orbitofrontal cortex, caudate, hippocampus, putamen, and thalamus in late-life depression, revealed significant volume reductions in the hypothalamus, the OFC, putamen, and thalamus, in patients with late-life depression compared to never-depressed patients (Sexton et al., 2013). Other studies also confirmed the role of the right dorsolateral prefrontal cortex in geriatric depression: a decrease in the gray matter in left and right DLPFC, a reduction in pyramidal neuronal size, and microstructural changes in the white matter of the right superior frontal gyrus have been reported (Chang et al., 2019; Khundakar et al., 2018; Taylor et al., 2004). Alexoupoulos et al., in their model of late-life depression, describes frontolimbic abnormalities as predisposing factors of late-life depression, which are influenced by etiological factors such as vascular abnormalities, inflammation, genetic predisposition and others, and affect dysfunction in cognitive control, reward and salience networks

(Alexoupoulos et al., 2019). An ample list of neuroimaging and neuropathological features of late-life depression is presented in the illustration adapted from Naismith et al., 2012 (**Fig.3).**

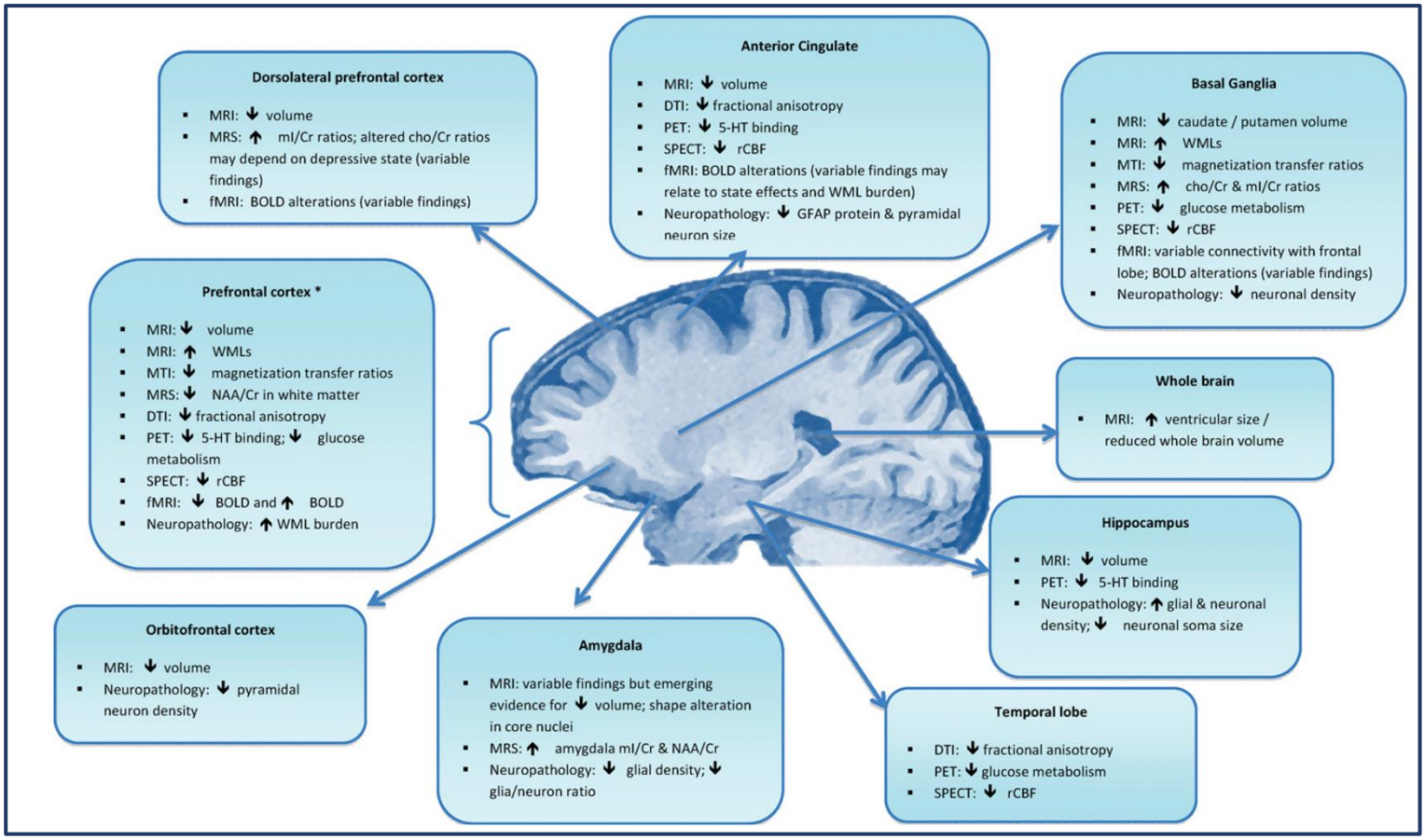


Fig.3 Neuroimaging and neuropathological characteristics associated with late-life depression (Adapted from Naismith et al., 2012).

However, many researchers agree that the heterogeneity of late-life depression is likely to be reflected at the biological level, and late-onset depression may have distinct neuropathological features. As such, Naismith et al. argues that the biological characteristics of early-onset geriatric depression possibly reflect the long-term effects of depression on the brain, while in case of late-onset depression, it's the pre-existing abnormalities that predispose to the emergence of the symptoms (Naismith et al., 2012). The neuroimaging differentiation between late-onset and early-onset depression is far from clear: even hippocampal shrinkage, although widely recognised as a consequence of recurrent depression, has been shown by some studies to be more pronounced in LOD compared to EOD, suggesting that hippocampal volume loss in LOD may have different origins than glucocorticoid neurotoxicity (Sheline et al., 2016; Ballmeier et al., 2008; Lloyd et al., 2004).

Late-onset depression has been linked to higher burden of white matter hyperintensities observed on MRI than early-onset depression (Salo et al., 2019). A substantial proportion of late-onset cases may be constituted by what is currently widely recognised as "vascular depression" – a phenotype which is closely associated with cerebrovascular disease (CVD), including small vessel ischemic changes, which can precipitate or perpetuate geriatric depressive symptoms as a consequence of structural damage to frontal–subcortical circuits, with disruption of cortico–striato–pallido–thalamo–cortical pathways as their underlying systems (Aizenstein et al., 2016). A MRI-based study in the Korean population showed that up to 50% of late-life depression may be attributed to vascular depression (Park et al., 2015). Cerebrovascular pathology can impair brain metabolism and provoke neuroinflammation.

Although fewer reviews or meta-analyses focused on neuroinflammation specifically in late-life depression, those which did highlighted increased concentrations of IL-8, IL-6, IL-1β and TNF-α in geriatric depressed patients (Martínez-Cengotitabengoa et al., 2016; Ng et al., 2018). Whether there is a difference in inflammatory status between late-onset and early-onset geriatric depression, remains to be established with certainty, since the majority of studies still do not distinguish between the two phenotypes. A study by Rozing et al. showed that levels of C-reactive protein are elevated in LOD compared to EOD; this was also confirmed by Vogelzangs et al., although only in men (Rozing et al., 2019; Vogelzangs et al., 2012). The latter study also showed elevated TNF-α in men with a later onset of depression. Mishra et al. showed elevated CRP levels in LOD patients compared to healthy controls, and a positive correlation between depression severity and plasma CRP concentrations, but this study had no EOD patients (Mishra et al., 2018). Two studies compared the levels of IL-1β between LOD and EOD patients, but only one demonstrated a significant elevation in EOD compared to both LOD and healthy controls (Thomas et al., 2005; Diniz et al., 2010). One study showed higher plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels in geriatric depression regardless of age of onset; another reported attenuated levels of extravascular intercellular adhesion molecule-1 (ICAM-1) immunoreactivity specifically in late-onset depression, although an earlier study by Thomas et al. did not find differences in ICAM-1, nor an effect of age of onset (Naude et al., 2013; Thomas et al., 2007; Miguel-Hidalgo, 2019). Fanelli et al investigated only late-onset depression and demonstrated that CXCL10/IP-10 levels were higher in subjects with MDD compared to healthy controls, while the opposite was observed for CXCL1/GRO (Fanelli et al., 2019). No other studies out of the 29 identified effectively distinguished between late- and early-onset depression phenotypes.

Most recent studies have focused on the role of proteinopathy in late-life, and specifically late-onset depression. One of the more widely studied proteins is the brain-derived neurotrophic factor (BDNF). Reduced BDNF levels have been reported in non-treated late-life depression, and decrease in BDNF levels has been observed longitudinally in geriatric depression with comorbid MCI (Diniz et al., 2010; Diniz et al., 2014). Besides, a meta-analysis has shown that the BDNF Val66Met polymorphism is associated with geriatric depression (Pei et al., 2012). Shi et al. showed lower BDNF, as well as tissue-type plasminogen activator (tPA) activator, were decreased specifically in late-onset depression (Shi et al., 2010).

Conflicting results have been produced with regards to amyloid burden in LLD. A study by Namekawa et al. showed that serum Aβ40/Aβ42 ratio was significantly higher in patients with both early- and late-onset MDD than in controls (early-onset, $p=0.010$; late-onset, $p=0.043$), and was negatively correlated with the age at MDD onset ($R=-0.201$, $p=0.032$) (Namekawa et al., 2013). Later PET studies, however, showed reduced accumulation of amyloid peptides in LLD (De Winter et al., 2018; Mackin et al., 2020). At the same time, other types of proteinopathy widely implicated in various dementia subtypes have drawn attention lately. One recent study investigated the role of α-synuclein, a protein found in presynaptic neuronal terminals, in the CSF of geriatric depressed patients, and while they didn't find differences between depressive patients and controls on its concentration, they demonstrated a significant correlation between levels of α-synuclein and neurogranin, a proposed CSF cognitive biomarker of AD (Bruno et al., 2021; Liu et al., 2020). In addition, a recent PET study showed a positive correlation between GDS score and inferior temporal and entorhinal cortex tau accumulation (Gatchel et al., 2019). More research has been initiated into the involvement of so-called suspected non-amyloid pathology (SNAP), which encompasses using next generation tau tracer [18F]MK-6240 which targets tau associated with neurofibrillary tangles, and [11C]UCB-J which targets the Synaptic Vesicle Glycoprotein 2A receptor to estimate synaptic density (Emsell et al., 2021).

1.2 DEMENTIA

1.2.1 Definition, epidemiology and healthcare implications of dementia

Dementia is a general term used to describe a syndrome characterised by significant progressive loss of memory and impairments in language, problem-solving and other cognitive functions which interfere markedly with everyday life and lead to severe disability. Dementia represents a syndrome which can be attributed to a number of nosological entities. The most common cause of dementia is Alzheimer's disease, a disorder characterised by the pathological accumulation of neuritic plaques and neurofibrillary tangles in the brain. The second most prevalent type of dementia is vascular dementia, caused by macro- and microvascular infarctions. Other frequently diagnosed types of dementia include frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB). While studies have shown that late-life depression, as well as anxiety, may represent prodromal states of both FTD and DLB (Newrick et al., 2017; Rasmussen et al., 2018; Sweet et al., 2004), this association lies beyond the scope of the present thesis, therefore the further sections will focus only on AD and VaD.

Around 50 million people worldwide are currently affected by dementia, and its prevalence (as defined by the proportion of older people living with dementia worldwide) is continuously on the rise. Between 1990 and 2016, the number of prevalent dementia cases increased by 117% (95% UI 114–121), and by 2050, the number of people living with dementia is predicted to increase to 150 million (Nichols et al., 2016; Patterson et al., 2018, Ferri et al., 2005). Only in the UK, according to the recent Lancet Commission report, a 57% increase in the number of people with dementia is predicted from 2016 to 2040, resulting in 1.2 million people living with dementia by 2040 (Livingston et al., 2020). The global costs of dementia are currently estimated at US$1 trillion, and the cost is projected to rise to US$2 trillion by 2030. he combined cost of health care and loss of earnings due to dementia, already at $81 billion (USD) per year, is predicted to rise to $2 trillion by 2030 annually (Livingston et al., 2020). The cost of social care for people with dementia in the UK is expected to nearly treble by 2040, increasing from £15.7 to £45.4 billion (Wittenberg et al., 2019).

At the same time, the structure of dementia burden may be undergoing changes: at present, high-income countries are more affected, however, total numbers of people with dementia are rising most rapidly in many low- and middle-income countries, according to estimates from the Global Burden of Disease (GBD) 2013 Collaborators (Nichols et al., 2019).

Alzheimer's disease is the most common cause of dementia, it may account for 60-70% of all dementia causes (WHO, 2020). In a meta-analysis, the prevalence of Alzheimer's in Europe was estimated at 5.05%, and the incidence, at 11.08 per 1000 person-years (Niu et al., 2017).

Vascular dementia is the second most frequent cause of dementia, accounting for about 20% of all cases. However, the distinction between AD and VaD is often not clear-cut, many cases may have mixed etiology, and some authors believe that the dementia syndrome should be seen as a continuum between pure cerebrovascular disease and pure Alzheimer's disease (Rizzi et al., 2014).

Mild Cognitive Impairment is a relatively recently emerged concept, with varying definitions, therefore there is little precision in the estimation of its prevalence. A systematic review from 2012 reported the prevalence ranging from 3% to 42% for Mild Cognitive Impairment, 0.5%-31.9% for aMCI, 5.1%-35.9% for "Cognitive Impairment No Dementia" and 3.6% - 38.4% for "Age-Associated Memory Impairment" (Ward et al., 2012). Incidence estimates also varied considerably.

1.2.2 Diagnostic criteria of dementia subtypes

In the latest DSM edition, the term "Dementia" was subsumed by the term "Major Neurocognitive Disorder; the category of "Mild Neurocognitive Disorder" is also specified.

1.2.2.1 Cognitive domains according to DSM-5

There is no full consensus regarding the classification of cognitive domains, especially for research purposes (Harvey et al., 2019). DSM-5 proposes the following clinical typology, which serves as the basis for the diagnosis of neurocognitive disorders:

- Complex attention (including sustained attention, divided attention, selective attention and processing speed);
- Executive function (planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility)
- Learning and memory (immediate recall, recent memory, "very-long-term" memory, and implicit learning)

- Language (naming, word finding, fluency, grammar and syntax, and receptive language)
- Perceptual-motor function (visual perception, visuo-constructional, perceptual-motor praxis and gnosis)
- Social cognition (recognition of emotions, theory of mind).

1.2.2.2 Alzheimer's Disease: DSM-5 diagnostic criteria

The diagnosis of dementia of Alzheimer's type subsumes the categories of "probable" and "possible" Alzheimer's disease. Alzheimer's dementia is one of the few psychiatric diagnoses whose criteria include a biomarker. For major neurocognitive disorder, "probable" Alzheimer's Disease (or "Major Neurocognitive Disorder (NCD) due to Alzheimer's Disease") is diagnosed if there is evidence of a causative Alzheimer's genetic mutation from either genetic testing or family history, clear evidence of decline in memory and learning and at least one other cognitive domain, steadily progressive, gradual decline in cognition, without stable plateaus, and no evidence of mixed etiology.

The major difference between **major** and **minor** NCD is that the impairment in major NCD significantly affects independent everyday functioning while the impairment in minor NCD does not impede daily functioning. The diagnosis of minor NCD does not require impairment on domains other than memory and learning (American Psychiatric Association, 2013). In minor NCD, "probable" Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history; "possible" Alzheimer's disease is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present: clear evidence of decline in memory and learning; steadily progressive, gradual decline in cognition, without extended plateaus; no evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).

1.2.2.3 ICD-10 diagnostic criteria

The primary criterion of dementia according to ICD-10 is evidence of significant decline in memory, which primarily manifests itself in the decline in registration, storage, and retrieval of new information; and thinking, predominantly attention and processing speed. The three other criteria include: Insidious onset with slow deterioration; absence of evidence suggesting an alternative brain disease; and absence of a sudden, apoplectic onset, or of neurological signs of focal damage. ICD-10 distinguishes between early-onset and late-onset Alzheimer's disease (with onset before and after the age of 65), but does not require evidence of genetic polymorphisms or family history of AD for either diagnosis.

1.2.2.4 Vascular Dementia: DSM-5 and ICD-10 diagnostic criteria

Major and Mild Vascular Neurocognitive Disorder is diagnosed if the onset of the cognitive deficits is temporally related to one or more cerebrovascular events or there is prominent evidence for decline in complex attention (including processing speed) and frontal-executive functioning; and there is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits, and the symptoms are not better explained by another brain disease or systemic disorder.

VaD is classified as "probable" if one of the following criteria are satisfied: clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported); the neurocognitive syndrome is temporally related to one or more documented cere-brovascular events; both clinical and genetic (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present. If none of these are satisfied, the diagnosis of "possible" VaD is made.

ICD-10 distinguishes between VaD of acute onset, multi-infarct dementia (characterised by a more gradual onset and a history of a number of minor ischaemic episodes), subcortical vascular dementia, mixed cortical and subcortical vascular dementia, etc.

1.2.3 Diagnostic criteria of neurocognitive disorders in research

In research, the diagnostic criteria developed by the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA) working group is mostly used. These criteria are applied in a two-step manner, where first the presence of dementia syndrome is identified, and further, criteria of AD-specific clinical presentation are applied (Dubois et al., 2007).

Unlike the DSM-5 criteria which require that significant impairment in daily life be present (for a diagnosis of major neurocognitive disorder due to AD), NINCDS–ADRDA "probable" AD does not necessarily need to satisfy the criterion of impairment in activities of daily life (ADL), but has to have an insidious onset, as well as not better be explained by another brain disease.

NINCDS-ADRDA allows for a diagnosis of definite Alzheimer's disease where there is neuropathological evidence, either post-mortem, or from brain biopsy. Possible AD is diagnosed when there is a presence of dementia syndrome with an atypical onset that cannot be explained by another brain disease; probable AD is diagnosed when dementia syndrome has been identified in clinical or neuropsychological evaluation, when cognitive decline affects at least two cognitive domains including memory and is insidious and progressive. Age of onset is not listed among criteria, nor is the presence of identified genetic biomarkers of family history of Alzheimer's disease.

Another important contribution of NINCDS-ADRDA criteria is that they distinguish other forms of cognitive decline such as preclinical AD, prodromal AD, and mild cognitive impairment (MCI), including its amnestic form (aMCI).

Preclinical AD is defined as "the long asymptomatic period between the first brain lesions and the first appearance of symptoms and which concerns normal individuals that later fulfill AD diagnostic criteria"

Prodromal AD is defined as "The symptomatic predementia phase of AD, generally included in the mild cognitive impairment category; this phase is characterised by symptoms not severe enough to meet currently accepted diagnostic criteria for AD"

For vascular dementia, the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences

(NINDS-AIREN) are used. Similarly to the diagnosis of AD, NINDS-AIREN criteria allow for a diagnosis of possible, probable and definite VaD (Roman et al., 1993).

Probable VaD is diagnosed if:

- Dementia syndrome is present and interferes with instrumental daily functioning
- Cerebrovascular disease, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI)
- A relationship between cognitive decline and CVD, manifesting in (a) onset of dementia within 3 months of recognised stroke and (b) abrupt deterioration of cognitive functions, or fluctuating, stepwise progression of cognitive deficits

Possible VaD is diagnosed if the syndrome of dementia is present along with focal neurologic signs, but there is no brain imaging confirmation of definite CVD, or no clear temporal relationship between the onset of cognitive impairment and cerebrovascular events, or subtle onset and variable course of cognitive symptoms with present evidence of relevant CVD.

Definite VaD is diagnosed if the criteria for probable VaD are met, plus there is histopathological evidence of CVD obtained from either biopsy or autopsy, absence of Alzheimer's pathology exceeding the age norm or other condition which better explains dementia syndrome.

1.2.4 Mild Cognitive Impairment

Mild Cognitive Impairment has been defined in several ways, but perhaps the most commonly used are criteria suggested by Petersen et al., followed by the Mayo Clinic criteria ("Minor Neurocognitive Disorder" in DSM-5 is also considered to reflect the MCI syndrome). The comparison of several diagnostic criteria are discussed in detail in reviews (Petersen et al., 2015; Pessoa et al., 2019). In brief, according to the criteria by Petersen et al., MCI is diagnosed if the following are present:

- Impaired memory, measured as decrease in Word List Delayed Recall score;
- Mini-Mental State Examination score of 25 or above;

- No instrumental impairments in daily functioning;
- The presence of subjective memory complaints; and
- No evidence for the diagnosis dementia.

MCI is classified as amnestic if memory is the primarily affected cognitive domain.

1.2.5 Neuropathological characteristics of Alzheimer's Disease and Vascular dementia

The most common concept of the pathology behind Alzheimer's disease is the "amyloid hypothesis". This hypothesis rose about three-four decades ago, with the identification of abnormal deposition of plaques of the Amyloid β (Aβ) peptide in brain parenchyma of patients with Down Syndrome suffering from Alzheimer's Dementia, where the trisomy of the 21st chromosome containing the amyloid precursor protein (APP) gene leads to excessive accumulation of amyloid peptides. (Hardy & Higgins, 1992). Another source of proof was the mutation in the presenilin gene, encoding the production of the intramembrane aspartyl protease which generates Aβ, identified in patients with a severe dominantly inherited form of early-onset AD (Klunk et al., 2007; Bateman et al., 2011).

Aβ deposits exist in the brain in the form of neuritic plaques, extracellular conglomerates with a dense central fibrillar Aβ core with inflammatory cells and dystrophic neurites in its periphery. Cerebral amyloid angiopathy (CAA) is another extracellular feature, it consists in fibrillar Aβ deposited in the wall of arterioles in both the leptomeninges and penetrating vessels (Jack et al., 2013). Patients may exhibit Aβ plaque pathology for up to or greater than a decade before any overt diagnosis of AD.

An important feature affecting the clinical presentation of cognitive decline may be the oligomerisation of Aβ. Esparza et al. have shown that patients experiencing cognitive decline had a higher correlation between Aβ plaque coverage and Aβ oligomer concentrations than non-demented subjects (Esparza et al., 2013).

Another type of protein implicated in Alzheimer's pathology is tau protein – this time intracellular deposits of hyperphosphorylated tau in the form of neurofibrillary tangles (NFT). Studies have shown that there may be a stereotypic pattern of progression of NFT deposition, where it first appears in the brainstem and NFT deposition follows a stereotypic topographic progression pattern first appearing in the brainstem and transentorhinal area, and then spreads to the hippocampus, to paralimbic and adjacent medial-basal temporal cortex, to cortical association areas, and finally to primary sensorymotor and visual areas; moreover,

neurodegeneration has been shown to map onto NFT, not Aβ amyloid distribution (Braak and Braak, 1994; Terry et al., 1991).

Accumulating evidence is suggesting the involvement of inflammation in the pathology of Alzheimer's disease. While acute inflammation is an essential mechanism of protecting the organism from infection, trauma or toxins, chronic inflammation, in particular, neuroinflammation, may have detrimental effects. As mentioned above, chronic inflammation in the brain is attributed to activated microglia and the release of a wide array of cytokines and chemokines.

A substantial body of research has now demonstrated that a persistent immune response in the brain is not only associated with neurodegeneration, but it also facilitates and exacerbates both Aβ and NFT pathologies. As any kind of inflammation, Brain inflammation appears to have a dual function, playing a neuroprotective role during an acute-phase response, but becomes detrimental when a chronic response is mounted.

For instance, some studies have shown that IL-6 can stimulate the release of CDK5, which is a kinase shown to hyperphosporylate tau. However, IL-6 is regulated by another inflammatory cytokine, IL-1β. The downregulation of IL-1β, in turn, has been shown to delay neurodegeneration. At the same time, in response to the activation of pro-inflammatory cytokines, anti-inflammatory cytokines are released by astrocytes and microglia, among them IL10 (Kinney et al., 2018; Koray et al). Elevated levels of IL10, IL6, and CDK5 have been demonstrated in dementia in a number of meta-analyses (Swardfager et al., 2010; Lai et al., 2017; Su et al., 2019).

The pathological features of VaD, in contrast, are tightly linked with cerebrovascular pathology from stroke to microinfarcts and diffuse white matter changes associated with small vessel disease (Kalaria et al., 2017). The clinical subtypes of VaD based on the localisation of vascular and tissue damage include subcortical VaD, thromboembolic dementia, dementia connected with cerebral vessel wall damage, dementia without structural vessel changes and other less common variants (Wallin et al., 1998).

At the same time, there exists a significant overlap between Alzheimer's Disease and Vascular Dementia. In particular, cerebrovascular disorders and associated lifestyle factors such as hypertension, atrial fibrillation, atherosclerosis, coronary artery disease, diabetes mellitus and smoking have all been shown to be significant contributors to increased risk of Alzheimer's disease; and the ApoE E4 allele has been associated with worse cardiovascular health (Davignon et al., 1988; Haan et al., 2020). From 60 to 90% of AD patients have been reported to exhibit varying degrees of cerebrovascular pathology on autopsy (Kalaria et al.,

2002). Evidence of impaired cholinergic neurotransmission in VaD has also been reported (Kalaria et al., 2002).

The type of dementia which occurs in patients with a neurodegenerative disorder (mainly Alzheimer's disease) and is accompanied by a cerebrovascular disease, has been referred to as mixed dementia; most typically, mixed dementia describes combined features of Alzheimer's disease and VaD). A review of evidence concerning mixed dementia has suggested its prevalence may be up to 22% in the elderly (Custodio et al., 2017).

In addition to high prevalence of both depression and dementia in the elderly, there is considerable evidence linking the two conditions. In particular, there is a substantial amount of literature showing that depression, or clinically significant depressive symptoms, in late life are associated with higher risk of progression to Alzheimer's disease and other neurocognitive disorders. The specific evidence for this association is discussed below.

1.3 The relationship between late-life depression, cognitive decline and dementia

1.3.1 Epidemiological evidence supporting the relationship between late-life depression, MCI and dementia

There are few associations in mental health research that have been established with as much consistency as the one between depression in late life and cognitive decline or dementia.

The evidence for the association between late-life depression and dementia comes from a number of cohort studies and meta-analyses. Cherbuin et al. performed a comprehensive meta-analysis of longitudinal studies of 14 cohorts, taking into account the methodological differences such as whether dementia and depression measurements are presented as binary or continuous data, and which psychometric tools are used for diagnosis. They showed that the relative risk RR) for dementia in case of the categorical diagnosis of depression are almost twice as high as that for the continuous measurement: 1.98 for all-cause dementia, 2.04 for AD vs 1.05 and 1.06 in case of continuous measurements, respectively (Cherbuin et al., 2015). Jorm et al. also reported a positive association from both case-control studies (RR 2.01) and prospective cohort studies (RR 1.87; Jorm et al., 2001). A recent meta-analysis of the association between depression in late life and dimensional cognitive performance showed that both dimensional and categorical measures of depression were associated with decline in cognition (β = −0.008, 95% CI −0.015 to −0.002, p = 0.012; OR 0.992, 95% CI 0.985–0.998;OR 1.36, 95% CI 1.05–1.76, p=0.02, respectively; John et al., 2018). However, it is notable from the results that the association, although significant, is rather weak. This was due to the high heterogeneity of studies reported by the authors for both continuous and categorical measurements. The heterogeneity decreased significantly when corrected for the following factors: publication year, mean age at baseline, length of follow-up, method of depression assessment (diagnosis or self-report) and quality of study, however, only by about 1/8, indicating that there may be other factors affecting it. Further meta-regression analyses including the length of follow-up showed significant between-study variability, whereby studies with shorter follow-up periods had significantly greater effect sizes than those with longer follow-up periods (John et al., 2018).

Many, though not all of, epidemiological studies addressing the link between depression and dementia, distinguished between Alzheimer's and Vascular dementia as the

primary outcomes. Diniz et al. analysed 23 studies which only used a categorical measurement of depression, and concluded that the RR was significantly higher for vascular dementia (2.52, 95% CI 1.77-3.59) compared to Alzheimer's disease (1.65, 95% CI 1.42-1.92) (Diniz et al., 2013). Later, a Swedish cohort study also confirmed that the association was stronger for VaD (adjusted OR 2.68, 95% CI 2.44–2.95; $p < 0.001$), although it was also quite strong for AD (aOR 1.79, 95% CI 1.68–1.92; $p < 0.001$; Holmquist et al., 2020). Ownby et al. performed a meta-analysis of the association between geriatric depression and Alzheimer's Disease only, and reported pooled odds ratios of 2.03 (95% confidence interval, 1.73-2.38) for case-control and of 1.90 (95% confidence interval, 1.55-2.33) for cohort studies (Ownby et al., 2006).

1.3.1.1 Possible mechanisms of the association between late-life depression and dementia

Most of the epidemiological studies mention that there are four major hypotheses explaining the possible associations between depression and dementia. The first one suggests that affective disorders may serve as etiological factors, increasing the susceptibility of an individual to cognitive decline (Butters et al., 2008). Another concept suggests that depression in old age may represent a prodromal state of dementia, meaning that affective symptoms and cognitive decline are different clinical manifestations of the same underlying conditions (Panza et al., 2010). Some authors argue that affective problems and decline in cognitive state are separate processes but may share common risk factors and underlying neurobiological substrates (Djernes, 2006; Enache et al., 2011). Finally, in some cases, depression in old age may represent a psychological reaction to the manifestations of cognitive decline.

It is clear from the very descriptions of these hypotheses that they are most likely not mutually exclusive, and rather point at a variety of pathways for the association between depression and dementia. This appears highly logical because depression and dementia are both highly heterogenous conditions.

1.3.1.2 The heterogeneity of late-life depression

As discussed above, there exists a substantial heterogeneity in the phenotypes of late-life depression. The role of specific symptoms and subtypes based on clinical presentation is discussed in ***Chapter 5***.

However, it is still largely unclear whether it is a history of depression with early or midlife onset or late-onset depression that is associated with increased risk of dementia. The conviction of many clinicians that it is specifically late-onset depression that predicts future onset of dementia (predominantly through being a prodromal state) is challenged by research

data which show that both early-onset and late-onset phenotypes may contribute to the association.

The most recent review on his subject was performed in 2013, and failed to reach a conclusion as to whether there is a difference in risk of conversion to dementia between early-onset and late-onset geriatric depression (Da Silva et al., 2013). Severity of depression and greater frequency of episodes, however, seemed to increase the likelihood.

Summarised below are several studies, including those mentioned in the reviews and those published later, which assessed the relationship between age of onset of geriatric depression and likelihood of conversion to dementia. The table below illustrates the inconsistency of findings with regards to this association.

Interestingly, the study assessing cognitive performance on dimensional scales showed that both patients with a history of depression requiring inpatient treatment and a late-life episode, and late-onset geriatric depressed patients, performed worse than controls on tests of processing speed, attention, executive functions, and verbal fluency; but performance was better in persons with self-reported recurrent unipolar depression. Remitted persons with inpatient history of unipolar depression exhibited no cognitive deficits.

Author, year	Study design	Assessment of history of depression	Phenotypes included in analysis	Phenotype associated with conversion	Dementia definition	Findings
Speck et al., 1995	Case-control	Self-report	EOD/LOD	EOD	AD	OR 2.0 (95% CI = 0.9-4.6) for EOD vs OR 0.9 (95% CI = 0.2-3.0) for LOD
Green et al., 2003	Case-control	Self-report	Years between occurrence of depressive symptoms and AD	Both, although higher with proximity to AD	AD	(OR, 4.57; 95% CI, 2.87-7.31) for depression occurring within a year of being diagnosed with Alzheimer's Disease; A modest association in depression with onset 25+ years before AD diagnosis
Singh-Manoux et al., 2017	Prospective cohort	Self-report on 12 occasions	Proximity of depression to dementia	Depression 11 years prior to AD diagnosis or closer was associated with higher risk of dementia	All-cause	HR 1.86, 95%CI 1.27-2.73 for depression 11 years prior to AD diagnosis
Barnes et al., 2013	Retrospective cohort	Self-report+ medical records	Midlife-only depressive symptoms/ late life – only/ midlife+late-life	Highest HR for midlife+late-life DS	AD or VaD	Midlife+Late-life: HR 1.77 [1.52-2.06] LOD was associated with AD risk, while EOD, with VaD risk
Sachs-Ericcson et al., 2014	Prospective cohort (NESDO)	DSM diagnosis	LOD/EOD, only melancholic subtype (no controls)	LOD	All-cause	Among participants who remained in the study for at least 1 year, in uncontrolled analyses, a greater percentage of LOD-M compared with EOD-M developed dementia (23.0% vs. 7.8%).
Li et al., 2011	Prospective cohort	Self-report	LOD/EOD	LOD	All-cause	LOD: HR 1.77; 95% CI, 1.39-2.25
Heser et al., 2013	Prospective cohort	Clinical assessment (CIDI)	LOD/EOD/Several thresholds (65+/70+/75+) for "very late onset" (VLOD)	VLOD	All-cause; AD	Only significant for VLOD (for both all-cause and AD; higher significance of association for each increase in threshold; highest HR 7.29 (2.98–17.80) for progression from VLOD(75+) to AD
Yu et al., 2020	Retrospective cohort	Medical records	Midlife (45-64y.o.) vs late-life onset	Midlife onset	All-cause	Highest OR for midlife depression onset: OR=2.72, 95% CI=1.41–5.24

Table 2. Summary of 8 studies investigating the role of age of onset of depression in the risk of progression to dementia

1.3.2 The role of depression in the conversion of MCI to dementia

The chapters of the present thesis will predominantly focus on depressed patients without a comorbid diagnosis of MCI at the time of depression diagnosis, i.e. on cognitively intact elderly depressed patients. Presented below is a brief overview of the role of depression in progression from MCI to dementia.

The amnestic form of mild cognitive impairment (aMCI) is a condition that often precedes the onset of AD. There has been accumulating evidence that depression may increase the speed of the conversion of aMCI to dementia. This is also relevant for depressive symptoms and apathy. It has even been hypothesized that late-life depression, MCI and AD may represent a possible clinical continuum.

Zadohne et al. showed that depression may be a sign of more aggressive neurodegenerative process compared to no depression in MCI patients, since it was associated with both reduced cortical thickness in the entorhinal cortex at baseline and accelerated atrophy in anterior cingulate cortex during follow-up. They also showed that depressive symptoms were more strongly associated with cortical atrophy on follow-up than symptoms of apathy (Zahodne et al., 2013).

A few other studies replicated these results, showing patients with chronic depressive symptoms had a shorter time of conversion to AD, which was associated with accelerated cortical atrophy in the anterior cingulate and frontal lobe (Sacuiu et al., 2016) and left hippocampus (Ku Chung et al., 2016), as well as white matter atrophy (Lee et al.). Moon et al. also showed that depression in MCI was associated with greater 2-year cognitive decline, but particularly high conversion rates were observed among MCI patients who were amyloid-positive.

At the same time, a study by Schönknechtet al. has shown that patients with late-life depression (a mixed sample of late-onset and early-onset recurrent cases) differed significantly from aMCI patients both at onset and at follow-up after 12 months in the proportion of conversion to

AD, as well as in baseline t-tau and p-tau levels. MCI converters also had significantly higher t-tau and p-tau levels than non-converters (Schönknecht et al., 2007).

This was partly confirmed by Ivanoiu et al., who showed that there was a significant difference in tau protein between elderly patients with anxiety and/or depression and MCI patients who were slow converters (i.e., over 20 months) to AD, but not between slow and fast MCi converters to AD. On the other hand, slow and fast converters did differ from each other in the levels of Aβ42, so that they were in the normal range in slow converters, and significantly decreased in fast converters (Ivanoiu et al., 2005).

These data may suggest that there is an important difference in the biomarker profiles of depression occurring in aMCI compared to depression in cognitively normal elderly patients. While depression in aMCI is associated with higher rates of neurodegeneration and may in fact be seen as an early sign of further cognitive deterioration, late-life depression in normal cognition leads to AD in fewer cases, and it may take a combination of biomarkers, e.g. CSF tau/amyloid or at least plasma Aβ40/Aβ42 profile, ApoE genotype, and measures of cortical atrophy, hippocampal loss and white matter lesions to establish a model that would predict the risk of dementia in elderly depressive patients.

1.4 Objectives

Research Question and project objectives

The primary aim of this thesis was to examine the factors associated with conversion to dementia in elderly patients suffering from late-life depression without dementia at the time of depression diagnosis, and to evaluate specific cognitive domains performance of which is affected by late-life depressive symptoms in the general population

Specific aims and objectives of this thesis

For the present thesis, data from three cohorts/datasets was used to address the research question:

- The CRIS dataset, a clinical records system of all patients seen in the South London and Maudsley (SLaM) secondary care services, and linked datasets: Hospital Episode Statistics (HES) and Office for National Statistics (ONS);
- The PROTECT cohort, an internet-based population cohort assessing factors affecting cognitive performance with annual follow-up in people aged 50 and above
- The PRODE cohort, a clinical cohort of elderly Norwegian inpatients with major depression followed up for 3 years, and COGNORM cohort – a cohort of cognitively normal non-depressed elderly participants followed up for 3 years.

Aim 1: A systematic review of longitudinal studies assessing the biomarkers predicting conversion to dementia, or cognitive decline at follow-up, in non-demented depressed elderly patients

Aim 2: A systematic review of longitudinal studies assessing cognitive domains affected in late-life depression that predict conversion to dementia

Aim 3: To investigate the factors associated with conversion to dementia in a cohort of patients referred to SLaM secondary care services for major depression

Objectives:

- To identify clinical symptoms of depression predictive of conversion to dementia
- To identify whether new-onset depression is associated with higher likelihood of conversion to dementia compared to recurrent depression

Aim 4: To examine the longitudinal relationship between depressive symptoms in the general population of people aged 50 and above and performance on four cognitive domains: working memory, executive function, episodic memory and general intelligence

Objectives:

- To identify which of the cognitive domains are affected by depressive symptoms cross-sectionally and longitudinally
- To examine the role of anxiety in this association
- To examine the role of history of depression in this association

Aim 5: To examine the role of systemic inflammatory markers in late-life depression, and the possible mediating role in conversion to dementia

Objectives:

- To analyse the differences in plasma inflammatory markers between elderly inpatients with late-life depression and non-depressed controls
- To analyse the effect of plasma inflammatory markers on the risk of conversion to dementia in elderly inpatients with major depression and no dementia at baseline
- To the risk of conversion to dementia and plasma biomarker levels between patients with early-onset depression and late-onset depression

Chapter 2. Methods

2.1 Study design

In the presented thesis, a variety of research techniques were used depending on the research question and aim and objective of each chapter. The study designs used in the thesis, in order of being reported, include: systematic review, a retrospective cohort study, an internet-based prospective cohort study, a cross-sectional study, and a clinical cohort study.

2.1.1 Systematic review

A systematic review is a research method that aims to identify, summarise and analyse empirical evidence in a specific field of knowledge and in accordance with pre-specified criteria developed as part of the systematic review protocol. Both systematic reviews presented in this thesis were performed in accordance with the recently revised Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2020)

2.1.2 Retrospective cohort study

Retrospective cohort studies are also referred to as historic cohort studies. This is a type of an observational study where researchers look back on participants' case histories using e.g. archives, to determine whether there is a relationship between their outcomes and predictors of interest. The main difference between retrospective cohort studies and case-control studies lies in the fact that in the former, subjects are enrolled and baseline data is collected before any subjects develop an outcome of interest – however, the study is only conceived after the participants have developed the outcome of interest.

2.1.3 Prospective cohort study

Prospective cohort study design refers to a longitudinal design where participants are recruited before the onset of outcome and are followed up for a set period of time by the team of researchers. In medical epidemiology, well-designed prospective cohort studies are considered the most accurate type of observational studies and are ranked high in the hierarchy of evidence.

In the present thesis, data from two prospective cohort studies is analysed: an *internet-based cohort*, where tens of thousands of participants aged over 50 were recruited over the internet and are followed up annually (three-year follow-up data presented here); and *a clinical cohort*, where patients were carefully selected by the clinician in charge of the study, thoroughly phenotyped and followed up by qualified clinicians for 3 years.

2.1.4 Cross-sectional study

Finally, a subset of data from the clinical prospective cohort was analysed using a cross-sectional design. Cross-sectional studies are observational studies that analyse the associations among variables of interest at a particular point in time, without follow-up. While cross-sectional studies are a useful way to explore hypotheses, they only provide inferences regarding association or correlation, without allowing to estimate causation.

2.2 A historical cohort study of the determinants of progression from late-life depression to dementia: Clinical Record Interactive Search (CRIS)/Hospital Episode Statistics(HES)/Office for National Statistics (ONS) data

2.2.1 Study background

Chapter 5 of the present thesis is based on the data from the Clinical Record Interactive Search (CRIS) cohort of the the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register. SLaM provides mental health services to a geographic area where more than 1.2 million people reside, and this includes four south London boroughs: Croydon, Lambeth, Lewisham, and Southwark – and also some regional/national specialist services. SLaM services provide treatment for most types of psychiatric disorders (Perera et al., 2016).

Since 2006, all clinical records in SLaM services have been electronic, and using the Patient Journey System, data was extracted from earlier service-specific electronic health records. The CRIS application was developed in 2007-2008 and comprised a number of data-processing pipelines which allowed to effectively anonymize patient data. Ethical approval as an anonymised database for secondary analysis was originally granted in 2008, and renewed
for a further 5 years in 2013 (Oxford C Research Ethics Committee, reference 08/H0606/71+5).

2.2.1.1 Natural Language Processing used for the creation of CRIS/HES/ONS datasets

The major challenge in using electronic health records (EHR) data lies in the fact that most of these records exist in the form of natural text and need to be transformed into coded data. This transformation is performed using Natural Language Processing (NLP) pipelines.

NLP applications are developed using the GATE (General Architecture for Text Engineering; www.gate.ac.uk) software (Cunningham, H., 2002; Cunningham et al., 2013). This is a development environment for writing applications that can process human language. Its principal

purpose is to extract required information as structured data from free text fields using algorithms developed for this purpose. GATE was originally developed at the University of Sheffield beginning in 1995, and a longstanding collaboration between the BRC Nucleus, which hosts the CRIS system, and engineers at University of Sheffield supports the development of new apps, as well as their maintenance and staff training.

In brief, data processing was performed in tight cooperation with trained clinicians (domain experts) who helped identify relevant variables and annotate the clinical records. These domain experts coded whether the variable of interest was present in the current document in accordance with pre-defined coding rules. Distinguishing between the positive and negative statements was done using the annotations of "negation" (affirmed/negated"; see Fig. 5). In general, the interest was in ascertaining positive mentions of given entities being present. Negation statements (e.g., 'not using any antipsychotic') were therefore not specifically captured as entities (Perera et al., 2016), but are combined with other unwanted text mentions in classification and performance estimation.

This data processing resulted in 526 hand-annotated unique clinical notes. These were used to develop and "train" the NLP model. Next, the hand-annotated clinical notes were used to develop a Named Entity Recognition (NER) neural model helping to rapidly annotate the remaining thousands of clinical notes, by means of an "active learning tool".

As described in detail in Vaci et al.(2020), there were several measures of model efficacy. First, the number of possible annotations (POS) were calculated in the corpus that contribute to the validation score by summarising correct, incorrect, partial and missing outcomes (true positive +false negative). In addition, the total or actual (ACT) number of annotations that the NLP model produced were calculated by summarising correct, incorrect, partial and spurious outcomes (true positives+false positives). These two measures were used to estimate the "precision" and "recall" of the system. In other words, precision (essentially positive predictive value) is the proportion of algorithm-derived named entities that are judged to be correct. Recall (sensitivity) is the proportion of gold standard named entities that are identified by the algorithm. The overall performance of the model was calculated as a function of both precision and recall, using the formula F1=(2*Recall*Precision)/(Recall+Precision).

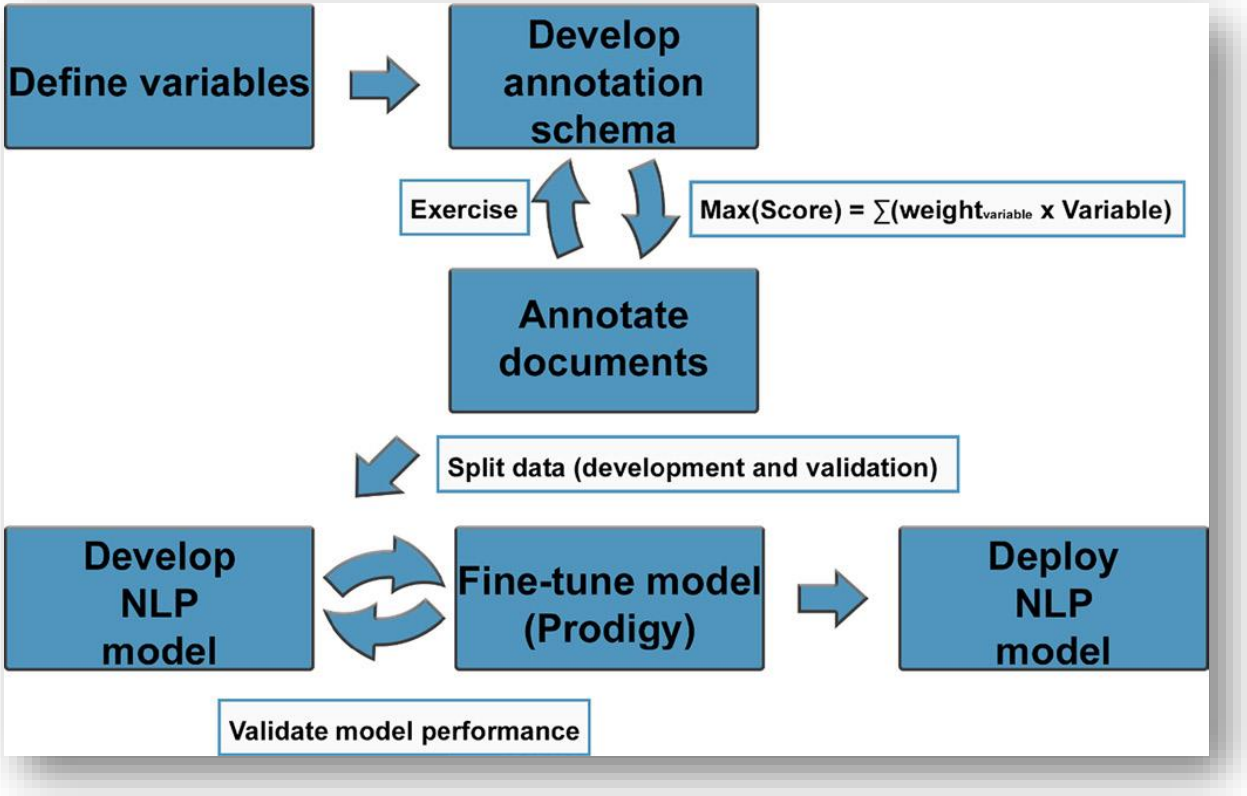


Figure 4. Illustration of the Natural Language Processing Pipeline; adapted from Vaci et al.(2020).

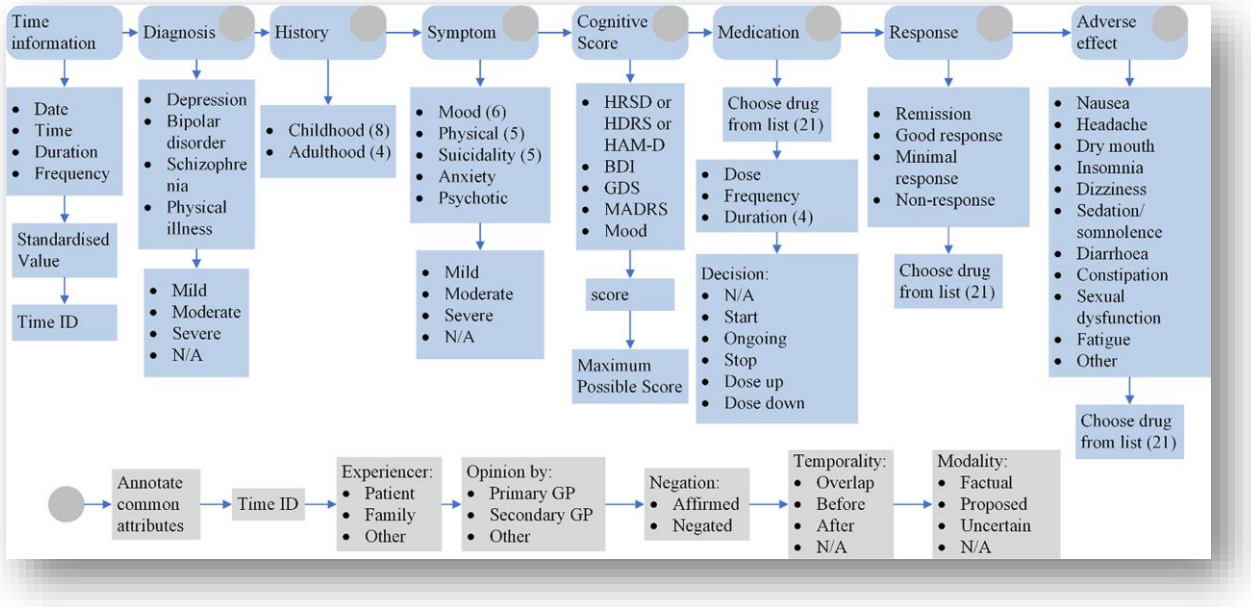


Figure 5. Illustration of the schema developed for the annotation of the RAW clinical text; adapted from Vaci et al.(2020).

In the CRIS dataset, diagnoses are generally made and entered into the structured fields by clinicians. NLP tools do not assess whether ICD-10 criteria for clinician-made diagnoses are met, as the clinicians will have checked that before they make the formal diagnosis.

However, there also exists a supplementary NLP-based diagnosis application, which extracts text strings indicating a patient's recorded diagnosis and the date the respective diagnosis was recorded. It is primarily intended to supplement diagnosis data from structured fields, which generally have high rates of completion but more limited updating following changes in diagnosis, or limited recording of comorbid diagnoses such as personality disorder. In other words,

the NLP app only helps to pick up the codes from free text, in clinic letters or events, in addition to structured fields. The NLP app is used where the clinician has written what they would otherwise (or usually have additionally) put into this structured field, e.g.:

……Diagnosis: Fxx.x diagnosis name……
……Diagnosis Fxx.x diagnosis name……
……Diagnosis: diagnosis name……
……Diagnosis: Fxx.x……

Most diagnoses in the data are through clinician-recorded ICD-10 diagnoses. While there is no definitive statistics with regards to how many diagnoses are additionally retrieved through the NLP app,
the approximate estimate is that NLP helps to identify 20-30% more patients with a specific diagnosis than using structured fields alone.

2.2.2 Access to anonymized patient data

In order to carry out CRIS-based research, all researchers have to meet the necessary security requirements of data access, analysis and publication. A CRIS project application was submitted to the CRIS Oversight Committee on 22.11.2018, approval was granted on 17.01.2019 (Project 18-119 “Depression prodromal to Alzheimer’s disease: mechanisms, biomarkers and potential drug targets”).

Access to linked external datasets – Hospital Episode Statistics (HES) and Office for National Statistics (ONS) - required obtaining a Honorary Contract which was granted on 08.04.2019. Extensions on the Honorary contract were granted in April 2020 and February 2021.

2.2.3. Study design and participants

The study was performed using retrospective data on outpatient clinical assessments obtained from CRIS records; on patients' hospitalisation using the Hospital Episode Statistics (HES), and mortality data from the records of the Office for National Statistics (ONS). The study flowchart is presented in Fig. 4. Data was extracted from the CRIS system using the list of criteria pre-specified in the data extraction sheet.

Data was extracted on all patients aged 65 or above who were referred to SLaM services between January 1st, 2008 and March 31st , 2017 and were diagnosed with major depression in accordance with the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes (WHO, 2004), both from diagnoses recorded in structured fields and in free text within clinical correspondence, through a bespoke natural language processing algorithm.

The sample included 3845 patients. Follow-up period was defined as the period from 3 months after the initial diagnosis of depression has been made to either a diagnosis of dementia and/or death registered in CRIS, ONS or HES records, or until censoring date on March 31st, 2017.

For the analysis performed in this thesis, the following categories of variables were used:

- Depression diagnosis

  All subjects had a diagnosis of depression on inclusion. ICD-10 codes used for selecting participants are listed below.
- Symptoms of depression

  Using natural language processing, data on the presence of 17 specific symptoms was extracted. Data was presented as binary variables indicating the presence or absence of a symptom, as mentioned in the patients' record within 6 months around the date of diagnosis.
- Dementia diagnosis

  Dementia diagnosis was ascertained using ICD-10 criteria from CRIS, HES or ONS records.
- Demographic variables

  The available sociodemographic characteristics of the sample included age, gender, ethnicity, and marital status

- Baseline cognition and other health-related measures

  Cognitive performance at the time of depression diagnosis and a number of other characteristics related to the patients' health were assessed using the Health of the Nation Outcome Scales (HONOS) 65+ scale.

  The HONOS scale was developed as a brief standardised measure of clinical outcomes for medical settings, and was later adapted for use in the elderly (Wing et al., 1998; Burns et al., 1998). The scale has been proven to have good concurrent and criterion validity (Orrell et al., 1999; Shergill et al., 1999), and was later shown to meet the criteria for a clinical outcome indicator for community mental health services for older people and to be sensitive to change (Spear et al., 2002).

- Medication use:

  Data on use of medication in the period of 6 months around the index date (date of depression diagnosis) was available for all participants; several psychotropic and general physical medication groups were included. For each medication category, a dichotomous variable was created ("0" = not using"/ "1" = using).

The full description of variables by category is presented in Table 3.

Variable	Characteristics
Depression characteristics	
Depression diagnosis	All subjects had one of the following ICD-10 diagnoses at baseline: • F32.0 (Mild depressive episode) • F32.1 (Moderate depressive episode) • F32.2 (Severe depressive episode without psychotic symptoms) • F32.3 (Severe depressive episode with psychotic symptoms) • F33.0 (Recurrent depressive disorder, current mild depressive episode) • F33.1 (Recurrent depressive disorder, current moderate depressive episode) • F33.2 (Recurrent depressive disorder, current severe depressive episode without psychotic symptoms) • F33.3 (Recurrent depressive disorder, current severe depressive episode with psychotic symptoms)
Recurrent depression	1 = F33* 0 = F32*
Severe depression	1 = F32.2/ F32.3/ F33.2 /F33.3 0 = F32.0/F32.1/F33.0/F33.2
Psychotic depression	1 = F32.3/F33.3 0 = F32.0/F32.1/F32.2/F33.0/F33.1/F33.2
Symptoms of depression	The following list of symptoms was available as binary variables (0=absent/1=present): • feeling helpless • feeling hopeless • feeling worthless • anhedonia • poor motivation • apathy • low mood • poor concentration • agitation

	• irritability • low energy • insomnia • appetite loss • anergia • hallucinations • delusions • suicidal ideation
Outcome: Dementia	
Dementia diagnosis	1 = Dementia at follow-up, if the following diagnoses were registered in CRIS, HES or ONS records during the period from 3 months after the initial diagnosis of depression until censoring date on March 31st, 2017: • F00* (Dementia in Alzheimer's disease), F01* (Vascular dementia) • F02* (Dementia in other diseases classified elsewhere) • F03* (Unspecified dementia) 0 = No diagnosis of dementia in CRIS, HES or ONS records until censoring date on March 31st, 2017
COVARIATES:	
Demographics	
Age	Age in years, range 65-98 Subgroup analysis was performed by stratifying patients into the "65-79" and "80+"("oldest old") groups
Gender	0 = male 1 = female
Ethnicity	0 = White 1 = Other
Marital status	0 = Married 1 = Widowed/Separated 2 = Single
Baseline cognition and other health-related measures	
Health of the Nation Outcome Scales (HoNOS) 65+	The scale consists of 12 items: (1) Behavioural disturbance e.g. overactive, aggressive, disruptive or agitated behaviour, uncooperative or resistive behaviour (2) Non-accidental self-injury

	(3) Problem-drinking or drug-use (4) Cognitive problems (5) Problems related to physical illness or disability (6) Problems associated with hallucinations and/or delusions (or false beliefs) (7) Other mental and behavioural problems (8) Problems with depressive symptoms (9) Problems with relationships (10) Problems with activities of daily living (11) Problems with living conditions (12) Problems with activities Each item is rated on a scale from 0 to 4 where 0 indicates no problem, and 4 indicates severe to very severe problem.
Medication use	
Psychotropic medication	The following group of medication was available as binary variables (0=absent/1=present): • Antidepressant medication (all types) • Selective serotonin reuptake inhibitors (SSRI) • Serotonin–norepinephrine reuptake inhibitors (SNRI) • Mirtazapine • Tricyclic antidepressants (TCA) • Antipsychotic medication
Somatic medication	• Antihypertensive medication • Anticoagulant/antiplatelet medication • Antilipid medication • Antihyperglycaemic medication

Table 3. The description of variables used for the analysis performed in Chapter 5.

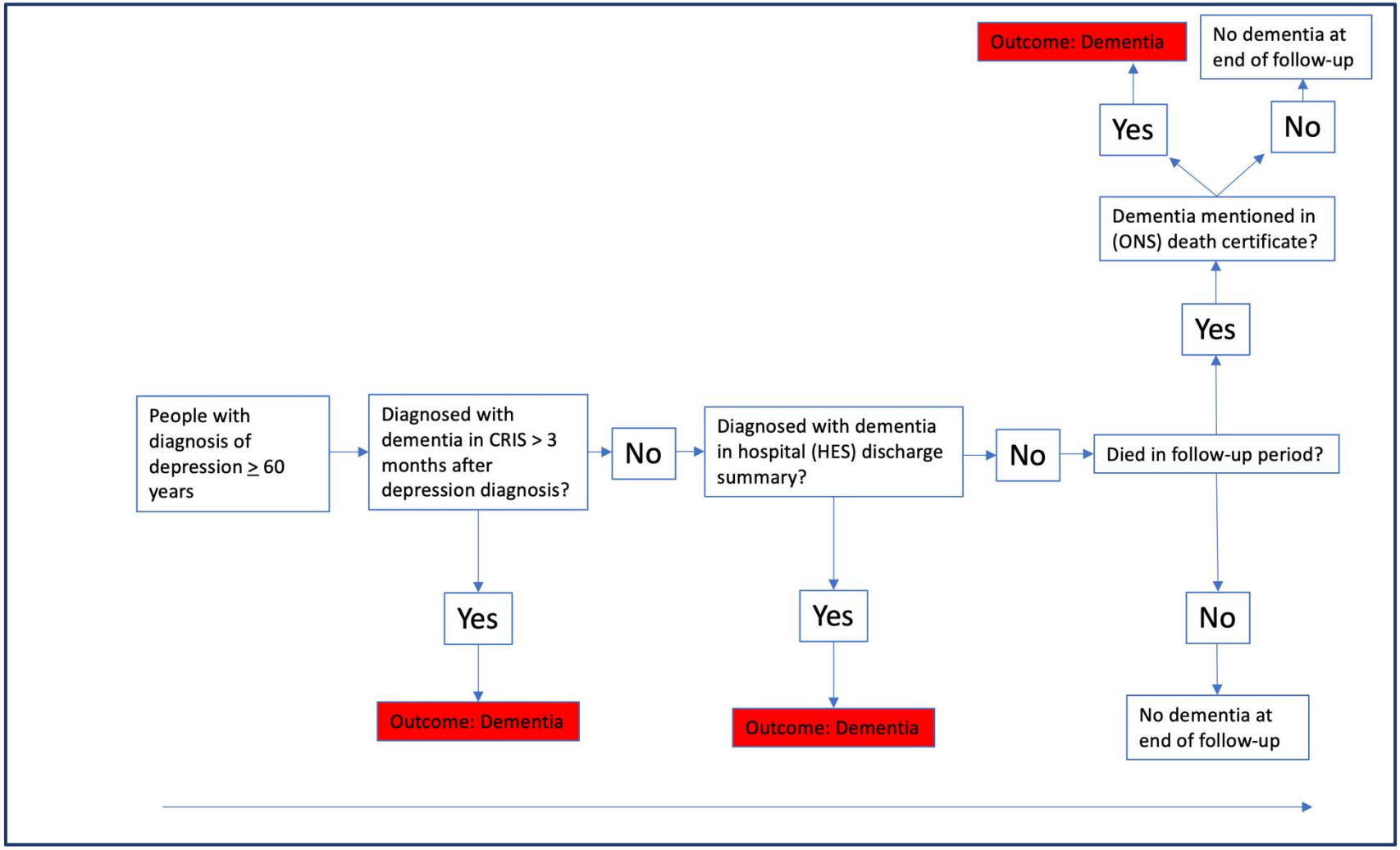


Fig. 6. Flowchart of data extraction from CRIS, ONS and HES datasets

2.2.4 Statistical analysis

2.2.4.1 Data cleaning and descriptive statistics

Initial data cleaning was performed in Microsoft Excel. Variables reflecting depression and dementia diagnoses were extracted from the list of ICD-10 codes using the following command: [=IF(ISNUMBER(FIND("How",A1,1)),TRUE,FALSE)]. Patients with ICD-10 codes for diagnoses of MCI, schizophrenia, substance abuse, organic brain damage, delirium, Parkinson's disease, and stroke were excluded from the sample. The inclusion of patients with these codes could have introduced substantial bias into the sample: our primary aim was to investigate what clinical features of depression in late life are predictive of progression to dementia, so the exclusion was performed to ensure that depression was not secondary to a neurological or mental condition (i.e. stroke or schizophrenia), and that dementia was not better explained by the presence of a neurological condition (i.e. Parkinson's disease, stroke, organic brain damage, or MCI). That said, in cohort studies of the association between depression and dementia, it is not always feasible to rule out the presence of MCI at baseline, as it may be difficult to differentiate it from the cognitive symptoms of depression. In this case, however, it was possible to exclude patients with a pre-existing diagnosis of MCI. As mentioned above (see 1.3.2), depression in MCI is associated with a higher risk of conversion to dementia than MCI alone; however, this association is outside the scope of the present thesis.

Follow-up duration was calculated as a numerical variable reflecting time (in years) between the index date (date of depression diagnosis) and either date of dementia diagnosis in CRIS, HES or ONS records, or censoring date (March 31st , 2017). Participants with follow-up duration below 0.25 years (3 months) were excluded to avoid potential overlap of depression and dementia diagnosis.

All statistical analyses were performed using Stata/MP version 16.1.

The distribution of continuous data was checked by describing the variable (mean, standard deviation, median and interquartile range (IQR)) and plotting histograms to identify the distribution and potential incorrect data points. Binary and categorical demographic variables were summarised using frequencies and percentages.

2.2.4.2 Exploratory analysis

Exploratory analysis was performed by comparing baseline characteristics between the group dichotomised by outcome, using bivariate hypothesis tests.

Differences in the distribution of continuous/discrete variables were compared using two independent samples t-tests or, in case of skewed distribution, Mann-Whitney U tests.

The two independent samples t-test, also known as Student's t-test, is a parametric statistical test allowing to compare means of a continuous variable (e.g. age) between two groups (e.g. binary outcome, i.e. dementia at follow-up). The test assumes normality of the data and equality of variances across comparison groups (Bland et al., 1995).

The Mann-Whitney U test is used to compare differences between two independent groups when the dependent variable is either continuous but skewed, or discrete (incl. ordinal with 5+ levels). Mann-Whitney U test compares medians between the two groups.

Differences in proportions of categorical variables were analysed using Pearson's chi-squared (χ^2) test.

Pearson's chi-squared test is used to analyse whether there is a statistically significant difference between the expected frequencies and observed frequencies of a categorical variable. An assumption of the chi-squared test is that not more that 20% of cells have expected values below 5 (in the opposite case, Fisher's exact test is recommended; not applicable to any analysis in the present thesis).

2.2.4.3 Main analysis

The analysis of predictors of conversion to dementia was performed using Cox proportional hazards regression.

Cox proportional hazards model is a regression model often used in medical research to analyse the association between the survival time of patients and one or more predictor variables (Cox, 1972). "Survival time" refers to time to the occurrence of outcome event (dementia diagnosis, in the present case).

Cox proportional hazards regression analysis allows to include both continuous and categorical predictor variables in a multivariate model. The result is expressed as Hazard Ratio (HR) with 95% confidence intervals (CI).

An HR of 1 indicates no effect, HR < 1 indicates reduction in hazard; HR > 1 - increase in hazard. Performing Cox regression requires assessing the assumption of proportionality of hazards, although the usefulness of this test has been debated in recent publications (Stensrud et al., 2020).

2.2.4.4 Confounder selection

The selection of confounders was based on prior knowledge. Confounders chosen for each model and explanation of selection and type of variable is described in *Chapter 5.*

2.2.4.5 Missing data

Missing data refers to values that are not available and that would be meaningful for analysis if they were observed (Little et al., 2013).

Missing data may cause several problems. The absence of data may reduce statistical power, bias the estimation of parameters, and reduce the representativeness of the study, leading to invalid conclusions (Kang et al., 2013). Therefore, it is crucial that missing data not be ignored and that relevant steps are taking to assess the source and type of missingness and use appropriate analysis to minimise potential bias.

The following three types of missing data have been described:

- Missing Completely At Random (MCAR): This type of missing data is observed when the probability of missingness is completely independent of all other variables. MCAR is a rare situation in which complete cases are representative of the original sample, and inferences made on the basis of complete case analysis can be generalised on the population of interest.
- Missing At Random (MAR): This type of missingness refers to a situation when the probability of missingness is not dependent on the unobserved observations, but is related to the observed data – i.e. pattern of missingness is dependent on the values of another variable.
- Missing Not At Random (MNAR): This type of missingness occurs when missing data are dependent on unobserved data. This type of missingness can potentially lead to biased inferences.

In reality, however, the type of missingness is rarely fully described by one particular mechanism, instead, a mix of all three mechanisms in varying proportions can be present. (Graham, 2009).

In *Chapter 5* (The CRIS study), 27% of values on each of HoNOS subscales were missing. Missingness pattern identified best matched the MAR mechanism. In order to minimise potential bias, missing data was handled by means of multiple imputation, using

ordinal logistic regression to predict missing values of scores on HoNOS subscales. The comparison of results obtained from imputed sample and complete case analysis showed no substantial differences, therefore, complete case analysis results were presented.

2.3 An internet-based prospective cohort designed for investigating longitudinal cognitive performance in people aged 50 and above: the PROTECT study

2.3.1 PROTECT study background

The PROTECT study is an on-going ten-year longitudinal study collecting data on cognitively healthy individuals aged 50 years and over, founded by the University of Exeter in cooperation with King's College London. The study commenced in November 2015, and data is collected on a yearly basis (baseline data were collected between November 2015 and November 2016; one-year follow-up data collected between November 2016 and November 2017, etc.)

Data were collected via an on-line portal where participants were guided through a series of questionnaires and a battery of cognitive assessments. Researchers from the PROTECT team contacted participants at regular intervals to keep them up-to-date with the study and prompt them to log on to complete study related tasks as and when required.

The PROTECT study received ethical approval from the London Bridge NHS Research Committee (Ref: 13/LO/1578).

2.3.2 Obtaining access to PROTECT data

The application for data access was submitted to the project lead, Dr Anne Corbett, on 10.02.2019, using an exhaustive data dictionary of the PROTECT study (i.e. a "menu" all data items available in the PROTECT database). Extracts of the dara dictionary are presented in Fig.5 for illustration. The data usage agreements were signed on 20.05.2019.

2.3.3 Study design and participants

PROTECT is a prospective internet-based cohort study with annual follow-up. For the present thesis, data from 3 years of follow-up has been analysed. The flowchart illustrating waves of assessment, number of participants at each stage and key variables included in the assessment, is presented in Fig.6.

Questionnaire	Question	Possible Responses	Analyse?	Analyse (infromant)?
Medical History	1. Your Medical History			
Medical History	1.1 What is your height?		☑ Yes	N/A
Medical History	1.2 What is your current weight?		☑ Yes	N/A
Medical History	1.3 Has a doctor ever given you a diagnosis of, or told you that you have, any of the following?:	1 = High blood pressure 2 = Stroke 3 = Heart disease / Heart attack / Angina 4 = Diabetes 5 = Mild cognitive impairment (MCI) 6 = Parkinson's Disease 7 = High cholesterol 8 = Hypothythroidism 9 = Hyperthyroidism 10 = Arthritic condition	☑ Yes	N/A
Medical History	1.4 Please list any medications you are currently taking in the box below (including pills, injections etc.)?		☑ Yes	N/A
Medical History	1.5 Do you have problems with your hearing?	0 = No (go to question 7) 1 = Yes	☐ Yes	N/A
Medical History	1.6 …if yes how long have you had problems with your hearing?	0 = Less than 1 year 1 = 1 – 5 years 2 = 6 – 10 years 3 = More than 10 years	☐ Yes	N/A
Medical History	1.7 Do you use a hearing aid?	0 = No 1 = Yes	☐ Yes	N/A
Medical History	1.8 Do you have any visual impairment that requires you to wear glasses / contact lenses?	0 = No (go to question 10) 1 = Yes, I wear glasses 2 = Yes, I use contact lenses 3 = Yes, I use both glasses and contact lenses	☐ Yes	N/A
Medical History	1.9 …if yes how long have you used glasses and / or contact lenses?	0 = Less than 1 year 1 = 1 – 5 years 2 = 6 – 10 years 3 = More than 10 years	☐ Yes	N/A
Medical History	1.10 Have you ever experienced a head injury where you lost consciousness?	0 = No 1 = Yes	☐ Yes	N/A
Medical History	1.11 Do you regularly experience pain that interferes with your day-to-day life?	0 = No (go to question 16) 1 = Yes	☐ Yes	N/A
Medical History	1.12 In the past 7 days how much did pain interfere with your day to day activities?	0 = Not at all 1 = A little bit 2 = Somewhat 3 = Quite a lot 4 = Very much	☐ Yes	N/A
Medical History	1.13 In the past 7 days how much did pain interfere with work around the home?	0 = Not at all 1 = A little bit 2 = Somewhat 3 = Quite a lot 4 = Very much	☐ Yes	N/A
Medical History	1.14 In the past 7 days how much did pain interfere with your ability to participate in social activities?	0 = Not at all 1 = A little bit 2 = Somewhat 3 = Quite a lot 4 = Very much	☐ Yes	N/A

Fig.7. An extract from the data dictionary illustrating the process of data request from the PROTECT cohort

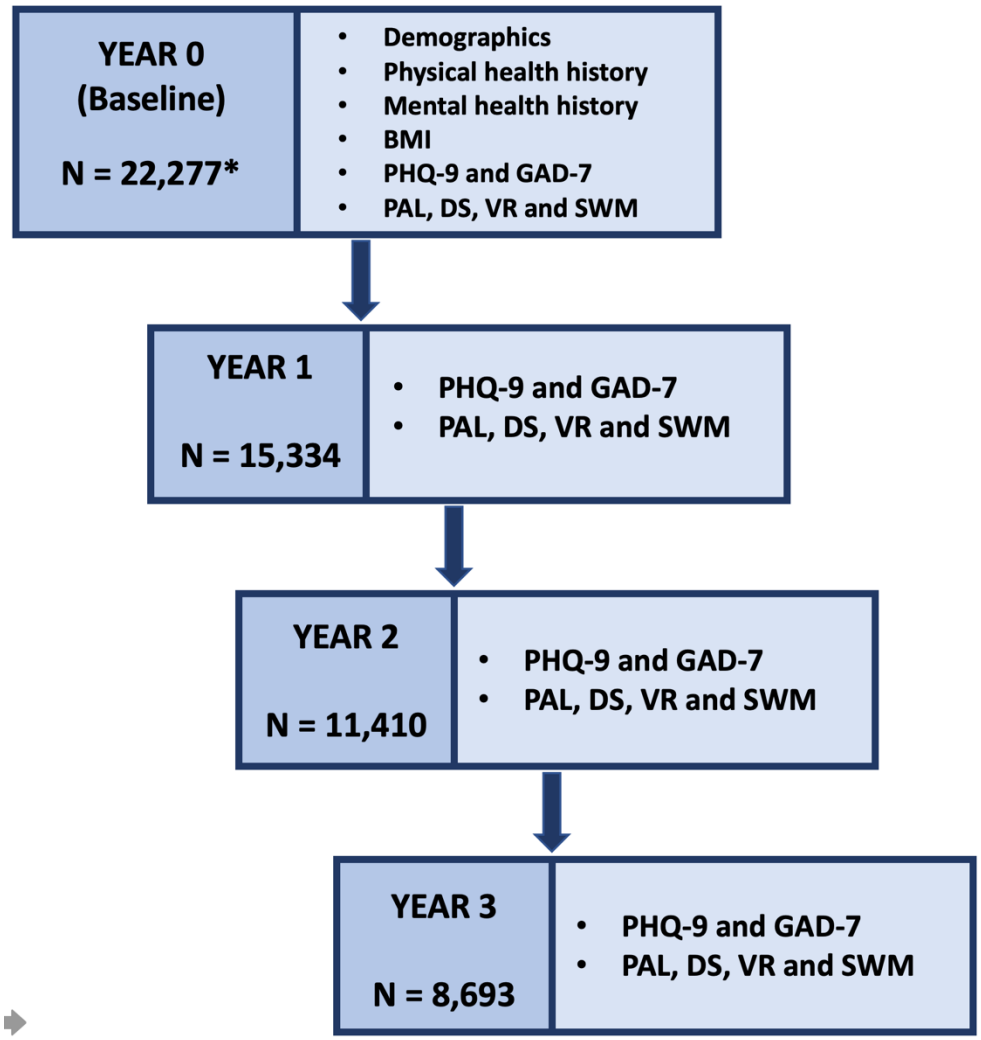


Fig.8. Flowchart of the PROTECT study. Numbers are presented after the exclusion of participants with MCI, Parkinson's disease and a history of stroke

2.3.4 Variables

For the analysis performed in this thesis, the following categories of variables were used:

- Demographics

Each participant's age, gender, ethnicity, level of education, and employment status were registered.

- Cognitive Function

Scores on computerized tests assessing core aspects of cognitive function including attention, memory, reasoning and processing were registered on every assessment.

An online version of all cognitive tests was performed, which was shown to have equal performance compared to in-person computerized testing (Cornett et al., 2015).

- Mental health

Current anxiety and depression symptoms were measured at each wave; detailed information about past mental health history was collected at baseline

- Physical health and medical history

All participants reported their height and weight, medical history and current medical diagnoses.

The full description of variables by category is presented below, in Tables 4-7:

Demographics	
Age	Participants' age ranged from 50 to 92
Gender	0 = male 1 = female
Ethnicity	Participants came from a variety of ethnic backgrounds: 1 = White: English / Welsh / Scottish / Northern Irish / British 2 = White: Irish 3 = White: Gypsy or Irish Traveller 4 = White: European 5 = White: Non-European 6 = Mixed: White and Black Caribbean 7 = Mixed: White and Black African 8 = Mixed: White and Asian 9 = Mixed: Any other Mixed / Multiple ethnic background 10 = Asian / Asian British: Indian 11 = Asian / Asian British: Pakistani 12 = Asian / Asian British: Bangladeshi 13 = Asian / Asian British: Chinese 14 = Asian / Asian British: Any other Asian background 15 = Black / African / Caribbean / Black British: African 16 = Black / African / Caribbean / Black British: Caribbean 17 = Any other Black / African / Caribbean background 18 = Other ethnic group: Arab 19 = Any other ethnic group However, the vast majority of participants were white, therefore the variable was dichotomised into 0 = White 1 = Other
Education	1 = Secondary Education (GCSE/O-Levels) 2 = Post-Secondary Education (College, A-Levels, NVQ3 or below, or

	similar) 3 = Vocational Qualification (Diploma, Certificate, BTEC, NVQ 4 and above, or similar) 4 = Undergraduate Degree (BA, BSc etc.) 5 = Post-graduate Degree (MA, MSc etc.) 6 = Doctorate (PhD)
Employment status	= Select your current employment status 1 = Employed (full-time) 2 = Employed (part-time) 3 = Self-employed 4 = Retired 5 = Unemployed

Table 4. The description of demograhic variables used for the analysis performed in Chapter 6

Cognitive functions		
Test name	Type of cognitive functioning	Test description

Digit Span test	Executive function	Verbal working memory	Participants are asked to reproduce a sequence of digits, with each successful trial being followed by a sequence 1 digit longer than the previous, and each unsuccessful trial being followed by a sequence 1 digit shorter than the last. Main outcome: the average number of digits in all successfully completed trials
Self-ordered search (Spatial working memory)		Visuospatial working memory	Participants are asked to search for a series of on-screen boxes to find a hidden symbol. Once the symbol has been found, they are asked to search for a new symbol, keeping in mind that the symbol can not be hidden in the same box again. Main outcome: the number of boxes in successfully completed trial
Paired Associates Learning	Episodic memory		Participants are shown a number of objects, one at a time, and asked to select the correct location of each object in windows they had previously seen. Main outcome: the average number of correctly completed object-place associations ("paired associates")
Verbal Reasoning	General intelligence		Participants are asked to evaluate the accuracy of a series of grammatical statements about a picture. Outcome measure: the total number of trials answered correctly in 90 seconds, minus the number answered incorrectly.

Table 5. The description of cognitive variables used for the analysis performed in Chapter 6

Mental Health			
Domain	Measure	Description	Cut-off(where applicable)/criteria
Depression(current symptoms)	Patient Health Questionnaire – 9 (PHQ-9)	Nine-item self-report questionnaire The participants were asked to rate their condition over the two weeks preceding the completion of the questionnaire on a scale from 0 (“Not at all”) to 3 (“Nearly every day”)	Developer-recommended cut-off: ≥ 10 (Martin et al., 2006) Relying on a meta-analysis, the present study used a lower threshold: ≥ 8 to define “clinically significant depressive symptoms” (Manea et al., 2012)
Anxiety (current symptoms)	Generalised Anxiety Disorder Assessment (GAD-7)	Seven-item self-report questionnaire The participants were asked to rate their condition over the two weeks preceding the completion of the questionnaire on a scale from 0 (“Not at all”) to 3 (“Nearly every day”)	Developer-recommended cut-off: ≥ 10 (Spitzer et al., 2006) A lower threshold has been shown to have sufficient sensitivity and specificity: ≥ 8 was used to define “clinically significant anxiety symptoms” (Plummer et al., 2016)
History of depression	Self-report	(a)“Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don’t have it currently? (check all that apply): (01) Depression” (b)“Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?” (c)“Have you ever had a time in your life lasting two weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure?”	Participants were categorized as: - Having a history of depression (1) if they answered “yes” to (a) and either (b) or (c) - Having no history of depression (2) if they answered “no” to *all three questions*
Age of onset	Self-report	About how old were you the FIRST time you had a period of two weeks like this? (Whether or not you received any help for it.)	Age of onset of depression was reported by 2,693 of those who satisfied the criteria for having a history of depression (see above) Median 33 (IQR 22-48)

Table 6. The description of mental health-related variables used for the analysis performed in Chapter 6

Physical health		
Type	Measure	Range/Variables
BMI	• Weight and height were manually converted to kg/meters using Stata's "replace" command • BMI was calculated from weight and height using the formula: (weight in kg)/(height in m)^2 • Extreme values (below 16 and above 42) were dropped as potential typos (as associated with severe morbid conditions)	Median 25.15 (IQR 22.71 - 28.34)
Diagnosed conditions	• Self-reported diagnosis: "Has a doctor ever given you a diagnosis of, or told you that you have, any of the following?": 1 = High blood pressure 2 = Stroke 3 = Heart disease / Heart attack / Angina 4 = Diabetes 5 = Mild cognitive impairment (MCI) 6 = Parkinson's Disease 7 = High cholesterol 8 = Hypothythroidism 9 = Hyperthyroidism 10 = Arthritic condition	Extracted variables: Hypertension (0/1) Heart disease (0/1) Diabetes(0/1) Participants who reported a history of stroke, Parkinson's disease, and MCI, were excluded from the sample.

Table 7. The description of physical health-related variables used for the analysis performed in Chapter 6

2.3.5 Statistical analysis

2.3.5.1 Data cleaning and descriptive statistics

Initial data was received as Microsoft Excel files.

For the four cognitive tests, results from more than one attempt were available for the majority of participants. There were 3338 subjects without duplicates (i.e. with only one attempt on each test), 4160 subjects with 1 duplicate (i.e. had two attempts on each test), and 15,247 subjects with 2 duplicates (i.e. had three attempts on each test). For those without duplicate scores, original scores were preserved. For those with duplicates, an average score of either 2 or 3 attempts was calculated.

Summary statistics were analysed and univariate associations analysed as described in 2.2.4.1-2.2.4.2. Extreme values of cognitive scores were explored using the "extremes" command in Stata. Values exceeding 3 standard deviations were winsorised (replaced with values 3SD around the mean).

2.3.5.2 Cross-sectional associations between depressive symptoms, anxiety and cognition: linear regression

The associations between depressive symptoms, anxiety symptoms and cognitive performance at baseline were analysed using multiple linear regression analysis.

Multiple linear regression is a linear approach to modelling which allows to explore the relationship of a continuous dependent variable with several independent variables, both categorical and continuous.

As a first step, simple linear regressions were fitted, with one continuous dependent variable and one main predictor. For example, the first step of assessing the relationship between the severity of depressive symptoms and performance on Digit Span test at baseline was regressing DS score at baseline on PHQ-9 score. Next, each model was adjusted for potential confounders in three steps (detailed in the relevant chapter).

The equation for multiple linear regression is presented below:

$$\boldsymbol{y} = \boldsymbol{\beta 0} + \boldsymbol{\beta 1 x}_1 + \boldsymbol{\beta} 2\boldsymbol{x}_2 + \boldsymbol{\beta} 3\boldsymbol{x}_3 \ldots + \boldsymbol{\beta} \mathrm{n}\boldsymbol{x}_\mathrm{n} + \boldsymbol{\varepsilon},$$

where:
$\boldsymbol{y}$ is the dependent continuous variable (outcome of interest)
$\boldsymbol{\beta_0}$ is the intercept
$\boldsymbol{x}_{1\ldots}\ \boldsymbol{x}_\mathrm{n}$ are the independent (predictor) variables (categorical or numerical)
$\boldsymbol{\beta_1 \ldots \beta}_\mathrm{n}$ are the regression coefficients, or the gradient of the regression line, representing the change in the outcome variable per one unit change in predictor variable
$\boldsymbol{\varepsilon}$ is the residual (the distance between the data points and the regression line)

Performing a linear regression analysis requires that the following assumptions are met:

1) Normality of the distribution of residuals
2) Linearity of relationship
3) Homoscedasticity of residuals, i.e. the homogeneity of variance of residuals

The following Stata commands were used to check the normality and homoscedasticity of residuals:

predict r, resid
kdensity r
pnorm r
qnorm r
rvfplot, yline(0)

In addition to grapjhcal assessment, heteroscedasticity was assessed numerically using the Breusch-Pagan/ Cook-Weisberg test for heteroskedasticity (using the *"estat hettest"* command)

Examples of diagnostic plots for linear regression are presented below in Fig. 7.

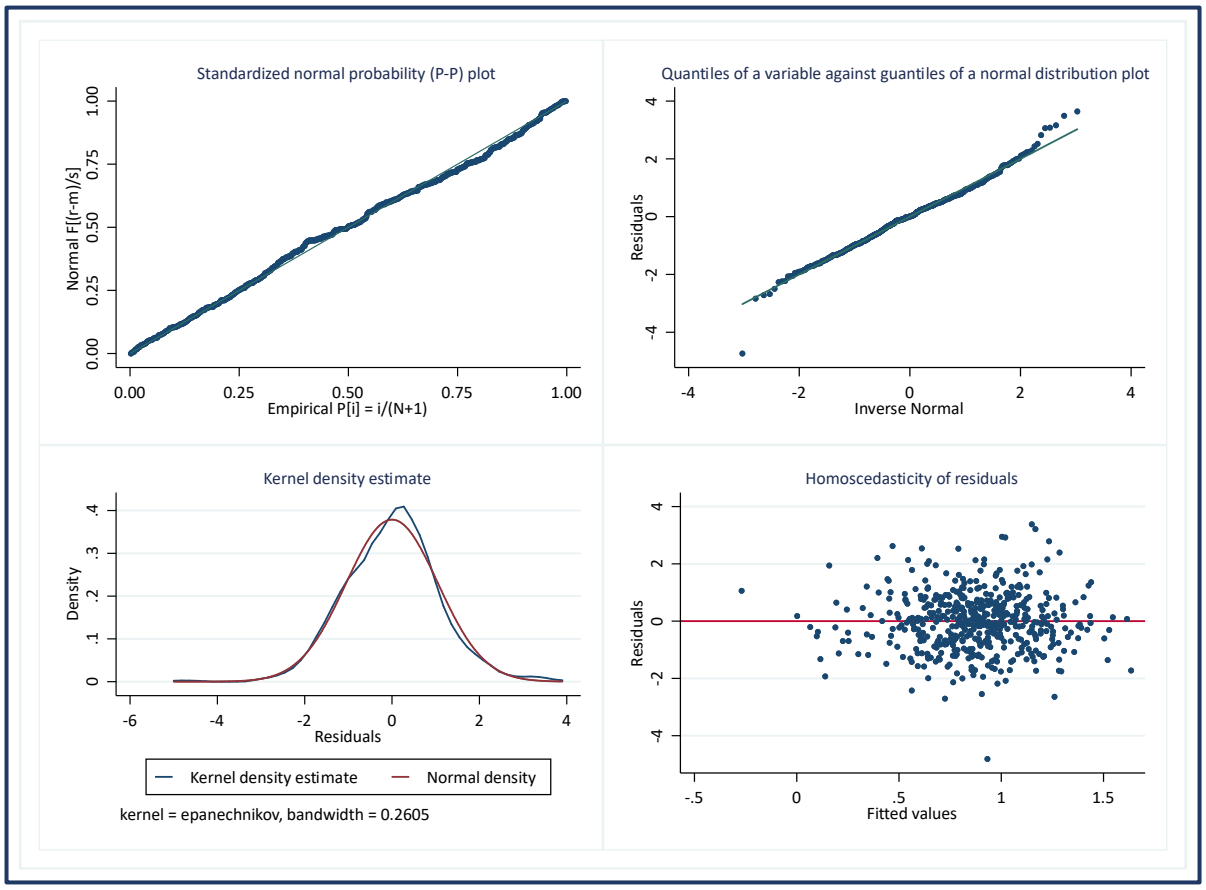


Fig.9 Diagnostic plots for linear regression analysis

The following steps were taken to avoid violation of assumptions:

- PHQ-9 and GAD-7 scores had severely positively skewed distributions, therefore models including either of or both variables were bootstrapped using 1000 replications

- When heteroscedasticity was detected, robust heteroskedasticity-consistent (HC) standard errors were calculated

2.3.5.2 Cross-sectional differences in cognitive performance between groups on depression history: ANOVA

One-way analysis of variance is a statistical method used to compare the mean of a continuous variable between three or more groups. In order to avoid spurious statistical results, p values were adjusted to account for multiple comparisons.

An assumption of ANOVA test is that the variance of the continuous variable across groups is homogenous. This assumption was tested using Bartlett's test for equal variances. It tests the null hypothesis that there is no difference in variances. When this assumption was violated, Dunn's test was performed (Dunn et al., 1961). Dunn's test is a version of non-parametric ANOVA test which allows to measure differences regardless of the distributions, as well as to adjust for multiple comparisons (Dinno et al., 2015).

2.3.5.3 Longitudinal associations between depressive symptoms, anxiety symptoms and cognitive performance: Structural Equation Models

2.3.5.3.1 Cross-lagged panel models

Cross-lagged panel analysis of longitudinal data allows to examine the relationships between variables over time, assessing the reciprocal effects variables have on each other. An example of the simplest cross-lagged panel model is presented below (Fig.8):

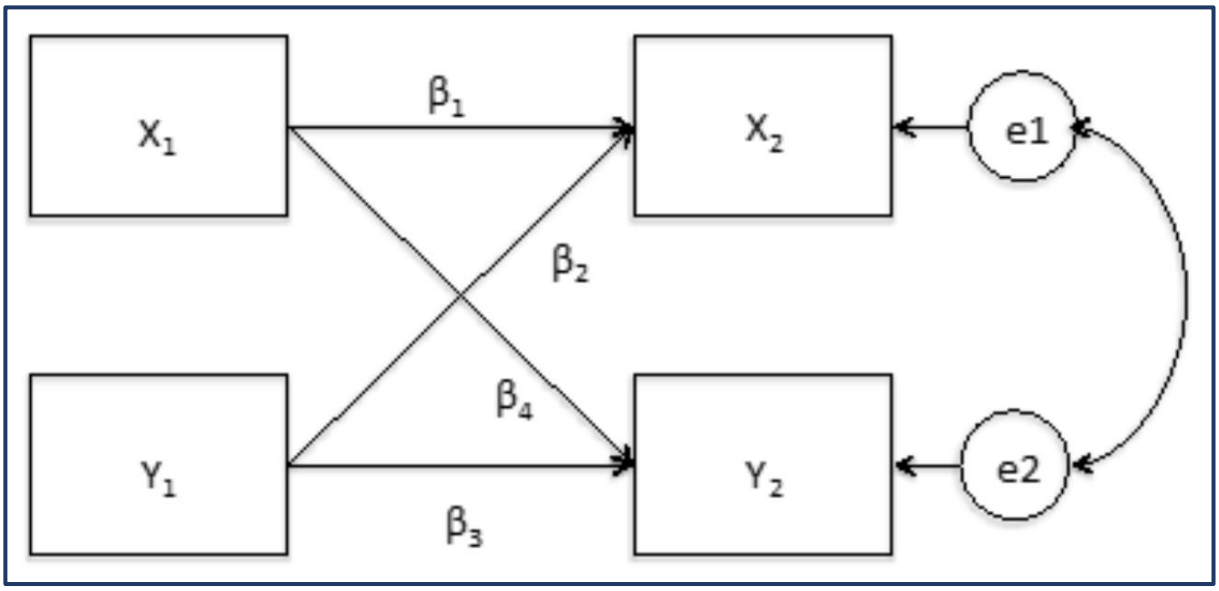


Fig.10. An example of a simple cross-lagged model, with coefficients

The output of cross-lagged panel models is presented as a regression coefficient $\boldsymbol{\beta}$; the results of a model like the one presented above can be summarised using the following regression equations:

$X_2 = \boldsymbol{\beta}_1 X_1 + \boldsymbol{\beta}_2 Y_1 + \boldsymbol{\varepsilon}_1$
$Y_2 = \boldsymbol{\beta}_3 Y_1 + \boldsymbol{\beta}_4 X_1 + \boldsymbol{\varepsilon}_2$

In *Chapter 6*, two types of cross-lagged panel analysis were performed.

- First, we performed a cross-lagged panel analysis of the association between affective symptoms and cognitive performance at baseline and at Year 3.

The analysis was performed in three stages:

A) unadjusted CLPM analysis of the association between either PHQ-9 or GAD-7 and one of the four cognitive measures was performed. An example of univariate model is illustrated in Fig.9A. In total, 8 unadjusted models were fitted. Unadjusted models were just identified (in SEM, this term describes models in which the number of free parameters (effects of interest, error variances, covariances, etc) are exactly the same as number of known values (i.e. zero degrees of freedom).

B) a model incorporating depression, anxiety and all four cognitive measures was performed (Fig,9B):

C) The previous model was further adjusted for confounders. The effects of confounders are not illustrated for clarity; arrows from each confounder were fitted to baseline and Year 3 values of each model.

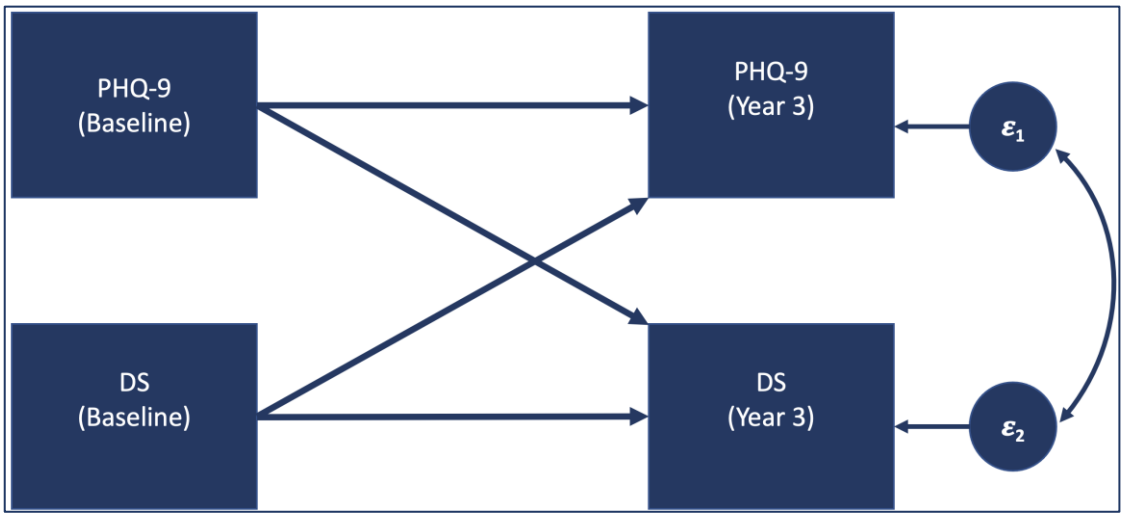


Fig.11A. One of the 8 univariate cross-lagged models.

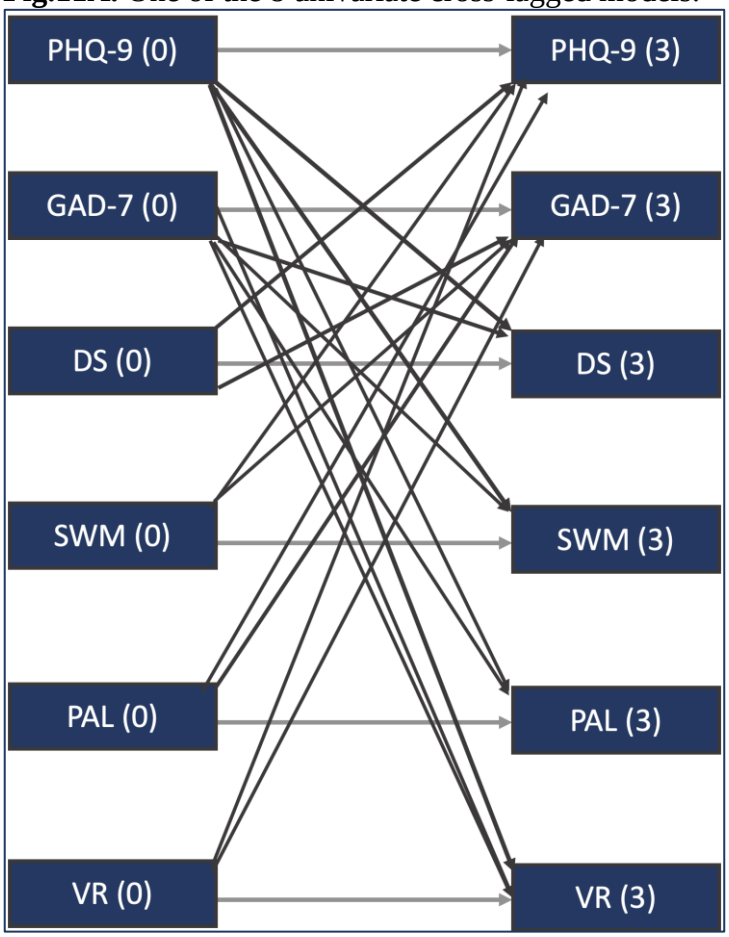


Fig.11B. A cross-lagged model accounting for the effectis of depressive symptoms, anxiety symptoms, and all four cognitive domains.

In addition, to explore the effect of categorical measures of depressive and anxiety symptoms ("clinically significant depressive symptoms"/"clinically significant anxiety symptoms"), generalised structural equation models (GSEM) were fitted. GSEM is an extension of the SEM model allowing for the analysis of categorical values.

For the binary measures of "clinically significant depressive/anxiety symptoms", Bernoulli logit distribution was assumed; for continuous cognition measures, Gaussian identity distribution was assumed.

- Second, we performed a cross-lagged panel analysis of the association between affective symptoms and cognitive performance on all four waves. The same three steps as described above were followed. An example of a univariate four-wave cross-lagged panel model is presented in Fig.10:

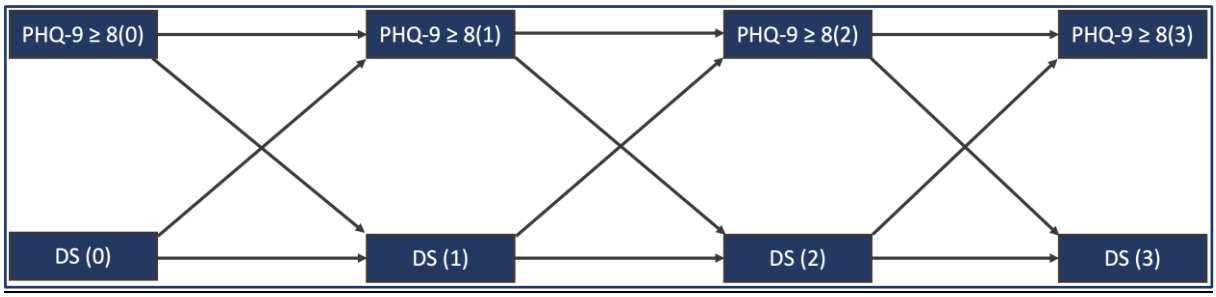


Fig.12 One of the 8 univariate four-wave cross-lagged panel models

- Third, the relationship between affective symptoms and cognitive performance was analysed using latent growth curve (LGC) models

Latent growth curves allow to predict trajectories rather than a person's score on a variable. The analysis was performed in two stages:

A) Fitting individual LGC

Each individual LGC includes two latent factors representing random effects of a growth trajectory. The first random effect is the intercept, or initial level. This variable reflects the initial levels of each of the longitudinally assessed variables (PHQ-9, GAD-

7, DS, VR, PAL, and SWM scores). The second random effect is the slope, or the rate of change over follow-up. The inclusion of a random effect for slope allows to account for individual differences between subjects in the rate of decline or improvement in symptoms.

An example of an individual latent growth curve is presented in Fig.11.

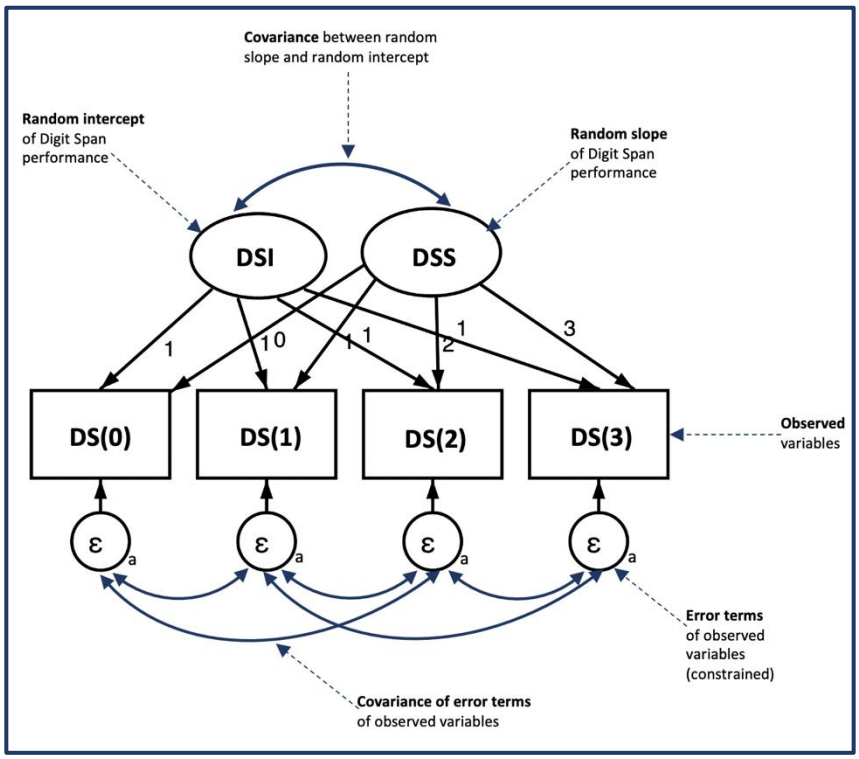


Fig. 13 An example of an individual latent growth curve for Digit Span performance over 4 waves of observation. DSI = Digit Span Intercept; DSS = Digit Span Slope

The main effects of interest in latent growth curve are covariances between latent factors representing random effects. For example, a positive covariance between the factors indicates that the higher the initial levels of a variable, the steeper the growth of score on this variable over time.

At the second stage of LGC analysis of the PROTECT cohort, the six individual LGCMs as the one illustrated above were joined in one model by allowing all random effects to intercorrelate. This was done to investigate whether, e.g. initial levels of depression were associated with worse initial performance on a cognitive test and/or decline in functioning longitudinally, or whether the slope of depressive symptoms predicted/was predicted by the slope of any of the cognitive function tests, - and the analysis was performed in one model to allow adjustment for the effect of all other longitudinal variables of interest. In addition, in the

full model, each random intercept and random slope was adjusted for the participant's age and gender.

Assessing model fit

There are several criteria for assessing the goodness of fit of a structural equation model to determine to what extent the specified model fits the data:

- χ^2 test statistic

Chi-square test statistic is used to evaluate the appropriateness of a structural equation model. However, it should be noted that χ^2 increases along with the increase in sample size, therefore in very large samples, it should be interpreted critically and within the context of other measures of goodness of fit, otherwise plausible models may be rejected (Schermelleh-Engel et al., 2003).

- Root Mean Square Error of Approximation (RMSEA)

RMSEA may be a more sensible approach to evaluating goodness of fit for large sample sizes than χ^2. In this approach, the null hypothesis of exact fit is replaced by the null hypothesis of "close fit" (Browne & Cudeck, 1993, p. 146). Steiger (1990) as well as Browne and Cudeck (1993) have estimated that a "close fit" can be determined if RMSEA value is ≤ 0.05. Values between 0.05 and 0.08 are considered adequate fit (all models presented in the thesis had a good fit).

- Comparative Fit Index (CFI)

The CFI is an adjusted version of the previously used Relative Noncentrality Index (Bentler, 1990). In brief, values of CFI range from 0 to 1, where higher values indicate better fit. Values of 0.97 and above are indicative of good fit; values of 0.95-0.96 indicate acceptable fit (all models presented in the thesis had a good fit).

2.3.6 Missing data

Mechanisms of missingness are described in 2.2.4.5.

Data missing in the PROTECT cohort as baseline were classified as MAR, and cross-sectional analyses were performed using multiple imputation.

During follow-up, there was substantial attrition: only 39% of participants had complete follow-up data. Differences between participants with complete and incomplete follow-up data are discussed in Chapter 6 (6.3.7.2). In brief, subjects who dropped out by year 3 had worse baseline performance on all four cognitive tests, and higher depression and anxiety scores. This presents an obvious limitation which is discussed in the relevant section (Chapter 6.5).

All SEM models were performed using Full information maximum likelihood (FIML) method to handle missing data. FIML calculates the parameter estimates based on all the available information rather than imputing or deleting cases. FIML is recommended as the preferred way of handling missing data (Schlomer, Bauman, & Card, 2010)."

2.4 Investigating the role of inflammation in late-life depression and progression to dementia: analysis using the PRODE and COGNORM data

2.4.1 Study background

PRODE (Prognosis of Depression in the Elderly) is a clinical cohort of 169 patients recruited across nine clinical centres in Norway Oslo University Hospital, Ullevål and Aker; Diakonhjemmet Hospital; Vestre Viken Hospital Trust; Innlandet Hospital Trust, Sanderud and Reinsvoll; Stavanger University Hospital; St. Olavs Hospital, Trondheim University Hospital; and Haukeland University Hospital. The cohort was designed by the study lead, Dr Tom Borza, to investigate the clinical course of depression in elderly patients.

COGNORM is a cohort of 125 cognitively normal older adults recruited from Oslo University Hospital and Diakonhjemmet Hospital, Oslo, Norway and followed up for 3 years.

2.4.2 Obtaining access to PRODE and COGNORM data

The application for data access was submitted to the project lead, Dr Tom Borza, on 02.10.2019. The Clinical Research Forms (CRFs) were obtained in October 2019 and were translated from Norwegian into English by November 2019. Full data from the PRODE cohort was obtained by January 2020.

Application for COGNORM data was submitted separately to the project lead, Dr Leiv Otto Watne, in November 2020, data was obtained in December 2020.

2.4.3 Study design and participants

Both cohorts were assessed longitudinally. The vast majority (96%) of patients in the PRODE cohort were admitted to inpatient psychiatric units for depression. The patients were assessed in four waves: at baseline, at discharge, and at 1 and 3 years post-discharge. Control subjects were assessed at baseline and at Year 3. The flowchart for both studies is illustrated in Fig.12.

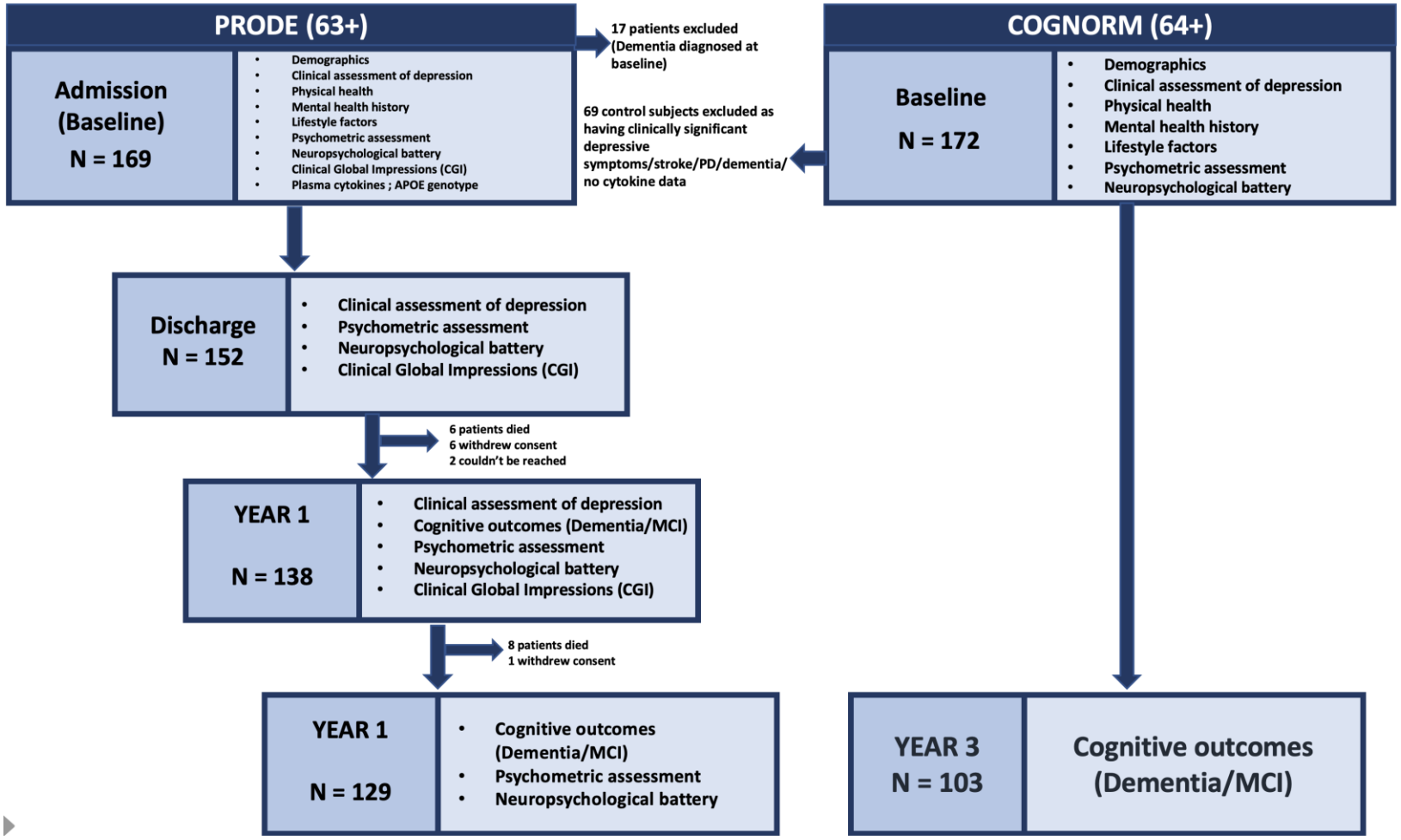


Fig.14. PROTECT and COGNORM study flowchart

2.4.4 Variables

In the control sample (COGNORM), none of the participants developed dementia by year 3, and only 6 participants developed MCI by year 3. Therefore, longitudinal analysis was only performed in PRODE patients.

The following categories of variables were used for the cross-sectional analysis of differences in plasma cytokines between depressed patients and control subjects
(PRODE vs COGNORM, see *Chapter 7a*):

- Demographics

  All participants were of Northern European origin. Each participant's age, gender, marital status and level of education were registered.

- Diagnosis of depression

  Diagnosis of depression was made by psychiatrist during clinical assessment

- Mental health history

  Chronic and acute somatic disorders were reported using ICD-10 codes. Self-reported smoking status was measured as well.

- Psychometric scales

  The severity of depressive symptoms was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS); Mini-mental state examination (MMSE) scale was used to assess cognitive performance

- Plasma cytokines

An array of plasma cytokines and chemokines was measured for 136 depressed participants and 103 controls.
The full description of variables by category is presented below, in Tables 8-9.

Demographics	
Age	Participants' age ranged from 50 to 92
Gender	0 = male 1 - female
Marital status	0= married 1 = widowed 2 = single 3 = divorced/separated
Education	Education was measured in total number of years (range 3-23)
Depression diagnosis and mental health history	
Depression diagnosis	• Depression diagnosis was made using ICD-10 criteria • No control subjects had depression at baseline
History of past depression	Clinical interview (0/1)
Physical health	
Data about physical comorbidities was extracted from provided ICD-10 codes using Stata *strops* command. Each variable was dichotomised (0= absent/1 = present). Presented below are the ICD-10 codes used to define categories of somatic comorbidities; *indicates truncated ICD-10 code	
Hypertension	I1*
Coronary heart disease	I2*/I7*/I8*
Heart failure	I5*
Cerebrovascular events	G4*/I6*
Head injury	S*
Arrythmia	I49*/R00*
Autoimmune disorders	E06.3/M06*/M32*/K50*
Cancer	C*
Psychometric scales	
Montgomery-Asberg Depression Rating Scale (MADRS)	• Clinician-rated 10-item depression scale with each item rated from 0 (no symptoms) to 6 (maximum severity) • The scale has been validated in Norwegian sample of elderly subjects (Engedal et al., 2012) • Cut-off points: <7 - no depression 7-19 – mild depression 20-34 – moderate depression >34 – severe depression However, there is evidence that a score below 10 is sufficient to define remission (Hawley et al., 2002)
Mini-Mental State Examination (MMSE)	A 30-point clinician-rated scale of cognitive performance validated in Norway (Strobel et al., 2008) The scale assesses functioning on a range of cognitive domains. The cut-off score 25 was used in sensitivity analysis to define cognitively intact participants (Ismail et al., 2010)

Table 8. Clinical and demographic variables used for the analysis presented in Chapter 7a&b.

Cytokine/chemokine	Description/function	Previous evidence of role in depression
Chemokine (C-C motif) ligand 2 (CCL-2)* * also known as monocyte chemoattractant protein 1 (MCP-1)	Have a pro-inflammatory function, secreted in response to proinflammatory cytokines. Play a role in neuron–glia communication, synaptic transmission, neurogenesis, neurodevelopment and plasticity	Higher CCL-2 in MDD vs controls (Eyre et al., 2016; Leighton et al., 2018) Lower CCL-4 in MDD (Leighton et al., 2018)
Chemokine (C-C motif) ligand 4* *also known as macrophage inflammatory protein-1β (MIP-1β)		
Interleukin 1-beta (IL-1β)	Pro-inflammatory cytokine, member of the IL-1 family of cytokines; closely linked to the innate immune response, drives the production of T helper-2 (Th2)-associated cytokines; induces production of TNF-α and IFN-γ (Maes et al., 2012)	Higher IL-1β in depressed patients vs controls (Osimo et al., 2020; higher IL-1β in LLD vs controls (Thomas et al, 2015)
Interleukin 33 (IL-33)	Pro-inflammatory cytokine, member of the IL-1 family	Some evidence of elevated IL-33 in MDD compared to controls (Kudinova et al., 2016)
Interleukin-1 receptor antagonist (IL-1ra)	Anti-inflammatory cytokine, prevents detrimental effects of IL-1β	Higher IL-1ra in depressed patients vs controls (Howren et al., 2009; Osimo et al., 2020);
Interleukin-18(IL-18)* * Also known as interferon-gamma inducing factor	Pro-inflammatory cytokine, plays an important role in the T-cell-helper type 1 response IL-18 receptors widely expressed in the CNS in regions related to emotional regulation, has been shown to be associated with elevated cortisol levels (Alboni et al., 2010; Wedervang-Resell et al., 2020)	Higher IL-18 in depressed patients vs controls (Osimo et al., 2020);
Interleukin 10 (IL-10)	Anti-inflammatory cytokine, inhibits IFN-γ, IL-2, IL-3, TNFα cytokines, downregulates corticosteroid production (Roque et al., 2009)	Higher IL-10 in depressed patients vs controls (Osimo et al., 2020);
Interleukin-17 (IL-17a)	Pro-inflammatory cytokine, secreted by T-helper 17 (Th17) lymphocytes, interacts with IL-1 and TNF-α to promote inflammation	IL-17 linked to depressive symptoms in animal models; not increased in LLD in one human study (Kim et al., 2012)
Interleukin-6 (IL-6)	Pro-inflammatory cytokine, may affect HPA-axis function, neurotransmitter system, decrease BDNF expression	Substantial evidence of elevated IL-6 in major depression (Ting et al., 2020; Osimo et al., 2020)
Turner Necrosis Factor alpha (TNF-α)	Pro-inflammatory cytokine, induces apoptosis, has an anorexigenic effect	Elevated in MDD vs controls (Osimo et al., 2020)
Interferon-gamma (IFN-y)	Mostly pro-inflammatory, although anti-inflammatory fucntions such as inducing the production of IL-1ra or IL-18 Binding Protein have been described (Muehl et al., 2003). Induces indoleamine 2,3-dioxygenase 1 (IDO1), which degrades tryptophan increasing kyneurine and quinolinic acid, may lead to hyposerotonergia and hyperglutamatergia	Inconsistent results regrding concentration in depressed patients (Koehler et al., 2017; Osimo et al., 2020)
Subunit beta of interleukin-12 (IL12p40)*	Pro-inflammatory; Natural killer cell stimulatory factor 2	IL-12 elevated in MDD vs controls (Osimo et al., 2020)

Table 9. Biomarker variables used for the analysis in chapter 7 a&b: plasma cytokines and chemokines.
*Only investigated in the PRODE cohort

The following additional variables were used for the longitudinal analysis of the prediction of progression of late-life depression to dementia (using the PROTECT cohort; see Chapter 7b):

- APOE genotype:

In additional, for PRODE patients, information on APOE genotype was available. The variable was dichotomised to reflect the presence/absence of the ε4 allele, which is known to be associated with increased risk of Alzheimer's disease and higher amyloid deposition (Liu et al., 2013).

- Longitudinal outcomes:

the incidence of dementia was assessed in the PRODE sample by clinical consensus using ICD-10 criteria

- Neurocognitive test battery

The neurocognitive tests used in the analysis reported in Chapter 7b are summarized in Table 10.

Cognitive functions		
Test name	Type of cognitive functioning	Test description
Trail Making Test (Part A&B)	Executive function/visuospatial processing speed/attention	Part A: participants are asked to connect a sequence of numbers randomly scattered on page Part B: participants are asked to connect circles in alternating numerical (1–13) and alphabetical (A–L) sequences Results on the TMT were re-scored in accordance with existing age-adjusted norms (Ivnik et al., 1996)
COWAT word and category fluency	Verbal fluency/category fluency are attributed to executive functions (Whiteside et al., 2016)	Verbal fluency: Participants are asked to name as many words as possible starting with the letters F,A,S within one minute Category fluency: Participants are asked to name as many words as possible belonging to the categories "animals" and "clothing"
CERAD battery	Immediate recall (working memory)	Participants are asked to recall as many words as possible from a list of 10 words, immediately, over 3 attempts
	Delayed recall (episodic memory)	Participants are asked to reproduce the same list of words after a 10-minute delay
	Recognition (episodic memory)	Participants are asked to recognise whether a word was part of the original list or not

Table 10. Neurocognitive test battery used for the analysis performed in Chapter 8b.

2.4.4 Blood sample handling and plasma cytokine analysis

Blood samples were drawn by venipuncture and stored in sterile serum tubes. For PRODE cohort, samlpes were taken on admission to psychiatric unit; for COGNORM cohort, on admission to surgical unit. The samples were further frozen and stored at -70^{o}C.

Plasma inflammatory markers were analysed using a bead-based multiplex immunoassay panel (Bio-Techne, Minneapolis, MN) based on xMAP Technology (Luminex, Austin, TX). Inflammatory marker concentrations were calculated using a 5-parameter standard curve based on standards that were supplied by the manufacturer. Values below the lower limit of quantification (LLOQ) were set to 25% of LLOQ, and standard curves with a high LLOQ were selected to obtain a similar sensitivity for all samples analyzed.

One of the plates (plate G) had to be reanalysed to assure quality since it gave a lower signal for some of the analytes, which affected the standard curve. The data from reanalysis was not used for all of the analytes, because a reanalysis also has encumbrances in that it is run not simultaneously with other analyses, and the kit is produced later with a different lot, which affects the analytes to varying degrees. Therefore, for the analytes where the technical error seemed not to to have a large impact, the first analysis results were retained. For CD40L and IL-10, reanalysis data was used.

Several of the analytes had a few values below the lower detection range, including IL-1β, IFN-g, IL-22, IL-12p40 and IL-10, as well as, to some extent, IL-33. IL-22, for some of the samples, showed no signal at all. This is often observed in cytokine analysis, because several cytokines are normally not expressed in the circulation. For IL-22 and IL-12p40, this resulted in high degree of missingness (esp. for control data), therefore IL-22 was not analysed in either study, and IL-12p40 was not analysed in the cross-sectional study. For the samples that had a fluorescence value just outside the detection range, the software itself calculated an estimated value. If an estimated value was below 25% of the lower detection range, it was set to 25% of the lower detection range.

2.4.5 Statistical analysis

Descriptive statistics were approached in the same manner as described in 2.2.4.1. Statistical methods used for analysis of hypotheses (Cox proportional hazards regression, multiple linear regression, ANCOVA) were also described in prior sections.

The distribution of cytokine values was examined with special rigour. Extreme values(those exceeding 4 SD from the mean) were dropped (up to 5.8% of values); remaining values were winsorised at 2.5 standard deviations.

Table 11 presents the details of the distribution of cytokine values before and after data cleaning.

Interleukin	Raw values		Winsorised values		N OOR	% OOR	N OOR	% OOR
	PRODE: (N=136)	COGNORM (N=103)	PRODE: (N=136)	COGNORM (N=103)	PRODE: (N=136)		COGNORM (N=103)	
IL-1β	**Range**: 0.15-7.0 **M(SD):** 0.92(1.08) **IQR**: 0.15-14.01	**Range**: 0.15-15.98 **M(SD):** 1.18 (2.24) **IQR**: 0.15 - 1.15	**Range:** 0.145-3.09 **M(SD):** 0.85 (0.80) **IQR:** 0.15-0.88	**Range:** 0.15-4.52 **M(SD):** 0.9(1.1) **IQR:** 0.15-1.15	**60**	**44**	**63**	**61.8**
IL-18	**Range**: 0.7-1319.24 **M(SD):** 196.80 (124.10) **IQR**: 131.47 – 231.91	**Range**: 42.07 - 2037.41 **M(SD):** 228.46 (210.66) **IQR**: 137.42 - 259.68	**Range:** 78.8 – 324.42 **M(SD):** 188.70 (71.55) **IQR:** 141.47 – 231.91	**Range:** 9.6-217.19 **M(SD):** 37.89 (47.28) **IQR:** 25.82-30.02	**0**	**0**	**0**	**0**
IL-6	**Range**: 0.62-26.11 **M(SD):** 3.68(3.97) **IQR**: 1.39-3.79	**Range**: 0.05 - 19.49 **M(SD):** 2.74 (2.95) **IQR**: 1.03 - 3.28	**Range:** 0.71 – 12.65 **M(SD):** 3.49 (3.25) **IQR:** 1.39 – 3.79	**Range:** 0.52-9.43 **M(SD):** 2.60 (2.31) **IQR:**1.03 – 3.28	**0**	**0**	**1**	**0.1**
CCL-2	**Range**: 118.20-1113.19 **M(SD):** 438.47(158.13) **IQR**: 340.87 - 512.59	**Range**: 77.02 - 996.23 **M(SD):** 381.10 (135.79) **IQR**: 299.51 - 465.73	**Range:** 226.8 – 747.56 **M(SD):** 434.81 (140.24) **IQR:** 340.87 – 512.59	**Range:** 199.49-570.35 **M(SD):** 375.88 (110.17) **IQR:** 299.51-469.65	**0**	**0**	**0**	**0**
CCL-4	**Range**: 9.51-1414.50 **M(SD):** 202.10 (149.40) **IQR**: 158.66-242.52	**Range**: 9.51 - 466.09 **M(SD):** 146.00 (92.87) **IQR**: 299.51 - 469.65	**Range:** 50,76 – 350.25 **M(SD):** 189.02 (80.21) **IQR:** 158.66 – 242.52	**Range:** 9.57 – 303.64 **M(SD):** 142.55 (82.89) **IQR:** 76.08	**4**	**2.9**	**17**	**16.7**
CD40L	**Range**: 2.14-9250.90 **M(SD):** 4303.66(1885.34) **IQR**: 2989.43 - 7662.13	**Range**: 7.55 - 23117.96 **M(SD):** 4259.46 (2612.32) **IQR**:3056.23 - 5193.55	**Range:** 1216.89 – 7662.13 **M(SD):** 4302.98 (1742.08) **IQR:** 2989.43 – 5482.05	**Range:** 1251.55 – 6208.24 **M(SD):** 4001.48 (1385.44) **IQR:** 3065.23-5193.55	**0**	**0**	**1**	**0.1**
Il12p40	**Range:** 9.60 – 494.66 **M(SD):** 33.32 (46.11) **IQR:** 25.82 – 29.10	**Range:** 9.60 – 767.39 **M(SD):** 47.67 (96.79) **IQR:** 25.82 – 30.02	**Range:** 9.60 – 30.02 **M(SD):** 25.44 (5.46) **IQR:** 25.82 – 29.10	**Range:** 9.60 – 217.19 **M(SD):** 37.89 (47.28) **IQR:** 25.82 – 30.02	**111**	**81.6**	**86**	**84**
IFNg	**Range**: .31 – 41.77 **M(SD):** 8.90 (10.32) **IQR**: 0.46 – 16.09	**Range**: 0.19 - 32.21 **M(SD):** 4.98(7.42) **IQR**: 0.31 - 6.99	**Range:** 0.31 – 29.55 **M(SD):** 8.73 (9.82) **IQR:** 0.46 – 16.09	**Range:** 0.31-21.59 **M(SD):** 4.64(6.31) **IQR:**0.31-6.99	**54**	**39.7**	**50**	**49.0**
IL10	**Range**: 0.76 – 164.56 M(SD): 11.30 (23.28) **IQR**: 0.89 – 13.51	**Range**: 0.76 - 109.50 M(SD): 7.12(14.11) **IQR**: 0.81 - 7.02	**Range:** 0.81 – 35.73 **M(SD):** 8.64 (11.84) **IQR:** 0.89 – 13.51	**Range:** 0.76-29.57 **M(SD):** 6.18 (9.59) **IQR:** 0.81-7.02	**76**	**55.9**	**66**	**64.7**
IL-17a	**Range**: 0.19 – 11.74 **M(SD):** 1.34 (1.83) **IQR**: 0.22 - 1.69	**Range**: 0.19 - 19.35 **M(SD):** 1.35(2.83) **IQR**: 0.21 - 1.19	**Range:** 0.19 – 4.04 **M(SD):** 1.16 (1.13) **IQR:** 0.21 – 1.69	**Range:** 0.19 – 4.6 **M(SD):** 0.99 (1.23) **IQR:** 0.21-1.19	**57**	**41.9**	**40**	**39.2**
IL-1ra	**Range**: 285.87 – 27504.70 **M(SD):** 1261.96 (2378) **IQR**: 642.38-1259.11	**Range**: 289.22 - 2400.97 **M(SD):** 690.85(355.42) **IQR**: 458.00 - 785.02	**Range:** 421.47 – 2428.2 **M(SD):** 1034.30 (421.47 – 2428.2) **IQR:** 642.38 – 1259.11	**Range:** 325.73 – 1441.86 **M(SD):** 672.18 (287.48) **IQR:** 458 – 794.24	**0**	**0**	**0**	**0**
IL33	**Range**: 0.14-21.19 **M(SD):** 2.67 (6.46) **IQR**: 0.59-2.91	**Range**: 0.14 - 32.42 **M(SD):** 1.98(3.83) **IQR**: 0.34-2.09	**Range:** 0.14 – 7.32 **M(SD):** 2.08 (1.93) **IQR:** 0.59 – 2.91	**Range:** 0.33-6.0 **M(SD):** 1.54(1.63) **IQR:**0.34-2.09	**13**	**9.56**	**29**	**28.4**
TNFa	**Range**: 0.09 - 17.11 M(SD): 4.33 (2.62) **IQR**: 3.01-5.37	**Range**: 0.01-13.89 M(SD): 3.65(2.16) **IQR**: 2.07-4.50	**Range:** 0.32 – 9.42 **M(SD):** 4.24 (2.30) **IQR:** 3.01-5.37	**Range:** 0.73-7.11 **M(SD):** 3.56(1.76) **IQR:**2.07-4.5	**6**	**4.4**	**6**	**5.9**

Table 11.. Summary statistics for raw values and winsorised values of inflammatory markers, and frequencies and percentages of values outside detection range (OOR) for each of the markers. M(SD) = mean(standard deviation); IQR = interquartile range

Chapter 3. Biomarkers predicting the progression from late-life depression to dementia: a systematic review of longitudinal studies

Abstract

Objective: To conduct a systematic review of longitudinal studies investigating biomarkers predicting dementia or cognitive decline in people with late-life depression (LLD).

Methods: We searched MEDLINE, Embase and PsycINFO databases from inception to December 2021. Studies were included if they had a longitudinal design, in aged people 55 or above, reported depressive symptoms and a biomarker/s at baseline and cognitive outcome at follow-up.

Results: 40 studies met inclusion criteria. Biomarkers from these studies fell into one of seven following groups: volumetric measures (structural MRI studies, n= 13); functional connectivity (fMRI studies, n = 6); white matter hyperintensities (n = 9); APoE genotype (n=11); inflammatory and metabolomic markers (n = 5); HPA-axis-related markers (n = 3), and Alzheimer's pathology markers (amyloid and neurofibrillary tangles; n=5). There was some evidence to suggest that decreased hippocampal volume, decreased functional connectivity in the hippocampus, right parahippocampal gyrus, posterior cingulate cortex, the APOE ε4 gene, inflammation, several SNPs and AA/DHA ratio predicted cognitive progression in LLD. The results for other the biomarkers were inconclusive or yielded negative results.

Conclusion: Several biomarkers are found to predictive of cognitive progression in people with LLD and provide an important step in differentiating the LLD and prodromal dementia phenotypes. The implications for clinical practice and further research are discussed.

3.1 Introduction

Prevalence of dementia is increasing as the population of the world ages, with estimates suggesting that between 2020 and 2040, the number of dementia sufferers may double (Ferri et al., 2005). Depression is one of several potentially modifiable risk factors of dementia, as highlighted by the most recent Lancet commission report (Livingston et al., 2020), but the relationship between the two diagnoses is complex and uncertain (Dafsari et al., 2020).

A multitude of studies and meta-analyses have confirmed the association between depression and incidence of dementia (Jorm et al., 2001, Ownby et al., 2006, Cherbuin et al., 2015). A recent meta-analysis showed that history of depression increased the likelihood of cognitive decline, despite a low cumulative risk (OR of 1.36 for categorical measures of depression and 0.992 for continuous measures). This may reflect unaccounted heterogeneity, particularly in subtypes of depression and cognitive domains affected (John et al., 2018).

Exploring the association between depression and dementia is complicated by the fact that both conditions are highly heterogenous. In particular, one meta-analysis showed that the association between late-life depression and dementia is stronger for vascular dementia compared to Alzheimer's disease, although the latter is still strong and significant (OR 2.52 vs OR 1.65; Diniz et al., 2013). "Depression" itself represents a broad category of disorders with varying pathogenetic mechanisms and clinical courses (Penninx et al., 2015, Juruena et al., 2018). Van den Berg et al. suggest that there can be three etiopathological types of late-life depression alone (Van den Berg et al., 2001). Moreover, it is still largely unclear whether it is a history of depression with early or midlife onset or late-onset depression that is associated with increased risk of dementia. In a meta-analysis of 8 studies, Da Silva et al. showed that it is not possible to link the increased incidence of dementia and age of onset of depression in general and that likelihood of dementia may be increased by depression of any onset age. However, greater frequency and severity of depressive episodes did increase the risk of subsequent dementia (Da Silva et al., 2013).

The relationship between depression and dementia is most likely explained by several mechanisms. Depression may be a risk factor for dementia, a prodromal state, (i.e. early manifestation), or a reaction to the early symptoms of dementia. Late-life depression and dementia may also manifest independently from shared underlying mechanisms. Studies to date have failed to answer which mechanism is predominant and it is likely that they are not mutually exclusive and more than one is involved.

One way to explore possible mechanisms for how depression leads to increased risk of dementia is to investigate the effect of biological markers. Biomarkers are defined as "objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly". The present review aims to investigate biomarkers that may assist in predicting the development of dementia or cognitive decline as outcome of LLD, including structural and functional imaging, blood-based markers, genetics and others, and provide insights into the pathophysiological links between LLD and cognitive impairment.
This study aims to systematically review existing studies of biomarkers in progression of people with LLD to dementia or cognitive decline.

3.1.1 Objective

The objective of this chapter is to systematically review and summarise existing evidence of the biomarkers of progression of late-life depression to dementia and/or cognitive decline. We aimed to analyse all relevant longitudinal studies that examined the roles of several groups of biomarkers in the association between late-life depression at baseline and risk of progression to dementia or/and cognitive decline at follow-up.

3.2. Methods

This review conformed with the updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2020). The study protocol was registered in the PROSPERO international prospective register of systematic reviews (registration number CRD42022297126). A systematic literature search was conducted using the OVID platform, across MEDLINE, PsycINFO and Embase databases. The search terms used are presented in Table 1.

Studies were included if they were: longitudinal cohort studies of people aged 55 or above; reported a measure of depression or depressive symptoms at baseline; reported a measure of at least one biomarker at baseline; reported cognitive outcome at follow-up; and reported the statistical association between the biomarker at baseline and the cognitive outcome at follow-up. Studies were excluded if the study population had a diagnosis of dementia or MCI at baseline; or were conducted on special populations (e.g. if the study population only included people with hypertension).

Field	Related terms
Late-life depression	“late-life depress*” or “late-onset depress*” or “late life depress*” or “late onset depress*” or “geriatric depress*”
Dementia or cognitive decline	Alzheimer* or dement* or MCI or cognit* or “cognitive impairment” or “cognitive decline” or memory or “executive function” or “episodic memory” or “processing speed” or “working memory” or "attention” or “language” or “verbal fluency” or recall or “delayed recall” or “immediate recall”
Biomarkers	predict* or biomarker* or MRI or fMRI or PET or serum or plasma or CSF or “white matter” or “gray matter” or volum* or “brain volume” or hippocamp* or connectivity or synaptic or proteomic* or metabolomic* or inflamm* or cytokin* or tau or amyloid or genetic* or cortisol or DTI or EEG
Type of study	longitudinal* or follow-up or "follow up" or prospective or retrospective or cohort or case-control

Table 12. Search terms used for the systematic review. Truncated to allow multiple word endings

3.2.1 Inclusion criteria

Studies were sought for inclusion if they satisfied the following criteria:

- Were performed in people aged 55 or over
- Were performed in patients with a diagnosis of major depression (including remitted geriatric depression) at baseline, or with clinically significant depressive symptoms at baseline, as measured by an above-threshold score on a validated psychometric scale
- Reported a measure of at least one biomarker at baseline, or at baseline and at follow-up

- Had a longitudinal design
- Reported a measure of cognitive performance at follow-up (either a diagnosis of dementia or MCI, or measures of cognitive performance on a scale)
- Reported an effect of the biomarker on the likelihood of the cognitive outcome (if binary) or cognitive performance at follow-up (if continuous) in patients with depression/clinically significant depressive symptoms at baseline, or a model incorporating a cognitive outcome and both a measure of depression and biomarker as outcome

3.2.2 Exclusion criteria

Studies performed in participants who were not cognitively intact at baseline were excluded from the selection. For example, studies were excluded if they were performed only in patients with a pre-existing diagnosis of MCI or dementia at baseline, as explicitly stated in the sample characteristics. However, studies performed in depressed patients manifesting with cognitive impairment at the time of enrolment and without the pre-existing diagnosis of dementia or MCI were retained in the review; the potential implications of this are discussed in the "limitations" section.

Studies which were performed in a population with specific characteristics, i.e. only in patients with type 2 diabetes, patients with pre-existing small vessel disease, or patients treated with ECT, were included, however the characteristics of the population were highlighted in the review and the corresponding tables.

Studies which were RCTs in design were not the primary focus of this review; however, two studies with an RCT design were included (Van Dyk et al., 2020; Krause-Sorio et al., 2021), since in both, one of the groups received escitalopram+placebo, which represents a TAU scenario, and therefore the associations between biomarkers and outcome in this group may yield important insights into the topic of interest.

3.2.3 Search process

The initial search yielded 3,244 results across all three databases, which was reduced to 2,347 following deduplication. The title/abstract screen yielded 115 articles, filtering out the

articles that did not assess depression at baseline, dementia/cognitive decline at follow-up and at least one biomarker at the same time.

The full-text screen resulted in the selection of 28 articles. Twelve more articles were selected by backward and forward citation tracking. The search strategy and stepwise selection of articles is presented in the PRISMA flowchart In Fig. 15.

The quality of all included papers was assessed using the Joanna Briggs Institute critical appraisal checklist for cohort studies (JBI assessment tool; Moola et al., 2017). The JBI assessment tool uses a pragmatic approach to assess the risk of bias on 11 domains. For the purposes of the current review, it was pre-determined that studies with nine or more quality domains rated as 'low' risk would be given an overall low risk of bias rating. Studies with between eight and six quality domains rated 'low' risk would be given an overall medium risk of bias rating and studies with five or fewer items rated 'low' risk would be given an overall high risk of bias rating.

3.2.4 Data extraction

One reviewer (MB) completed the title and abstract search, the full text search and the risk of bias assessment, with a second (RD) independently double rating 10% of each of these steps. Disagreements were resolved in consensus meetings.

3.3 Results

3.3.1 Study selection

A total of 40 studies were selected for inclusion in the review See Table 2 for details of included studies. These studies reported biomarker data that fell into seven groups: volumetric measures (n=13); functional connectivity (FC) (n=6); white matter hyperintensities (WMH) (n=9); genotype or genetic factors (n=11); tau- and beta-amyloid (n=5); inflammation-related (n=5); H HPA-axis (n=3).

3.3.2 The role of volumetric measures

Twelve studies used volumetric brain measures to predict cognitive progression at follow-up. With six of these studies using dementia or MCI as an outcome and six using cognitive decline as an outcome and one study reporting results for both cognitive decline and dementia.

3.3.2.1 Volumetric measures and binary cognitive outcomte (dementia or MCI; See Table 13)

One study found that a history of depression increased the risk of developing AD, but baseline depressive symptoms did not. Adjustment for bilateral hippocampal and amygdalar volume did not alter this association, indicating no mediating effect of volumes of these areas on the increased risk of AD in early-onset depression. (Geerlings et al., 2008).

In contrast, Steffens et al. found that left hippocampal volume in the lowest quartile at baseline was significantly associated with subsequent emergence of dementia. The authors concluded that reduced left hippocampal size on MRI may be a marker for dementia in depressed patients without a clinical diagnosis of dementia (2002).

Lebedeva et al., found that right hippocampal volumes were an important component of a model discriminating between LLD which progressed to dementia/MCI over 1-year follow-up, and those who remained cognitively stable. (Lebedeva et al., 2017) In this study, age of onset did not affect conversion rates; however, in a different cross-sectional study by the same group of authors, performance on MMSE was significantly positively correlated with the thickness of prefrontal cortex only in late-onset cases, not early-onset depression.(Lebedeva et al., 2015).Other studies found depressive symptoms predicted dementia independently of

medial temporal atrophy (Uden et al., 2016); and elderly patients with MRI-defined white matter changes, grey matter volume also did not alter the effect of depressive symptoms on risk of AD (Verdelho et al., 2017). Oudega et al. indicated no association between baseline medial temporal atrophy and risk of dementia at follow-up (Oudega et al., 2015).

Finally, a recent study created a prognostic index encompassing several AD-related biomarkers (the "CARE" index) which predicted conversion from remitted LOD to AD with an accuracy of 74.5%, a sensitivity of 80.0%, and a specificity of 69.0%. The authors showed that hippocampal volumes and fusiform gyrus volumes did not predict conversion from rLOD to AD individually, but the CARE index, combining these two markers with functional connectivity markers, baseline MMSE and auditory verbal learning test (AVLT), predicted conversion with an HR 2.143 (Lu et al., 2020).

3.3.2.2 Volumetric measures and scale cognitive outcomes (Table 14)

Hou et al. found that patients with decreased right hippocampal volume had lower scores at follow-up on auditory verbal learning and digital span tests compared to control subjects. Longitudinal hippocampal volume changes differed between the two groups only in terms of right hippocampal volume, but not left nor bilateral. In the depressed group, increase in right and left hippocampal volume over time was positively correlated with performance on symbol digit modalities test (SDMT) and MMSE, respectively (Hou et al., 2011).

Another study in the same cohort classified RGD patients at follow-up as "cognitively declining" or "cognitively stable" based on their performance on the Mattis Dementia Rating Scale-2 (MDRS-2). It showed that hippocampal volume did not differentiate the declining group from the stable one (Ye et al., 2017).

Alternatively, Sawyer et al. found that baseline depression was not predictive of worse performance on MMSE at follow-up in any of the models. In logistic regression, depression was associated with change in right hippocampal volume over time; however, SEM model indicated that change in both right and left hippocampal volumes predicted MMSE changes (Sawyer et al., 2012).

Koehler et al. revealed that differences in either memory, executive function and processing speed z-scores at 18 months between the depression group and the control group were not shown to be moderated by other volumetric measures than white matter

hyperintensities. (Koehler et al., 2014). Similarly, Oudega et al. found no effect of volumetric measures on the score on the Informant Questionnaire on Cognitive Decline in the Elderly (IQ CODE)(2015).

O'Brien et al. applied a neuropsychological test battery consisting of 10 tests at baseline and follow-up, and derived a memory z-score. There was a significant correlation between reduction in both left and right hippocampal volumes and worse memory z-scores in depressed patients at follow-up (O'Brien et al. 2004).

Steffens et al. showed that both right and left hippocampal volume reduction from baseline to 2 years was associated with subsequent decline in MMSE score from 2 to 2.5 years (2011).O'Brien et al. showed that worse follow-up memory performance at follow-up were associated with smaller right hippocampal volumes (O'Brien et al., 2014).

3.3.3 Functional connectivity studies

We identified 6 studies using measures of functional connectivity as predictors of cognitive outcomes in patients with late-life depression, three of which reported categorical cognitive outcomes, and three reported a measure of cognitive decline.

3.3.3.1 Binary cognitive outcomes (See Table 15)

In the study by Lu et al. (design described in 3.1.1), functional connectivity indices for hippocampus and posterior cingulate cortex were individually predictive of AD at follow-up, both with sensitivity of 90%, specificity of 55.2%, and an accuracy of 72.6% (2020).Wang et al. indicated that patients with persistent cognitive impairment (PCI) had significantly decreased activation at baseline in the dorsal anterior cingulate cortex, hippocampus, inferior frontal cortex, and insula compared to non-PCI patients (2012, see table 4 for classification details).

Finally, an early study from Halloran et al. using SPECT imaging as a measure of functional connectivity showed that lower perfusion in anterior cingulate coordinates and left posterior temporal cortex coordinates predicted dementia. However, the results did not survive correction for multiple comparisons (1999).

3.3.3.2 Scale cognitive outcomes (See Table 16)

In this category, all three studies were performed in a Chinese cohort of RGD patients (Jiang et al., 2014; Wang et al., 2017; Ye et al., 2017). Jiang et al. showed that the change between PCC and cerebellum posterior lobe was positively correlated with the change in the AVLT-recall score; longitudinal change in PCC functional connectivity between PCC and right parahippocampal gyrus was positively correlated with the longitudinal change in TMT-A score. Wang et al. showed that longitudinal changes in functional connectivity between the left cornu ammonis and posterior cingulate gyrus/precuneus were positively correlated with longitudinal changes in the SDMT and DS test scores. Ye et al. found that in CLU-CT/TT carriers with remitted geriatric depression, decreased functional connectivity in the right parahippocampal gyrus was associated with greater decline of episodic memory over 35 months.

3.3.4 The role of white matter hyperintensities (WMH)

Among the 9 studies assessing the role of white matter changes, 4 evaluated dementia as outcome, 4 evaluated longitudinal cognitive decline, and 1 used both.

3.3.4.1 Binary cognitive outcomes (See Table 17)

The LADIS (Leukoaraiosis And DISability in the elderly) study found "Moderate to severe" WMC predicted poor cognitive outcomes, and so did depressive symptoms. However, WMC and depressive symptoms predicted cognitive decline *independently* of each other (Verdelho et al. 2017).

In the RUN DMC study, depressive symptoms at baseline increased the risk of all-cause dementia. This was entirely accounted for by late-onset cases. When severity of WML, lacunes and microbleeds was adjusted for, it did not alter the association (Uden et al., 2016).

Steffens et al. found that the severity of WML was significantly yet weakly associated with risk of incident dementia (HR 1.091),. WML no longer significantly increased the risk of dementia with those who developed dementia within 2 years were excluded. Nevertheless, there were no significant differences in the volume of WML between those who developed dementia before or after 2 years. This suggests that in those with a more proximal onset of

dementia, WML are more strongly associated with the incidence of dementia than in those with a more distal onset. (Steffens et al., 2007)

In a cohort of severely depressed patients who underwent ECT, there was no association between WMH and dementia at follow-up (Oudega et al., 2015). Finally, conversion to dementia (all-cause) was predicted by hyperintensities in the pontine raphe and severe paraventricular hyperintensities in an older study (Baldwin et al., 2000).

3.3.4.2 Continuous cognitive outcomes (See table 18)

Koehler et al. (design described above) assessed the effect of WMH on cognitive decline. showing differences in memory and executive function z-scores, but not processing speed. With every one-point increase in white matter hyperintensities severity, the score on memory and executive function declined by 0.21 and 0.18 standard deviations in individuals with depression, respectively. Group difference in memory z-scores were moderated by deep and periventricular white matter hyperintensities,while differences in executive functions were moderated by deep white matter hyperintensities. (Koehler et al., 2014).Oudega et al. (design described above) found no association of WMH with cognitive decline (IQ CODE) after 8 years on average. Sachs-Ericcsson et al. explored whether WML mediated cognitive decline in elderly depressed patients who had attempted suicide compared to depressed patients who had not attempted suicide. They found that right WML predicted cognitive decline (MMSE), independent of suicide attempt status. There was no difference in MMSE either at baseline or at follow-up between groups. Meanwhile, attempt status predicted WML at baseline, with attempters having more left WML than non-attempters. Lifetime number of episodes predicted growth in WML (Sachs-Ericcsson et al., 2014).

A study by Tully et al. included patients whose blood pressure variablility (BPV) was assessed along with the role of WMH severity. In depressed patients, there was a significant three-way interaction between BPV, WMH and time on verbal fluency performance (Isaac's Set Test). Besides, significant interaction between BVP and WMH associated with decline on MMSE (2018).

In a study withRGD patients, cognitive decline was predicted by higher severity of WMH at baseline. Besides, increasesin WHM volume correlated with decreases in MMSE scores (Ye et al., 2017).

3.3.5 APOE genotype (See Tables 19)

While the role of APOE genotype in predicting late-onset AD has been established with consistency, the studies reviewed investigated whether the presence of ε4 allele could serve as a predictor of subsequent development of dementia in late-life depression or depressive symptoms.

Out of 11 included studies, three studies reported that the interaction between depression/depressive symptoms and ε4 carriership predicted conversion to dementia; one reported the same for MCI, and another one, for 1-point decrease in MMSE at follow-up (Kim et al., 2010; Geda et al., 2014; Niti et al., 2014; Burke et al., 2016). In the first study by Kim et al., depressive symptoms at baseline and ε4 carriership were independently associated with dementia onset (OR 2.54 and 2.44, respectively), and the interaction between depressive symptoms (although not depression) and ε4 carriership had a similar effect (OR 2.04).

In the study by Geda et al., ε3/ε4 or ε4/ε4 genotype in the absence of depression was not associated with subsequent MCI, and depression had only a marginal association; however, the interaction was associated with a 5-fold increased risk (HR 5.1). Similarly, in a study by Niti et al., APOE ε4 carriership alone did not predict cognitive decline, nor did depression alone, yet the interaction was associated with an almost 3-fold increase in risk (OR 2.89).

Burke et al. showed that both people with a history of lifetime depression and those who had depression in the 2 years prior to AD diagnosis had higher risk of AD, and adjustment for APOE genotype did not alter this association. Interestingly, while the risk of AD was 3 times higher in ε4/ε4 carriers compared to ε3, ε3 carriers (HR = 3.22, 95%CI 1.91-5.40), the interaction of ε4/ε4 with depression in the past 2 years in an adjusted model resulted in a hazard almost 18 times (HR = 17.71, 95%CI 7.93-39.53) that of the reference group (Burke et al., 2016). Finally, a study by Qui et al. showed that in "amyloid-associated depression" (CES-D score ≥ 16 and a plasma Aβ40/Aβ42 ratio > median (7.1)), conversion to dementia was mediated by having at least one ε4 allele.

Nevertheless, there were a few studies that failed to illustrate an interactive effect of depression and APOE genotype on poor cognitive outcomes. O'Brien et al.(2004), Lenoir et al(2011), and Steffens et al. (2007) found no effect of APOE genotype on conversion to dementia in depressed patients.

However, in the most recent study by Steffens et al., interesting findings were presented considering other genetic factors potentially associated with progression from LLD to dementia. In this study, having a T allele of rs754804 (intergenic region of chromosome 1)

associated with 32-fold increase in risk of conversion to AD. However, this is yet to be established.

3.3.6 Biomarkers of Alzheimer's pathology: tau-protein, Aβ 40 and Aβ42 and their role in the association between depression and AD (See Table 20)

Our search identified 5 relevant articles. Three of them reported the role of plasma measures in conversion to dementia. Two other studies, one using PET imaging, another reporting autopsy findings, used a continuous measure of cognitive outcome.

3.3.6.1 Binary cognitive outcomes

The first plasma amyloid study found the interaction between depressive symptoms and plasma Aβ42 was not a significant predictor, nor was depression alone. Plasma Aβ42 independently predicted AD at 5 years (Blasko et al., 2010). Qui et al. showed that higher Aβ40:Aβ42 ratio in elderly patients with depression is associated with increased risk of AD. However, it is also notable that during a follow-up of 6.2 years, only 9% of amyloid-positive depressed patients developed AD, including ApoE carriers. (Qui et al. 2016). Direk et al. indicated that the likelihood of having clinically relevant depressive symptoms increased proportionally to the increase in Ab1-40 levels. However, these were accounted for by patients whose clinically relevant depressive symptoms preceded dementia onset, indicating that increase in Ab1-40 levels in this sample may have been a marker of prodromal dementia (Direk et al., 2013).

3.3.6.2 Scale cognitive outcomes

Wilson et al. found no significant interaction between depression and any of the neuropathological markers and depression (2016). However, a recent study by Krause-Sorio et al. evaluated [18F]FDDNP PET binding markers of delayed recall and executive function in an RCT assessing the efficacy of adding memantine to antidepressant medication. Greater frontal [18F]FDDNP binding was associated with greater improvement in executive function. No associations between [18F]FDDNP binding and delayed recall performance at follow-up was observed (2021).

3.3.7 The role of blood proteomic/metabolic factors and inflammation (See Table 21)

Our search identified 5 relevant studies addressing the role of inflammatory, proteomic or metabolic factors as links between late-life depression and cognitive decline, of them three focused on inflammatory factors, one on BDNF, and one on metabolic factors.

The longitudinal association between serum BDNF and cognitive decline was also measured In this cohort, BDNF plasma levels were associated with neither depression nor cognitive decline (Nettiksimmons et al., 2014).A study by Samieri et al. evaluated the role of polyunsaturated fatty acids, claiming the strongest predictor of dementia in depressed patients was the plasma ratio of arachidonic acid (AA) to docosahexaenoic acid (DHA) (HR 2.96, p=0.04); and the ratio of plasma n-6/n-3 fatty acids was marginally significant.

3.3.7.1. Inflammation

Gallagher et al. investigated whether inflammation played a role in the association between depression and cognitive decline. Baseline depression (no account of depression history) significantly predicted age-adjusted decline in delayed recall and verbal fluency, which was completely mediated by inflammation and low physical activity. C-reactive protein levels, in turn, were a significant partial mediator of the association between depression and cognitive decline (Gallagher et al., 2015).

In an RCT assessing the efficacy of augmenting escitalopram with memantine (vs placebo), b factor 2 (which had highest loadings for MIP-1β, IL-6, IL-8, and TNF-α) predicted decline in executive function at follow-up In the escitalopram and placebo group. No such associations were observed in the memantine augmentation group (van Dyk et al., 2020).The most recent study found that while plasma IL-6 and CRP were elevated in depressed participants (N=126), they did not mediate the relationship between depression and dementia (Carr et al., 2021).

3.3.8 HPA-axis abnormalities (See Table 22)

We identified three studies which investigated the role of HPA-axis related biomarkers: two measured 3-day salivary cortisol, and one measured serum cortisol.

Both studies mentioned in previous sections, by O'Brien et al. and Koehler et al., showed no effect of salivary cortisol on cognitive function at follow-up (O'Brien et al,

2004; Koehler et al, 2010). However, a study by Zhong et al. did find a significant effect of serum cortisol. (Zhong et al., 2018).

3.4 Discussion

Mechanisms underlying the increased risk of dementia and cognitive decline in people with LLD are complex. Yet it is commonly agreed that there is more than one pathway involved, and that the pathways are not mutually exclusive.

Out of the seven included studies, only two reported a significant role of volumetric measures in conversion from LLD to MCI or dementia (Steffens et al., 2002; Lebedeva et al., 2017). However, more studies (four out of seven) reported a significant role of hippocampal volumes, both left and right, in predicting cognitive decline in LLD patients (Hou et al., 2011; Sawyer et al., 2012; O'Brien et al., 2004; Steffens et al., 2011).

Decline in brain volume, specifically hippocampal volume, appears to be a common feature in both depression and dementia, and has been shown to be responsible for poorer performance on episodic memory tasks. (Videbech&Ravnkide, 2004; Tulwig & Markowitsch, 1998; Burgess et al., 2002). However, there doesn't seem to be enough evidence to indicate that loss of hippocampal volumes can be seen as a specific causal link between depression and cognitive decline, as opposed to a non-specific shared mechanism. Interestingly, the studies that did show a significant role of hippocampal measures in predicting dementia had shorter average follow-up duration (1 and 1.87 years) than those that reported that the effect of depression on AD risk was independent of hippocampal volumes (5 and 5.2 years, Steffens et al., 2002; Lebedeva et el., 2017, Geerlings et al., 2008, von Uden et at., 2016).

One of the common theories supporting the causal role of hippocampal damage in LLD is the glucocorticoid toxicity theory. According to this theory, the downregulation of feedback mechanisms on the hypothalamo-pituitary axis may lead to the oversecretion of cortisol, neurotoxicity, synaptic loss and subsequent shrinkage of the hippocampal area (Tata et al., 2010, Dafsari et al., 2020). Nevertheless, some observations included may challenge this widely accepted theory. In several studies, including a meta-analysis, have shown that the degree of hippocampal atrophy is higher in late-onset depression compared to early-onset depression (Lloyd et al., 2018, Geerlings et al., 2008). In the study which showed higher likelihood of progression to dementia in early-onset compared to late-onset depression, hippocampal volumes were not significant predictive factors (Geerlings et al., 2008). One

possible interpretation is that late-onset depression represents a prodromal state of dementia, while both conditions are characterised by a reduction in hippocampal volume. LLD is a result of different dementia-related mechanism rather than of glucocorticoid neurotoxicity. In this scenario, an alternative causation can be present, with underlying dementia pathology being responsible for biological changes and symptoms including LLD. At the same time, a [18F]flutemetamol PET study showed that hippocampal volume loss in late-life depression was not associated with amyloid binding, regardless of age of onset (De Winter et al., 2017).

Moreover, included studies assessing the role of hippocampal volumes have not been entirely consistent in the laterality of implicated hippocampal regions. Studies exploring the role of hippocampus in dementia or cognitive performance have indeed demonstrated that there may be differential patterns of hippocampal atrophy related to different subtypes of dementia, or different types of memory impairment (Huang et al., 2020; Ezzati et al., 2017). One study demonstrated a predominant role of left hippocampus in connection with Alzheimer's dementia (Vijayakumar & Vijayakumar, 2013), and a meta-analysis implicated left hippocampus and parahippocampal gyrus in predicting AD (Ferreira et al., 2011). However, another prospective study showed similar risks for incident dementia per 1SD of reduction in left and right hippocampal volume over 10-year follow-up (den Heijer et al., 2010).

In contrast, disruptions in functional connectivity appear to be promising biomarkers of cognitive decline and conversion to dementia in LLD patients, especially in hippocampal areas and the PCC (parts of the default mode network (DMN)) and nterior cingulate cortex (dACC, part of the salience network). Several studies have shown that LLD is characterised by distinct changes in FC in DMN and salience networks. As such, there appears to be an increase inFC in the anterior areas of DMN (centered on the mPFC) and decrease in FC in the posterior areas (PCC and hippocampus) associated with LLD, as well as a decrease in the FC between the salience network and the executive control network (ECN). Increase in FC in the anterior DMN is often interpreted as the mobilisation of neuronal resources to compensate for ongoing neuronal loss in other regions (Yuan et al., 2008; Chen et al., 2012; Steffens et al., 2017). In some studies, higher amyloid burden has been correlated with a lower FC in the posterior DMN regions, whereas others have linked Aβ to increased connectivity in DMN regions (Adriaanse et al., 2011; Drzegza et al., 2011; Hedden et al., 2009; Caldwell et al., 2019).

The role of ***white matter hyperintensities*** as a biomarker appears complex as well: while higher degrees of WMH seem to be predictive of cognitive decline (memory, executive function and global cognition), only two studies reported a significant predictive role in dementia, especially non-Alzheimer's dementia. Besides, one study found that in the

population of patients with pre-existing small vessel disease, depression was an independent predictor of all-cause dementia, and another study found that dementia was independently predicted by depression and WMH. In general, white matter lesions are a common characteristic of late-life depression, specifically the subtype of late-onset depression referred as vascular depression, where underlying cerebrovascular changes contribute to the occurrence of depression and/or cognitive impairment (Rushia et al., 2020). It appears that in some patients, white matter hyperintensities represent a shared underlying mechanism which can manifest as either depression or cognitive decline, or depression followed by cognitive decline.

Studies focusing on cortisol mostly failed to indicateits role as a biomarker, with only one of three studies pointing towards increased baseline serum cortisol in those developing "reliable cognitive decline" at follow-up (Zhong et al., 2018). The other two reported no associations between GDS score and elevated cortisol levels, although the latter was linked to worse verbal memory performance, and worse attention/processing speed and global cognition, respectively (Kuningas et al., 2007; Segerstrom et al., 2016). While it has been shown that hypercortisolaemia may affect cognitive function in major depression even at a younger age, researchers are not certain as to whether this represents a state or a trait feature. Either case, continuous exposure to hypercortisolaemia may be a crucial element in the emergence of persistent cortisol-mediated cognitive impairments. Therefore, history, severity and number of episodes of major depression may be a substantial factor. Besides, while hypercortisolaemia has been widely recognised as a feature of major depression, studies have shown that it may frequently correspond to melancholic features of depression (Juruena et al., 2018). Subsequently, a higher emphasis on the homogeneity of depressive phenotypes might be crucial for attaining more consistent insights into the role of HPA-axis in the relationship between late-life depression and cognitive decline/dementia.

Inflammatory markers were significant predictors of cognitive decline in LLD patients in two studies (Gallagher et al., 2016; van Dyk et al., 2020). **BDNF** was not a significant predictor (Nettiksimmons et al., 2014); however, one study reported a significant effect of **arachidonic-to-docosahexaenoic acid ratio** on conversion to dementia (Samieri et al., 2008).Albeit not entirely consistent, findings have been demonstrated by studies looking into proteomic, metabolic and inflammatory markers as mediators between late-life depression and cognitive decline. DADespite the robust associations of inflammation with both depression and dementia, very few studies have investigated their role as a link between the two conditions. The studies included in the review pointed to the potential role of CRP (although not in a population of T2D patients), as well as an inflammatory factor with high loading for

MIP-1β, IL-6, IL-8, and TNF-α, in predicting adverse cognitive outcomes (Gallagher et al., 2016; van Dyk et al., 2020, Carr et al., 2021). A study by Royall et al. introduced a generic measure (δ for "dementia"), a latent variable for dimensional measurement of "disabling (i.e., "dementing") cognitive performance". It showed that an array of protein markers (including heparin-binding EGF-like growth factor (HB-EGF), insulin-like Growth Factor-1 (IGF-I), macrophage inflammatory protein type 1 alpha (MIP-1a), resistin, tissue inhibitor of metalloproteinase type 1 (TIMP-1), and vascular vell adhesion molecule type 1 (VCAM-1) were partial mediators of GDS association with δ (Royall et al., 2017). The largest effect was that of resistin, an adipokyne associated with insulin resistance, inflammation, and regulation of cytokine activity (Filková et al., 2009). Resistin has shown to be correlated with the C-reactive protein (CRP) in several autoimmune diseases. Demirci et al. reported that resistin levels were elevated in patients with AD and were moderately positively correlated with the levels of CRP and IL-18 (Demirci et al., 2017). More research into the role of this biomarker could be justified.

Apart from inflammation, intriguing findings were reported by Samieri et al., who showed that higher AA/DHA ratios and higher n-6 to n-3 fatty acids ratios in depressed subjects were associated with an increased risk of all-cause dementia. This is consistent with the findings of a number of studies that reported that fish oil consumption, or the higher plasma content of long chain n-3 polyunsaturated fatty acids (n-3 PUFAs), as opposed to n-6 PUFAs (mainly arachidonic acid) can be protective against dementia or cognitive decline (Heude et al., 2008; Beydoun et al., 2007; Liu et al., 2022). These long-chain n-3 PUFAs are believed to play a substantial role in maintaining the structure and function of neurone membranes, exert vascular and anti-inflammatory effects and modulate neuroinflammation and the expression of neuronal plasticity-related genes, as well as their potential ability to modulate neuroinflammation and the expression of genes regulating neuroplasticity (Alessandri et al., 2004). Given the accumulating knowledge about the protective effect of n-3 PUFAs on cognitive health, more research on the role of these biomarkers in depression-dementia association is warranted.

Quite surprisingly, only half of studies reported that having an ε4 allele of APOE gene was associated with adverse cognitive outcomes. However, only two studies dealt directly with AD as outcome. One investigated the interaction between depression and APOE status, showing a 3.6-fold increase in the likelihood of AD for those with verified depression carrying an ε4 allele (Burke et al., 2016). When all-cause dementia was considered, also half of the studies reported a significant role of APOE genotype. Assuming APOE ε4 carriers are more

likely to represent cases of prodromal dementia manifesting with depression, proportion of studies reporting its significant role may highlight the possibility other mechanisms are involved in the remaining cases. In general, while more research is needed, it appears that late-life depression occurring in the presence of at least one ε4 allele deserves attention as a potential predictor of subsequent dementia.

Finally, ***amyloid deposition*** is a distinguished feature of AD, and the presence of elevated levels of Aβ in plasma of elderly patients and especially using PET imaging may directly point to incipient AD. However, the role of late-life depression in this relationship is less clear. Not all studies have found higher amyloid accumulation in depressed subjects, some have even reported reduced cortical amyloid burden (Osorio et al., 2014; Mackin et al., 2020, Direk et al., 2014). Among the longitudinal studies selected for the review, ***two autopsy studies failed to show*** an interaction between depression and amyloid plaques or NFT in predicting dementia. However, ***one study using PiB PET*** showed that baseline amyloid distribution interacted with depressive symptoms to predict worse memory score, and another one using plasma measures of $Aß_{40}/Aß_{42}$ ratio showed that only patients with amyloid-associated depression progressed to dementia. However, in the latter study, the rate of conversion (3 in amyloid-associated depression vs 0 in non-amyloid-associated depression) may have been too low to draw generalisable conclusions. In another study, elevated $Aβ_{40,}$ not $Aβ_{42}$ levels were observed in patients with clinically significant depressive symptoms, but this was explained by patients who later progressed to dementia. This indicates that specifically elevated levels of $Aß_{40}$ may represent markers of prodromal dementia in patients with late-life depression.

Limitations and methodological considerations

As summarised in Table 12, studies included in the review differed markedly in sample size, inclusion criteria, measures of depression and cognitive decline, as well as follow-up duration, which makes comparison difficult. Studies incorporating several biomarker measures in one prediction index showed significant effects in predicting cognitive outcomes (Lebedeva et al., 2017; Lu et al, 2020). This possibly suggests that the contribution of individual biomarkers may be relatively small and not detectable by studies with limited sample sizes and conversion rates.

While the present review aimed to exclude participants with pre-existing cognitive impairment, it is not feasible to identify whether the presence of cognitive deficits at baseline(the time of depression diagnosis) is entirely due to depression. Technically,

distinguishing between dementia manifesting with depression (or prodromal dementia), and dementia occurring as consequence of the neurobiological changes evoked by depression, is difficult under research conditions. Longitudinal studies ought to allow for a rather long follow-up to distinguish between these mechanisms, as preclinical stages of dementia may span for over a decade. One possible way of addressing this in the future could be stratifying subjects by time until dementia diagnosis (e.g. within 3, 5, 10 or more years of depressive episode),which requires substantial sample sizes.

Additionally, different phenotypes of depression, particularly age of onset, may be associated with different underlying biological processes and cognitive prognoses. However, only 18 addressed the phenotypical differences in depression in selected studies. There was little consistency in the findings that did take into account either age of onset or number of previous episodes of depression , which implicates that depression is likely to be both a risk factor and a prodrome for conversion to dementia Both subtypes might bear a comparable risk of subsequent progression to dementia, however mechanisms likely differ. Therefore, it might be reasonable for future studies to focus more on either phenotype separately.

3.5 Conclusion

Presented studies indicate the potential role of changes in grey matter volume, particularly hippocampal volume, as a link between late life depression and subsequent dementia, and highlight the risk of subsequent cognitive decline conveyed by accumulating ß-amyloid and/or carriership of at least one ε4 allele in depressed patients. Inflammatory factors and disruptions in functional connectivity emerge as promising markers which require further exploration. Future research might need to better distinguish between the phenotypes of late-life depression, specifically age of onset and number of previous episodes, and types of dementia assessed as an outcome variable.

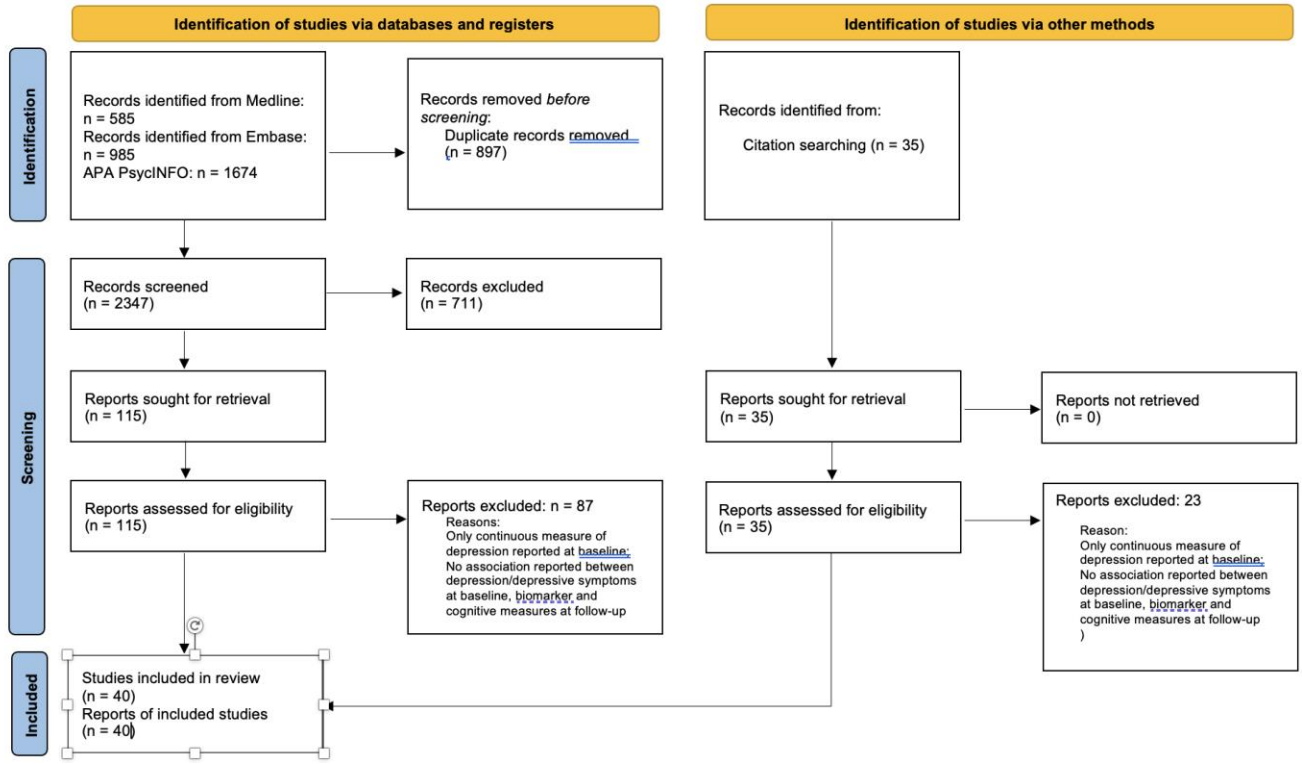


Fig. 15. PRISMA flowchart illustrating the search process and article selection for the systematic review.

Table 13. Volumetric measures; dementia/MCI as outcome

Author, year	Year	N depressed	N converters	Type of biomarker	Depression measure	Cognitive outcome measure	Follow-up duration (years)	Main findings
Steffens et al.	2002	150	15	Baseline sMRI for right and left hippocampal volume	DSM-IV	All-cause dementia	1.87(0.17 – 5.06)	Reduced LHV predicted progression to dementia (HR 2.663; CI: 1.034–6.859; p=0.0424); RHV not significant
Geerlings et al.	2008	134 with history of depression; 35 with baseline depression	44(of them 33 AD)	Baseline sMRI for total (bilateral) hippocampal and amygdalar volumes	Self-report for history of depression; CES-D ≥ 16 for baseline	All-cause dementia; AD	5.9(SD 1.6)	No effect of hippocampal volume at baseline on risk of AD
Lebedeva et al.	2017	61	21	Baseline sMRI for cortical thickness (CTH) and subcortical volumes (SV); regions used in prediction: right ventral diencephalon; middle anterior corpus callosum and right hippocampus	ICD-10	"MCI-DEM": MCI (21); AD(5); unspecified dementia (3)	1	CTH and SV discriminated MCI-DEM from stable cognition (SC) with 76%/55%/86% accuracy/sensitivity/specificity SV alone discriminated between MCI alone and SC with 76%/65%/86%; Most important regions were right ventral diencephalon, middle anterior corpus callosum and right hippocampus.
Verdelho et al.	2017	121	90* (all-cause dementia) 147 (cognitive decline not dementia) *N of converters	Baseline sMRI for medial temporal lobe atrophy: subjective MTA score, grade 0-4	GDS-15>5	All-cause dementia + "cognitive decline not dementia"	3	Depressive symptoms and medial temporal atrophy (3rd grade vs 0) predicted AD, but independently No effect of previous depression on cognitive outcome
Uden et al.	2016	167	41	Baseline sMRI for grey matter (GM) and hippocampal volume (bilateral)	CES-D ≥ 16	All-cause	5.2 (0.7)	Depression (particularly LOD) predicted dementia independently of hippocampal and GM volume
Oudega et al.	2015	39	7	Baseline sMRI for general cortical atrophy (GCA) and medial temporal atrophy (MTA)	DSM-IV severe depression, ***indication for ECT***	All-cause	8 (range 7-12)	No association between GCA and MTA with and dementia at follow-up.
Lu et al., 2020* *biomarkers as part of CARE index, as discussed in the text	2020	39	10	Baseline sMRI grey matter concentration indices (GMI) for a) the hippocampus (HIP) b) the fusiform gyrus (FUS)	DSM-IV	AD	2.25 (1.33 – 3.25)	Hippocampal and FG GMI were not individually predictive of conversion, but they were as part of the CARE index

Table 14. Volumetric measures, cognitive decline as outcome

Author, year	Year	N depressed	Depression measure	Biomarker measure	Cognitive assessment	Follow-up duration (years)	Main findings
Hou et al.	2011	14	DSM-IV Remitted geriatric depression (RGD)	**Repeat** sMRI for hippocampal volume (bilateral/left/right)	MMSE RAVLT-delayed recall Digit Span Test SDMT TMT-A&B	2.58	Significant increase in RHV in RGD patients positively correlated with SDMT scores
Sawyer et al.	2012	238	DSM-IV	**Repeat** sMRI for right and left hippocampal volume	MMSE	4	IN SEM models, both RHV and LHV were associated with worse MMSE independent of depression
O'Brien et al.	2004	49	DSM-IV	**Baseline** sMRI for right and left hippocampal volume	Memory z-scores derived from following tests: VIGIL FAS TMT A&B Digit Span RAVLT RVDLT Cambridge Automated Neuropsychological Test Battery memory tests	0.5	In depressed patients: significant correlation between reduced baseline HV (RHV and LHV) and memory z-scores at follow-up
Koehler et al.	2010	35	DSM-IV	Baseline sMRI for whole brain, frontal lobe and hippocampal volumes	z-scores for memory (RAVLT), executive function (FAS, SCWT and TMT A-B); processing speed (VIGIL)	1.5	Differences in cognitive performance between depressed and non-depressed groups were **not** moderated by overall/frontal/hippocampal brain volumes
Oudega et al.	2015	39	DSM-IV severe depression, ***indication for ECT***	Baseline sMRI for medial temporal lobe atrophy (MTA) and global cortical atrophy (GCA)	IQ CODE	8 (range 7-12)	No significant associations observed
Steffens et al.	2011	90	Duke Depression Evaluation Schedule (DDES)	**Repeat** sMRI at baseline and year 2	MMSE decline from year 2 to year 2.5	2.5	Both right and left hippocampal change from baseline to 2 years was associated with subsequent change in MMSE score from 2 to 2.5 years
Ye et al.	2017	41 (RGD)	DSM-IV, remission at least 6 months	**Repeat** sMRI at baseline and 35 months	"Declining" cognition defined as score below 130 or a 5-point drop on Mattis Dementia Rating Scale-2 (MDRS-2)	2.92	No differences in hippocampal volumes (left or right) between "declining" RGD patients and "stable" RGD patients

Table 15. Functional connectivity studies: categorical outcomes

Author, year	Year	N depressed (with biomarker and follow-up data available)	N converters/ N with outcome	Biomarker measure	Depression measure	Cognition measure	Follow-up duration	Main findings
Lu et al.* *biomarkers as part of CARE index, as discussed in the text	2020	39	10	Baseline fMRI for functional connectivity indices (FCI) of a) the hippocampus (HIP) b) the posterior cingular cortex (PCC) c)the fusiform gurys (FUS)	DSM-IV	AD	2.25 (1.33 – 3.25)	Hippocampal FCI (AUC 0.693) and PCC FCI (AUC 0.745) were significant independent markers of conversion to dementia
Wang et al.	2012	23	7	Baseline fMRI oddball task	DSM-IV	"Persistent cognitive impairment" defined as: 1) adjusted CERAD TS <85 at both Year 0 and Year 2; 2) no improvement in CERAD TS at Year 2 vs Year 0; 3) not active depressive state at Year 2	2	Patients with PCI at the two-year follow-up date had significantly decreased activation at Year 0 in the dorsal anterior cingulate cortex, hippocampus, inferior frontal cortex, and insula compared to non-PCI patients
Halloran et al.	1999	35	2	Baseline SPECT imaging	DSM-III-R	All-cause dementia	2	Lower perfusion in anterior cingulate coordinates and left posterior temporal cortex coordinates predicted dementia (did not survive correction for multiple comparisons)

Table 16. Functional connectivity studies: cognitive decline as outcome

Author, year	Year	N depressed (with biomarker and follow-up data available)	Biomarker measure	Depression measure	Cognition measure	Follow-up duration	Main findings
Ye et al.	2017	33 RGD	Baseline fMRI for functional connectivity (FC) in the DMN; Clusterin rs11136000 variant	DSM-IV	MMSE Executive function Episodic memory Visuospatial function Information processing speed	2.92	Decreased FC in the right parahippocampal gyrus was associated with greater decline of episodic memory scores in the RGD CLU-CT/TT subgroup
Jiang et al.* *RGD patients	2014	14 RGD	Repeat fMRI at baseline and at follow-up	DSM-IV, current HDRS < 7	MMSE, Auditory Verbal Memory Test-recall (AVLT), Digit Span Test (DST), Symbol Digit Modalities Test (SDMT), Trail Making Test-A and B (TMT-A & B)	1.75 (range 1–2.67)	In RGD patients, the change between PCC and cerebellum posterior lobe was positively correlated with the change in the AVLT-recall score; longitudinal change in PCC functional connectivity between PCC and right parahippocampal gyrus was positively correlated with the longitudinal change in TMT-A score
Wang et al.* *RGD patients	2017	14 RGD	Repeat fMRI at baseline and at follow-up	DSM-IV, current HDRS < 7	Auditory verbal memory test-delayed recall (AVLT-DR), Trail-making tests A and B (TMT-A and B) Symbol digit modalities test (SDMT) and the digit span test (DS)	1.75 (range 1–2.67)	In RGD patients, longitudinal changes in functional connectivity between the left cornu ammonis and posterior cingulate gyrus/precuneus were positively correlated with longitudinal changes in the SDMT and DS test scores

Table 17. White matter hyperintensities: dementia/MCI as outcome. RGD = remitted geriatric depression; aMCI = amnestic MCI

Author	Year	N depressed	N converters	Biomarker measure	Depression measure	Dementia measure	Follow-up duration	Main findings
Verdelho et al., 2017*	2017	121	237	Baseline sMRI for WMH severity	GDS-15>5	N=90 with dementia (VD n=54; AD and AD with vascular component n=34; frontotemporal dementia n=2); N = 147 with cognitive impairment no dementia (vascular cognitive impairment, no dementia n=86; MCI n=61).	3 years	Depressive symptoms and WMH severity predicted poor cognitive outcomes, but independently
Steffens et al.	2007	161	20	**Repeat** sMRI for WMHseverity at baseline and year 2	DSM-IV	All-cause	5.39 (2.37)	Two-year change in white matter hyperintensity volume (WMH) predicted dementia, especially among non-Alzheimer (HR 1.09; p=0.036)
Uden et al.	2016	167	41	Baseline sMRI for WMH severity	CES-D ≥ 16	All-cause	5.2 (0.7)	Depression (particularly LOD) predicted dementia independently of the severity of WMH, lacunes and microbleeds
Baldwin et al.	2000	37	6	Baseline sMRI for WMH severity	DSM-III-R	All-cause	3	Significant predictors of the diagnosis of dementia included: hyperintensities in the pontine raphe, and grade 3 paraventricular hyperintensities
Oudega et al.	2015	39	7	Baseline sMRI for WMH severity	DSM-IV severe depression, ***indication for ECT***	All-cause	8 (range 7-12)	No association between WMH and dementia at follow-up

*all participants had MRI-defined small vessel disease, therefore the severity of SVD characteristics was used as a biomarker
** low caseness and only fisher's exact test results are available

Table 18. White matter hyperintensities: cognitive decline as outcome

Author	Year	N depressed	Depression measure	Cognitive assessment	Biomarker measure	Follow-up duration	Main findings
Koehler et al.	2010	35	DSM-IV	z-scores for memory (RAVLT), executive function (FAS, SCWT and TMT A-B), processing speed (VIGIL)	Baseline sMRI for WMH severity	1.5	Differences in memory and executive function, but not processing speed, between depressed and non-depressed groups were moderated by the severity of white matter hyperintensities (ß =73.06, 95% CI 74.84 - 71.27, p=0.001)
Oudega et al.	2015	39	DSM-IV severe depression, ***indication for ECT***	IQ CODE	Baseline sMRI for WMH severity	8 (range 7-12)	No association between baseline WMH and IQ CODE performance at follow-up
Sachs-Ericsson et al.	2014	235 (of those, 20 suicide attempters)	DSM–IV	MMSE	**Repeat** sMRI at baseline, year 2 and year 4	2	Baseline right (not left) WML predicted cognitive decline, independent of suicide attempt status
Tully et al.	2018	346 (symptomatic depression at baseline)	CES-D≥ 16	MMSE Trail Making Test (TMT) Benton Visual Retention Test (BVRT) Finger Tapping Test (FTT) Isaac's Set Test (IST)	Baseline sMRI for WMH severity	10	In depressed patients, significant interaction between blood pressure variability (BPV), WMH severity and time associated with decline on IST (verbal fluency); Significant interaction between BVP and WMH associated with decline on MMSE
Ye et al.	2017	41 (RGD)	DSM-IV, remission at least 6 months	"Declining" cognition defined as score below 130 or a 5-point drop on Mattis Dementia Rating Scale-2 (MDRS-2)	**Repeat** sMRI for WMH severity	2.9	RGD declining group had greater baseline WMH volume than did the RGD stable group; greater increases in WHM volume correlated with greater decreases in MMSE scores

Table 19. APOE genotype and other gene variants

Author, year		N depressed with available follow-up	N converters	Depression measure	APOE measure	Cognitive outcome	Follow-up duration	Main findings
Kim et al.	2010	N = 57 (depression) N = 158 (depressive symptoms)	45	The Geriatric Mental State Schedule (GMS)	Binary (e4 Carriership)	All-cause dementia	2.4 (0.3) years	Interaction between depressive symptoms, not depression, and APOE was a significant predictor of dementia (HR 2.33)
Burke et al.	2016	N= 2,049 (depressed in the last 2 years = recent depression) N= 2,017 (lifetime depression) N = 1,164 (clinician verified)	330	DSM-IV	ε3/ε3; ε3/ε4; ε4/ε4; and "containing ε2"	AD	3.7 (range 0.78 – 8.85)	Significant interactions observed for: Recent depression (last 2 years) X ε4/ ε4 genotype (HR 17.71) Recent depression X "containing ε2" (HR 2.28) Lifetime depression X ε3/ε4 (HR 2.07) Verified depression X ε3/ε4 (HR 3.58) Verified depression X ε4/ε4 (HR = 20.26) *demographics-adjusted models
Geda et al.	2006	143	17	GDS-15 ≥ 6	Binary (e4 Carriership)	MCI	3.5 (range 0.4-12.8)	Significant interaction between depression and ε4 allele (HR 5.1)
Gallagher et al.	2018	2655	586 (22.1%)	DSM	Binary (e4 Carriership)	MCI	3.48 (0.67 – 11.58)	No effect of APOE genotype on risk of conversion to MCI
O'Brien et al.	2004	49	20	DSM-IV	Binary(e4 Carriership)	MCI	0.5	No differences in the proportion of APOE4 alleles
Steffens et al.	2007	161	20	DSM-IV	Binary(e4 Carriership)	All-cause dementia	5.39 (2.37)	No effect of difference in APOE prevalence between converters and non-converters
Steffens et al.	2020	273	31 (AD) 92 (cognitive impairment + AD)	DSM-IV	GWAS	AD; Cognitive impairment (broad definition, incl.delf-reported)	3	• T allele of rs754804 (intergenic region of chromosome 1) associated with 32-fold increase in risk of conversion to AD • C allele of rs17851751 (a nonsynonymous variant in ZMAT4 on chromosome 8) associated with 6.5-fold increase in risk of conversion to AD • A allele of rs79966641 (located in an intron of DMXL1 on chromosome 5) associated with a 6.3 – fold increase in risk of CI

Lenoir et al.	2011	n = 898 (major depression) 1053 (CS depressive symptoms)	276	CES-D ≥ 22 for women, ≥ 16 for men	Binary(e4 Carriership)	All-cause dementia	4	The risk of dementia associated with high level of depressive symptoms higher in non-carriers vs carriers (marginally significant); no other interactions significant
Blasko et al.	2010	62	33	DSM-IV/ sGDS	Binary(e4 Carriership)	AD	2.5	No effect of APOE allele on progression to AD
Qui et al.	2016	68	15	CES-D score ≥ 16	Binary(e4 Carriership)	All-cause dementia	6.2	Relationship between amyloid-associated depression (plasma Aβ40/Aβ42 ratio > median) and progression to dementia mediated by APOE genotype
Niti et al.	2009	134	n/a	GDS-15 ≥ 5	Binary(e4 Carriership)	At least 1-point drop in MMSE	1.46 (0.5)	Significant interaction between depression and e4 carriership

Table 20. Alzheimer's pathology

Author	Year	N depressed (with follow-up information available)	N converters (if applicable)	Depression measure	Biomarker measure	Measure of cognitive outcome	Follow-up duration (years)	Main findings
Blasko et al.	2010	62	33	DSM-IV/ sGDS	Plasma Aß42	AD	2.5	Interaction between GDS score and Aß42 not a significant predictor of conversion to AD
Qui et al.	2016	68	3	CES-D score ≥ 16	Plasma Aß40/Aß42 ratio	All-cause	6.2	Only 3 (9%) of those with "amyloid-associated depression" developed dementia, vs 0 among non-amyloid-associated
Direk et al.	2013	67	13	CES-D score ≥ 16	Plasma Aß40; plasma Aß42	All-cause	11	Elevated Aß40, not Aß42 in depression due to prodromal dementia; After excluding those who converted to dementia, depression was associated with reduced plasma amyloid levels
Wilson et al.	2016	74	Number for converters from depression to dementia not given	CES-D-10 score ≥ 3	**Autopsy**: Amyloid plaques Tangle density Gross infarcts Microinfarcts Lewy bodies Hippocampal sclerosis	z-score derived from 17 cognitive tests	7.8 (4.8)	No interaction between depressive symptoms and any of the neuropathological factors
Krause-Sorio et al.	2021	22 (11 escitalopram+placebo/ 11 escitalopram + memantine)* *one participant per group met MCI criteria	n/a	DSM-5; HAM-D ≥ 16	[18F]FDDNP PET binding in the frontal, parietal, and medial temporal lobes	Delayed recall composite score (California Verbal Learning Test, Verbal Paired Associates test, Rey–Osterrieth Complex Figure Test delayed recall) Executive function composite score (Trail-making Test part B, F.A.S. for verbal fluency)	0.5	In both groups: greater frontal [18F]FDDNP binding was associated with greater improvement in executive function

Table 21. Proteomic/metabolic/inflammatory factors

Author, year	Year	N depressed with follow-up data	Depression measure	Biomarker measure	Cognition measure	Follow-up duration (years)	Main findings
Gallagher et al.	2016	1133	CES-D-8 ≥4	Serum CRP	Delayed word recall Verbal fluency test	4	CRP mediated the relationship between depressive symptoms and both delayed recall and verbal fluency. CRP and low physical activity fully mediated the association between depression and cognition.
Van Dyk et al.	2020	62	DSM-5 diagnosis + HAM-D score ≥ 16	Four cytokine factors	Neuropsychological battery, incl. executive functioning (TMT-B)	0.5	In the escitalopram-only group, Factor 2 (highest loadings for MIP-1β, IL-6, IL-8, and TNF-α) was associated with decline in executive function at follow-up. No such associations observed in the escitalopram+memantine group
Carr et al.* *all patients with T2D	2021	126	HADS-D ≥8	Fibrinogen IL-6 CRP TNF-α	ICD-10 all-cause dementia (N=105)	10.6 (IQR 8.4–11.0)	Elevated IL-6 and CRP in depression, but inflammation did not mediate the relationship between depression and dementia
Nettiksimmons et al.	2014	56	CES-D-20 ≥ 16	Serum BDNF	Modified Mini-Mental State Examination (3MS), Digit Symbol Substitution Test (DSST)	10	Lower BDNF levels in LLD; no effect of BDNF on cognition
Samieri et al.	2008	90	CES-D ≥ 17 in men, CES-D ≥ 23 in women	Plasma n-6/n-3 fatty acids Eicosapentaenoic acid (EPA) Docosahexaenoic acid (DHA) Arachidonic acid (AA) AA/DHA ratio	All-cause dementia (N=65)	4	Marginally significant interaction between depression and n-6/n-3 ratio, and depression and AA/DHA ratio In depressed patients, dementia predicted by AA/DHA ratio (HR=2.96); and marginally by n-6/n-3 ratio (HR = 1.48)

Table 22. HPA-axis abnormalities

Author, year	Sample size	N depressed	Depression measure	Biomarker measure	Cognition measure	Follow-up duration (years)	Main findings
Zhong et al., 2018	148	67	DSM-IV	Serum morning cortisol	"Reliable cognitive impairment" (RCI) on MMSE	1	Higher cortisol in LLD with RCI compared to LLD with no RCI
O'Brien et al., 2004	79	39	DSM-IV	**Repeat** 3-day salivary cortisol (average AUC) at baseline and at 6 months	Memory z-scores derived from following tests: VIGIL FAS TMT A&B Digit Span RAVLT RVDLT Cambridge Automated Neuropsychological Test Battery memory tests	0.5	Baseline cortisol higher in depressed patients vs control, however no effect of cortisol on cognition
Koehler et al., 2010	34	42	DSM-IV	3-day salivary cortisol (average AUC)	z-scores for memory (RAVLT), executive function (FAS, SCWT and TMT A-B); processing speed (VIGIL)	1.5	No significant effect of interactions between depression and cortisol on any cognitive measure

Table 23. Demographic characteristics and depression phenotypes assessed in the 37 studies included in the review (in alphabetical order)

Authors, year	Cohort or recruitment centre	Follow-up duration, years	Sample size (N depressed with available biomarker and outcome data)	Age of participants(for depressed participants)	Gender (% female, for depressed participants)	Depression phenotype
Baldwin et al., 2000	Two old-age psychiatry Manchester services	3	38	Mean 74.5	57.9%	Mean AOn 63.2(55-72); 66% had onset after 65 All 6 dementia patients LOD
Blasko et al., 2010	VITA study	2.5	62	75.8 (0.5)	56.5%	LOD only (at 2.5years of follow-up); LOD did not predict AD at 5 years
Burke et al., 2016	National Alzheimer's Coordinating Center (NACC)	3.7 (range 0.78 – 8.85)	2,049(depressed in the last 2 years = recent depression) 2,017 (lifetime depression) 1,164 (clinician verified)	68.7 (10.8)	74.9%	Depressed in the last 2 years: HR 5.75 Lifetime depression: 3.20
Carr et al., 2021	Edinburgh Type 2 Diabetes Study	10.6 (IQR 8.4–11.0)	126	67.4 (4.2)	60.3 %	n/r
Direk et al., 2013	The Rotterdam Study	11	67	71.6 (6.8)	59.3%	Sensitivity analysis excluded participants with history of depression; effect unchanged
Gallagher et al., 2016	English Longitudinal study of Ageing (ELSA)	4	1133	68.1 (10.8)	66.9%	n/r
Gallagher et al., 2018	National Alzheimer's Coordinating Center (NACC)	3.48 (range 0.67 – 11.58)	2655	70.1 (SD 9.1)	72.9%	n/r
Geda et al., 2014	Mayo Alzheimer Disease Patient Registry for longitudinal studies of cognitive aging	3.5 (range 0.4-12.8)	143	84(65-102)	68.5%	History of depression: 57.3%, Conversion in pts with history of depression: HR 2.6
Geerlings et al., 2008	Rotterdam Scan Study	5.9 (SD 1.6)	134	74.3(8.0)	46.9%	EOD vs LOD: only EOD had a significantly higher risk of AD; No correlations of Aon with biomarkers
Hou et al., 2011	The Affiliated Brain Hospital of Nanjing Medical University	2.58	14	68.21(3.93)	50%	All subjects LOD, worse performance on RAVLT and Digit Span Test at follow-up vs controls
Jiang et al., 2014	The Affiliated Brain Hospital of Nanjing Medical University	1.75 (range 1–2.67)	14	68.21(3.93)	50%	All subjects LOD, worse performance on RAVLT and Digit Span Test at follow-up vs controls
Kim et al., 2010	A prospective community survey of late-life psychiatric Morbidity in Kwangju, South Korea	2.4 (0.3)	57 (depression); 158 (depressive symptoms)	MWA 71.83	54.4%	n/r

Koehler et al., 2010	n/a (recruitment from clinical centres in the UK)	1.5	35	74.1 (6.5)	80%	n/r
Krause-Sorio et al., 2021	The University of California Los Angeles Ahmanson & Lovelace Brain Mapping Center	0.5	22	72.32 (SD 6.92)	36.4%	Median age of onset 63.5 (8-80) in escitalopram+placebo group; effect of age of onset not reported
Lebedeva et al., 2017	PRODE	1	61	MWA = 77.11	MWP = 73.26%	No difference between cognitively stable and MCI-DEM groups in AOn and number of previous episodes
Lenoir et al., 2011	The Three-City (3C) study	4	1053 (clinically significant depressive symptoms)	74.0 (5.4)	61.4%	History of depression: 1672 (21%) No effect of AOn or recurrence on conversion rate
Lu et al., 2020	The Affiliated ZhongDa Hospital, Nanjing, China	2.25 (range 1.33 – 3.25)	39	MWA = 69.38	61.5%	Only remitted LOD patients were included, conversion rate vs controls: HR = 2.143
Nettiksimmons et al., 2014	The Health, Aging and Body Composition (Health ABC) study	10	56	WMA 75.0	55.3%	n/r
Niti et al., 2014	The Singapore Longitudinal Aging Studies cohort	1.46 (SD 0.5)	134	65.4 (7.0)	63.5%	n/r
O'Brien et al., 2004	n/a (recruitment from clinical centres in the UK)	0.5	49	73.9(6.7)	78.6%	LOD- 56% Melancholic depression – 56% Psychotic depression – 20% Associations for subtypes not reported
Oudega et al., 2015	The inpatient clinic for Geriatric Psychiatry of GGZ in Geestand the VU University Medical Center, the Netherlands	8 (range 7-12)	39	73.5 (8.1)	66.7 %	Psychotic depression: 19 (48.7%) Less cognitive decline in patients with psychotic depression (p=0.007)
Qui et al., 2016	The Nutrition, Aging and Memory in the Elderly (NAME) study	6.2	68	WMA 71.75	81.2%	n/r
Sachs-Ericsson et al., 2014	NCODE	2	235 (of those, 20 suicide attempters)	MWA 69.51	77.22%	Weighed mean AOn = 44.94 Weighed mean of number of episodes: 4.6 Lifetime number of depressive episodes predicted growth in left and right WML
Samieri et al., 2008	The Three-City (3C) study	4	90	WMA 70.3	WMP = 38.4%	n/r

Steffens et al., 2002	NESDO	1.87(range 0.17 – 5.06)	150	70.16 (0.68)	70.43%	Age at onset (AOn) reported; converters had higher AOn (43.06(2.00) vs 58.27(6.40))
Steffens et al., 2007	NESDO	5.39 (2.37)	161	69.23 (7.09)	62.11%	n/r
Steffens et al., 2011	NESDO	2.5	90	69.88 (6.799)	61.11%	Proportions of LOD vs EOD not reported; no differences in right or left hippocampal atrophy between LOD and EOD patients
Steffens et al., 2020	NESDO	3	273	WMA 70.71	WMP = 64.80%	
Tully et al., 2018	The Three-City (3C) study	10	346	72 [IQR 69–76]	63.6%	LOD = 105 (30.30%) EOD = 51(14.70%) Significant depressive symptoms at baseline with no depression history = 190 (26.0%) Higher systolic BPV was significantly associated with LOD; no results for cognition reported
Van Dyk et al., 2020	UCLA Neuropsychiatric Hospital inpatient and outpatient service/ community advertising	0.5	62	WMA 71.79	53.3%	Weighed mean age at onset 44.96 years; no associations reported for age at onset
Van Uden et al., 2016*	The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUNDMC study)	5.2 (0.7)	167	65.6 (8.8)	43.1%	Only LOD associated with increased risk of progression to dementia (HR 2.5, 95% CI 1.3– 4.8)
Verdelho et al., 2017	The LADIS study	3	121 with clinically significant depressive symptoms (639 in total)	74.1(5.0)	55%	History of depression (HoD): 176 (27.5) of the whole sample No effect of HoD on cognititve performance or dementia
Wang et al., 2012	The NIMH-sponsored Conte Center for the Neuroscience of Depression in Late-Life at Duke University Medical Center (DUMC)	2	23	WMA 67.99	56.5	n/r

Wang et al., 2017	The Affiliated Brain Hospital of Nanjing Medical University	1.75 (range 1–2.67)	14	67.6 ± 4.0	50%	All patients LOD. At follow-up, the performance in AVLT-DR and DST in LOD patients was significantly worse than in controls
Wilson et al., 2014	The Religious Orders Study; The Rush Memory and Aging Project; The Minority Aging Research Study	7.8 (SD 4.8)	582 with scale measure of CES-D	76.6 (7.5)	73.4%	n/r
Ye et al., 2017	Affiliated ZhongDa Hospital of Southeast University Research Ethics Committee	2.92	33 (remitted geriatric depression)	WMA = 68.08	69.7%	60(9.43) years, 84.8% with onset after 50 Worse performance on MMSE, episodic memory, executive function and visuospatial function in rGD vs controls
Ye et al., 2017 (2)	The Affiliated Brain Hospital of Nanjing Medical University	2.9	41 (RGD)	WMA = 68.4	55.4	Mean age of onset 60 (9.43) years
Zhong et al., 2018	Affiliated ZhongDa Hospital of Southeast University Research Ethics Committee	1	67	67.4 (7.0)	82.7%	LOD: 52.2%; LOD associated with reliable cognitive decline (p=0.027)

Table 24. Risk of bias assessment using the JBI checklist for cohort studies.

Author, year	1	2	3*	4	5	6	7	8**	9	10
Baldwin et al., 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Blasko et al., 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Burke et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Carr et al., 2021	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
Direk et al., 2013	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Gallagher et al., 2016	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gallagher et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Geda et al., 2006	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Geerlings et al., 2008	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hou et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Jiang et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Kim et al., 2010	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Koehler et al., 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Krause-Sorio et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Lebedeva et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lenoir et al., 2011	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
Lu et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Nettiksimmons et al., 2014	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Niti et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
O'Brien et al., 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Oudega et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Qui et al., 2016	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
Sachs-Ericsson et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Samieri et al., 2008	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Steffens et al., 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Steffens et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Steffens et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Steffens et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Tully et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Van Dyk et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Van Uden et al., 2016*	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Verdelho et al., 2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Wang et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Wang et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Wilson et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Ye et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Ye et al., 2017(2)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Zhong et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No

*This item was rated as high-risk if depression was assessed using a scale, as opposed to clinical diagnosis
** This item was rated as high-risk if the outcome was a diagnosis of dementia, and average follow-up duration was less than 3 years

Chapter 4. Cognitive predictors of the progression from late-life depression to dementia: a systematic review and meta-analysis of longitudinal studies.

Abstract

Objective: A systematic review and meta-analysis of studies investigating the cognitive test performance in people with late-life depression (LLD) to establish neurocognitive predictors of progression to dementia.

Methods: MEDLINE, Embase and PsycINFO were searched for relevant studies published by October 2021. Effect sizes for performance on various neuropsychological tests were extracted and pooled separately for all-cause dementia and Alzheimer's disease (AD) outcomes.

Result: Six studies were selected for inclusion. Conversion from LLD to all-cause dementia was predicted by worse performance on delayed recall (SMD 0.84 [0.64 – 1.05]), immediate recall (SMD 1.02 [0.63 – 1.41]), attention/working memory (SMD 1.17[0.82 – 1.52]), processing speed (SMD 1.23 [0.37 – 2.10]), verbal fluency (SMD 0.70 [0.50 – 0.91]), naming (SMD 0.54 [0.16 – 0.93]), construction (SMD 0.67 [0.37 – 0.98]), orientation (SMD 1.13 [0.90 – 1.36]), delayed recognition (SMD 1.30 [0.59 – 2.01]); but not intelligence. For AD, deficits in delayed recall (SMD 1.30 [0.59 – 2.01]), immediate recall (SMD 1.26 [0.74-1.79]), orientation (SMD 1.64 [0.67 – 2.62]), verbal fluency (SMD 0.47 [0.06 – 0.87]) and processing speed (0.66 [0.26 – 1.07]) were significant predictors, but not attention or naming.

Conclusion: There are subtle neurocognitive profile differences within LLD between those who convert to dementia and those who do not. Future studies should aim to establish a neuropsychological profile of LLD associated with risk of conversion to specific subtypes of dementia.

4.1 Background

Dementia currently affects over 55 million people, with nearly 10 million cases yearly, leading to significant impacts on quality of life for people living with dementia and their carers as well as economic impacts on society (World Health Organisation, 2017). In the absence of a cure, prevention has become a critical focus of research (Livingston et al., 2020). In particular, late life depression, defined as an episode of depression occurring at age 60 or over, is recognised as a key potential risk factor for dementia, although the mechanisms underpinning this relationship (true risk factor, reverse causality, prodromal state or psychological reaction) are unclear (Espinoza&Kaufman, 2014, Livingston et al., 2020). There is significant heterogeneity in symptoms of people with LLD, and it is currently unclear who with LLD is most likely to go on to develop dementia. One key factor that might impact this is cognitive performance within this group. The negative effect of major depression on cognitive performance has long been recognised by both clinicians and researchers. It has been described for patients of all age groups (Fiorillo et al., 2018, Allott et al., 2016), however, it appears especially relevant in LLD (Cherbuin et al., 2015). In terms of specific cognitive domains, many studies have highlighted executive (dys)function as the leading type of impairment associated with LLD. A systematic review showed that six out of eight studies reported an association between depression severity and performance on tests assessing executive function (Monteiro et al., 2016). An earlier study showed that it is specifically "processing resources" (working memory and information processing speed) that are decreased in elderly depressed patients, and this decrease may mediate impairments in several areas of neuropsychological functioning, including episodic memory and visuospatial performance (Nebes et al., 2000). A study by Sheline et al. (2006) showed that among five cognitive domains including episodic memory, language, working memory, executive function, and processing speed, the latter was the most important domain impaired in LLD, followed by executive function. Deficits in processing speed were shown to fully mediate the effect of depression on other cognitive domains. Similar findings were presented in a study by Sexton et al., who showed that processing speed and executive function were the core cognitive domains impaired in LLD, explaining differences in episodic memory and language skills (Sexton et al., 2012).

The cognitive domains impacted in LLD have significant overlap with the cognitive domains affected in the early stages of dementia. A meta-analysis combining 47 studies has shown significant deficits in episodic memory in patients with preclinical dementia, but not in "primary memory" (i.e. working memory as measured by the Digit Span–Forward subtest from

the WAIS–R and the primary memory score from the lag method; Bäckman et al., 2005). A later study by Harrington et al. (2013) showed that executive functioning, and in particular Stroop Color and Word Test (SCWT) performance, may be associated with preclinical Alzheimer's pathology and precede memory change in cognitively intact patients. Other memory domains implicated in preclinical dementia include semantic and implicit memory (Spaan et al., 2005).. Finally, processing speed, i.e. the speed at which information coding is performed and tasks are carried out, and attention are also proven to be important domains, the emerging deficits in which may indicate early preclinical signs of dementia (Prado et al., 2019; Mortamais et al., 2017; Silveri et al., 2007).

In general, it appears that executive functioning and processing speed are primarily impaired in LLD, and when studied alongside other cognitive domains, may explain the impairment observed on memory tasks., Since deficits on these domains have also been linked to preclinical stages of dementia, it is possible that impairment in particular cognitive domains can be attributed to prodromal dementia and predict the manifestation of dementia in several years.

We performed, to our knowledge, the first systematic review and meta-analysis of longitudinal studies exploring which cognitive domains affected by depression in older people are more likely to predict progression to all-cause dementia and Alzheimer's Disease.

4.2 Methods

Study search and selection was performed in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines (Page et al., 2020).

The studies were retrieved from Medline, Embase and PsychInfo databases. The search was performed combining the terms describing late life/geriatric depression, cognitive domains, deficits, dementia/Alzheimer's disease, and longitudinal/prospective design. Additional studies were retrieved by screening references of relevant articles. Each step of the search process was performed by both reviewers (MB and RD) independently, where one reviewer (MB) completed the title and abstract search and full text search with a second (RD) independently double rating 10% of each of these steps. Disagreements were resolved in

consensus meetings. The full study selection process is illustrated in the PRISMA flowchart in Fig.16.

4.2.1 Inclusion criteria

Studies were included if they utilised a longitudinal design and were performed in a population of participants aged 60 or above (one study included participants aged 55 and above, mean age was 65.9) with a diagnosis of depression at baseline, reporting cognitive measures, data on incident dementia (clinical diagnosis of AD or all-cause dementia) at follow-up, and a measure of association between performance on a specific cognitive domain and dementia status at follow-up.

Studies were excluded if participants had a diagnosis of dementia at baseline, only reported composite scores of global cognition, or did not have dementia diagnosis as an outcome at follow-up.

4.2.2 Quality assessment (QA)

We performed quality/risk of bias assessment using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies (von Elm et al., 2007). The checklist includes 22 items. Each checklist item was categorized as "yes" (met the criteria), "no" (did not meet the criteria), "partial" (met the criteria partially) or "not applicable." Each item was then rated as "1" for "yes", "0.5" for "partial" and "0" for "no". The total score for each article was divided by number of applicable items and the overall QA rating for each article was produced (See Table 28). The QA was completed independently by two authors (MB and RD) for all articles. Discrepancies were resolved through consensus meetings.

4.2.3 Data extraction and measure of effect size

Two researchers (MB and RD) extracted all the data presented in Table 25. The mean and standard deviation of the cognitive measure measured at baseline was extracted for each group (converters and non-converters). This information was used to calculate the standardised mean difference (SMD) between the two groups.

The tests were grouped into 9 categories in accordance with the cognitive domains and subdomains they assessed (based on classifications presented in Lezak et al., 2012). The categories were: delayed recall (MMSE, AVLT, CERAD delayed recall tasks); immediate recall (MMSE registration, CERAD word list learning); attention/working memory (MMSE

attention, DRS attention, Digit Span); language (verbal fluency and naming tests); intelligence (DRS conceptualization, SISCO intelligence); construction (MMSE construction, DRS construction, CERAD construction); orientation (MMSE orientation, SISCO orientation), delayed recognition (CERAD), processing speed (MST-L1; SDMT). In addition, within each category, sub-analyses were performed if at least two studies reported the results of exactly the same test (i.e. CERAD delayed recall). Table 27 summarizes all tests included in the meta-analysis by categories and subcategories. In the situation where a study reported results from the same or overlapping participant group, the study with the largest N was retained.

4.2.4 Stratification by type of dementia as outcome measure

Most studies included in the present review and meta-analysis used all-cause dementia as outcome measure. However, three studies (Visser et al., Jean et al., and Rushing et al.) reported data specifically on patients diagnosed with Alzheimer's Disease at follow-up. The meta-analysis presents results for all-cause dementia and Alzheimer's disease separately.

Analysis was conducted in the R environment (R Core Team, 2014) using package Metaphor (Viechtbauer, 2010). The meta-analyses were conducted using the random effects model (Hedges & Olkin, 1985). Effect sizes (SMD) and statistical significance ($p < .05$) were considered when assessing a measure's usefulness in predicting conversion from depression to dementia. SMD values of below 0.5, 0.5-0.8 and above 0,8 are considered small, moderate and large, respectively (Faraone et al., 2008). Measures of heterogeneity (I^2 and Q scores) were used to examine the interpretability of the results. I^2 values of 75%, 50% and 25% indicated high, medium and low heterogeneity respectively (Song et al., 2001; The Cochrane Collaboration, 2022).

4.3 Results

4.3.1 Study selection

A total of 948 articles were identified during the initial database search using the Ovid platform. After deduplication, 721 articles remained. Following title and abstract screen, ten articles were selected for full-text screen. Three articles were selected for inclusion by both reviewers; four more articles were identified from the references of selected studies. This

resulted in seven articles meeting inclusion criteria. However, it was not possible to calculate SMD data for one of the studies (Halloran et al., 1999); therefore, the meta-analysis was performed using six studies. The search process is described in detail in Fig.16. The interrater reliability for article selection was 90% (Cohen's k: 0.78).

4.3.2 Characteristics of the studies

All studies but one employed a prospective cohort design and used clinical diagnostic criteria (ICD or DSM) to ascertain depression at baseline. A study by Heser et al., however, was a retrospective cohort study, and the presence of clinically significant depressive symptoms at baseline was defined as a score of six or more on the GDS-15 scale. Average follow-up periods ranged from 1.25 to 7.5 years; the mean age of study samples ranged from 65.9 to 81 years, and all the study populations comprised a greater proportion of females (range 52.8%–78.0%). The full summary of participants' clinical and sociodemographic characteristics is presented in Table 25.

4.3.3 Meta-analysis

The results of meta-analyses are summarised in Table 26 for all-cause dementia and AD.

4.3.4 All-cause dementia as outcome

The results of the meta-analysis of neurocognitive predictors of conversion from late-life depression to all-cause dementia are presented in Figure 17.

4.3.4.1 Delayed recall

Five studies (Visser et al., Jean et al., von Gunten et al., Potter et al., Heser et al.) reported a measure of delayed recall. When the results from these studies were combined there was a significant difference at baseline between later converters and non-converters to dementia (SMD 1.04, 95%CI 0.68-1.40, $p<0.001$; Fig.19).

In a subgroup analysis of CERAD delayed recall scores (Potter et al., Heser et al.), worse performance was also found to discriminate between converters and non-converters (SMD 1.23, 95%CI 0.43 – 2.03, $p<0.01$; Fig.20).

4.3.4.2 Immediate recall

Four studies (Jean et al., von Gunten et al., Potter et al., Heser et al.) reported a measure of immediate recall. The meta-analysis showed that poorer performance on immediate recall

tests was significantly associated with conversion to dementia (SMD 1.02, 95%CI 0.63 – 1.41, p<0.001; Fig.21). In a subgroup analysis of CERAD word list learning (Potter et al., Heser et al), immediate recall also demonstrated a strong and significant effect (SMD 1.18, 95%CI 0.69 – 1.68, p<0.001; Fig.22).

4.3.4.3 Attention/Working memory (Digit Span)

The meta-analysis of the measures of attention comprised of the DRS Attention subscale score reported Jean et al.(all-cause dementia) and Digit Span combined score reported by Potter et al. Poorer performance on attention tasks was associated with progression to all-cause dementia (SMD 1.17; 95%CI 0.82 – 1.52, p<0.001; Fig.23).

4.3.4.4 Processing speed

The meta-analysis comprised of the scores on MST-L1 and SDMT tests, reported by Visser et al. and Potter et al., respectively. Poorer performance on processing speed tasks was associated with progression to all-cause dementia (SMD 1.23, 95% 0.37 – 2.10, p<0.01; Fig.24)

4.3.4.5 Language

Measures of language abilities were categorised unto verbal fluency and naming tests.

The meta-analysis of verbal fluency included four studies (Visser et al., von Gunten et al., Potter et al., Heser et al.); the meta-analysis of naming ability included three studies (Jean et al., von Gunten et al., Potter et al.). Both measures were significantly associated with conversion to dementia (SMD 0.70, 95%CI 0.50 – 0.91, p<0.001; SMD 1.01, 95%CI 0.64-1.37, p<0.001, respectively; Fig.25-26).

4.3.4.6 Intelligence

The meta-analysis of intelligence scores included three studies (Jean et al., von Gunten et al., Heser et al). Poorer intelligence performance was not associated with conversion to dementia (SMD 0.42, 95%CI -0.27 – 1.10; Fig.27).

4.3.4.7 Construction

The meta-analysis of construction scores included three studies (Jean et al., von Gunten et al., Potter et al.). Poorer construction performance was moderately associated with conversion to dementia (SMD 0.67, 95%CI 0.37 – 0.98, p<0.001; Fig.28).

4.3.4.8 Orientation

The meta-analysis of orientation scores included three studies (Jean et al., Rushing et al., Heser et al.). Poorer orientation performance was strongly associated with conversion to dementia (SMD 1.13; 95%CI 0.90 – 1.36, p<0.001; Fig.29).

4.3.4.9 Delayed recognition

Finally, two studies reported the scored on CERAD delayed recognition (Heser et al., Potter et al.). The pooled estimate produced a strong effect size for all-cause dementia (SMD 1.30, 95%CI 0.59 – 2.01, p<0.001; Fig.30).

4.3.5 AD dementia as outcome

The results of the meta-analysis of neurocognitive predictors of conversion from LLD to Alzheimer's disease specifically are presented in Figure 18.

4.3.5.1 Delayed recall

Three studies (Visser et al., Jean et al., Rushing et al) reported measures of delayed recall. The pooled estimate demonstrated that worse performance on delayed recall was strongly associated with conversion to dementia (SMD 1.05, 95%CI 0.67 – 1.42, p<0.001; Fig.31).

4.3.5.2 Immediate recall

Two studies (Jean et al., Rushing et al.) reported measures of immediate recall. The pooled estimate demonstrated that worse performance on immediate recall was strongly associated with conversion to dementia (SMD 1.26, 95%CI 0.74 – 1.79, p<0.001; Fig.32).

4.3.5.3 Attention

Two studies (Jean et al., Rushing et al.) reported measures of attention (MMSE). The pooled estimate showed no effect of attention deficits on likelihood of conversion to AD (SMD 1.12, 95%CI -0.39 – 2.62). However, when DRS attention scores were taken into account instead of MMSE attention scores (Jean et al.), the effect size became marginally significant (SMD 0.66, 95% CI -0.002 – 1.32, p=0.051; Fig.33a-b).

4.3.5.4 Processing speed

The meta-analysis comprised of the scores on MST-L1 and SDMT tests, reported by Visser et al. and Rushing et al., respectively. Poorer performance on processing speed tests was significantly associated with conversion to AD (SMD 0.66, 95%CI 0.26 – 1.07, p<0.01; Fig.34)

4.3.5.5 Language (Verbal Fluency and Naming)

Two studies (Visser et al., Rushing et al.) reported a measure of verbal fluency. Poorer performance was associated with conversion to AD, although less strongly than in all-cause dementia (SMD 0.47, 95%CI 0.06-0.87, p<0.05; Fig.33).

Poorer performance on naming tasks (reported by Jean et al. and Rushing et al.) were not significantly associated with conversion to AD (SMD 0.55, -0.13 – 1.23; Fig.35).

4.3.5.6 Orientation

Two studies (Jean et al., Rushing et al) reported a measure of orientation (MMSE). Poorer performance on orientation tasks was associated with conversion to AD with a strong effect size (SMD 1.64, 95%CI 0.67 – 2.62, p<0.001; Fig.36).

4.4 Discussion

This is the first review to our knowledge to examine whether performance in particular cognitive domains in the context of LLD predicts future all cause dementia and alzheimer's disease . We found that in individuals with late-life depression, cognitive tests of delayed recall, immediate recall, verbal fluency, processing speed, and orientation were strong predictors of later all-cause demetnia and AD. Tests of attention and naming were only significant predictors of all-cause dementia, not AD. The average effect sizes for verbal fluency and processing speed seem lower in respect to AD than all-cause dementia and the effect size for orientation was, conversely, higher for AD (although this conclusion should be treated with caution due to overlapping confidence intervals). Data on intelligence, construction and delayed recognition was only available for all-cause dementia; the latter two proved significant predictors of conversion, but not intelligence. However, some of the results should be interpreted with caution due to high heterogeneity shown by the I2 and Q scores (see Table 26).

The domain of episodic memory was represented in the present meta-analysis by delayed recall and delayed recognition tests. Memory impairments in late-life depression are likely related to hippocampal volume (Steffens et al., 2011; Burgess et al., 2002). Hippocampal

shrinkage resulting from the glucocorticoid cascade associated with HPA-axis abnormalities in major depression is currently viewed as one of the main possible mechanisms linking depression and dementia (Dafsari et al., 2020). Overall, both the results of the meta-analysis and the individual findings of at least four studies included in the review revealed that deficits in episodic memory can predict conversion to dementia in patients with LLD, and this is relevant both for all-cause dementia and AD specifically. Thus, the detection of episodic memory deficits in LLD patients appears important for the early identification of dementia.

The general domain of executive function was represented by tests of immediate recall (working memory), attention, processing speed, and language (verbal fluency and naming). Deficits in these domains (apart from immediate recall) appeared more prominent in prodromal all-cause dementia than in prodromal AD. One potential explanation for this is that executive deficits observed in LLD have underlying vascular abnormalities; and that LLD patients exhibiting deficits in attention, working memory, processing speed, and semantic fluency are at higher risk of developing non-Alzheimer's dementia (primarily vascular dementia). In support of this, previous studies have proven vascular risk scores (e.g Framingham risk score) to be associated with deficits in processing speed and executive function; and higher white matter hyperintensities (WMH) burden to be associated with executive dysfunction, perseveration, and slowed processing speed (Sheline et al., 2010; Jokinen et al., 2005). Future studies might need to address potential interactions between WMH intensity and performance on executive function tests as markers of progression to non-Alzheimer's dementia in older depressed patients.

Strengths and limitations

To our knowledge, this is the first meta-analysis to address the neurocognitive profile of late-life depression predicting conversion to dementia, and AD in particular. However, and partially since this is a relatively unestablished field, the study does have limitations.

First, while we have identified differences in the performance on neurocognitive tests between LLD converters and non-converters to all-cause and AD dementia, there was no opportunity to focus on non-AD (e.g. vascular) dementia specifically, as only one study reported results separately for non-AD dementia (Jean et al., 2004). Therefore, there is likely to be significant overlap in results for "all-cause" dementia and AD as all cause dementia outcomes will include many AD cases as well as other dementia subtypes. Future research should aim at better classification of dementia at outcome such that it would be possible to

establish with more clarity which neurocognitive deficits in LLD are associated with each specific subtype of dementia.

While in the majority of groupings for neurocognitive tests were relatively clear-cut, the selection of tests that constituted certain subdomains of executive functioning may appear more controversial. In particular, we chose to group DRS attention (Jean et al., 2004) with Digit Span total score (Potter et al., 2013), since DRS attention test is described as comprising Digit Span forward. However, only total Digit Span scores from Potter et al. were available for all-cause dementia attention/working memory grouping, and the relevance of backwards digit span for assessment of attention is questioned. Therefore, this combination may present a source of bias.

Besides, the problem the present meta-analysis investigates has only been addressed by a few studies, which limits our capacity to make solid inferences. Specifically, as mentioned above, there is serious debate as to whether depression in late life constitutes a prodromal state of dementia or a risk factor, with both mechanisms likely to be present in different cases. Given a larger number of studies, it could be possible to address this issue at by stratifying cases by duration of follow-up; however, this was not feasible in the current work. Although prospective design is preferable for establishing risk relationship, it can be associated with a small number of patients progressing to dementia, therefore some of the studies may have been underpowered in finding important associations. (although a number of strong associations were found, mitigating againgsthis) Finally, only one study considered the role of history of depression (although separately from baseline depression). This would be an important point to address in future research, since there is evidence to suggest that first-episode late-onset depression may differ substantially in cognitive profile and neurobiological underpinnings from early-onset depression with a recurrent episode in late life (Riddle et al., 2017).

Study		Study design	Population	Depression criteria	Dementia type	Gender (Female)	Age (mean, SD)	Follow-up duration	Cognitive tests at baseline (included in meta-analysis)	N depressed with dementia at FU	N depressed without dementia at FU	Baseline values of neurocognitive test (SD; dementia)	Baseline values of neurocognitive test (no dementia)	SMD (var; 95%CI)
Visser et al., 2000	2000	Prospective	Mild/moderate depression	DSM-IV; severity: HDRS	AD	52.8%	65.9*	5 years	Delayed recall (AVLT)	15	38	-1.78(1.3)	-0.60 (1.25)*	0.93 (0.10; 0.31-1.55)
									Processing speed (MST-L1)			-1.57(1.4)	-0.63(1.17)*	0.76 (0.098; 0.15-1.38)
									Verbal Fluency			-1.04(0.7)	-0.49 (0.95)*	0.62(0.097; 0.0099-1.23)
Jean et al., 2004	2004	Retrospective (historical cohort)	MDD	DSM-IV	All-cause/AD	66%	75.1*	7.5 years (3.4-12.7years)	Delayed recall (MMSE recall) – all-cause dementia	14	30	1.57 (1.09)*	2.30 (0.88)	0.77 (0.112; 0.11-1.42)
									Delayed recall (MMSE recall) – AD			1.14 (0.90)	2.30 (0.88)	1.31(0.20; 0.44 – 2.19)
									Immediate recall (MMSE registration) – all-cause dementia			2.93 (0.27)*	3.00 (0.00)	0.47 (0.11; -0.18 – 1.11)
									Immediate recall (MMSE registration) – AD			2.86 (0.38)	3.00 (0.00)	0.89 (0.19; 0.04 – 1.74)
									Attention (MMSE) – all-cause dementia			2.65 (1.39)*	4.73(0.52)	1.85 (0.14; 1.11-2.60)
									Attention (MMSE) - AD			3.00 (1.83)	4.8 (0.7)	0.40 (0.077; -0.15; 0.94)
									Attention (DRS) – all-cause dementia			33.5 (2.14)*	35.47 (1.43)	1.17 (0.12; 0.49-1.85)
									Attention (DRS) – AD			33.86 (1.68)	35.47 (1.43)	1.22 (0.044; 0.81 – 1.63)
									Language(naming) – all-cause dementia			6.93 (0.83)*	7.57 (0.68)	0.88 (0.11; 0.22-1.54)
									Language(naming) – all-cause dementia			6.86 (0.90)	7.57 (0.68)	0.98 (0.19; 0.13-1.84)
									Intelligence (DRS)			31.93 (5.20)*	36.40 (3.26)	1.13 (0.12; 0.45-1.81)
									Construction (MMSE)			0.58 (0.51)*	0.87 (0.35)	0.72(0.11; 0.071-1.37)
									Orientation (MMSE) – all-cause dementia			8.86 (1.03)*	9.83 (0.38)	1.49(0.13; 0.78-2.19)
									Orientation (MMSE) - AD			8.43 (1.27)	9.83 (0.38)	2.22 (0.24; 1.26-3.19)
Von Gunten et al., 2005	2005	Prospective	Mild/Moderate depression + SMD	ICD-10	All-cause	78%	72.3*	1.25y (0.5-2.2y)	Delayed recall (prose free recall)	9	32	5.44 (3.54)	9.47(4.83)	0.88 (0.15; 0.11-1.64)
									Immediate recall (prose free recall)			6.22 (2.59)	10.34(4.16)	1.059 (0.16; 0.28 – 1.83)
									Language (Naming)			9.67 (1.12)	10.32(1.05)	0.61 (0.15; 0.28 – 1.83)
									Language (Verbal fluency)**			10.56 (2.28)	12.60(3.63)	0.60 (0.15; -0.15 – 1.35)
									Intelligence			5.33 (0.71)	5.55 (0.81)	0.28 (0.14; -0.46; 1.02)
									Construction			2.11 (0.93)	2.55 (0.62)	0.63 (0.15; -0.12; 1.38)
Rushing et al., 2014	2014	Prospective	MDD	DSM-IV	AD	64.2%	68.2(6.7)	7.1y(SD 2.7y)	Delayed recall (MMSE)	15	105	4.5 (3.0)	6.3 (2.1)	0.81(0.079; 0.26-1.36)
									Delayed recall (CERAD)			2.0(1.1)	2.7(0.6)	1.03(0.081; 0.47-1.59)
									Immediate recall (CERAD)			14.30 (3.61)	20.21 (4.11)	1.47 (0.046; 1.045 – 1.89)
									Attention (MMSE)			4.5 (1.1)	4.8 (0.7)	0.40 (0.077; -0.15; 0.94)
									Processing speed (SDMT)			30.0 (14.5)	36.7 (10.9)	0.59 (0.078; 0.042 – 1.13)
									Language (CERAD category fluency)			14.3 (7.1)	16.1 (4.9)	0.35 (0.077; -0.20 – 0.89)
									Language (Naming)			13.5 (1.2)	13.9 (1.5)	0.27 (0.077; -0.27; 0.81)

									Orientation			8.4 (1.8)	9.5 (0.7)	1.22 (0.082; 0.66 – 1.78)
Potter et al., 2014	2014	Prospective	MDD	DSM-IV	All-cause	62.9%	72.19	6.33 (SD = 3.07)	Delayed recall (CERAD)	30	149	3.93 (2.41)	7.02 (1.74)	1.66 (0.048; 1.23-2.084)
									Immediate recall (CERAD)			14.30 (3.61)	20.21 (4.11)	1.47 (0.046; 1.045 – 1.89)
									Construction (CERAD)			9.20 (1.47)	9.94 (1.02)	0.67 (0.041; 0.27 – 1.067)
									Delayed Recognition (CERAD)			7.67 (2.15)	9.59 (0.81)	1.68 (0.048; 1.35 – 2.11)
									Verbal fluency (COWAT)			26.01 (10.67)	37.19 (12.42)	0.92 (0.04; 0.52 – 1.32)
									Naming (CERAD)			12.97 (2.66)	14.58 (0.83)	1.22 (0.04; 0.81 – 1.63)
									Digit Span (Forward and Backward)			11.89 (3.14)	16.39 (3.97)	1.17 (0.044; 0.76-1.58)
									SDMT			23.58 (13.24)	40.61 (9.69)	1.65 (0.48; 1.22 – 2.072)
Heser et al., 2016	2016	Prospective	Elevated depressive symptoms	GDS score ≥6	All-cause	65%	81.0	6 years	Delayed recall (CERAD)	69	242	3.15 (0.26)	5.18 (0.14)	0.94 (0.020; 0.66 – 1.21)
									Immediate recall (CERAD)			14.12 (0.47)	18.24 (0.25)	1.062 (0.020; 0.78-1.34)
									Verbal fluency			15.05 (0.65)	18.41 (0.34)	0.63 (0.019; 0.36 – 0.91)
									Intelligence (SISCO)			4.56 (0.08)	4.55 (0.04)	-0.016 (0.019; -0.28 – 0.25)
									Orientation (SISCO)			9.29 (0.06)	9.70 (0.03)	0.87 (0.020; 0.59 – 1.14)
									Recognition (CERAD)			7.17 (0.18)	8.81 (0.10)	1.067(0.020; 0.79 – 1.35)

Table 25. Summary characteristics of the studies included in the meta-analysis. FU = follow-up; SMD = standardized mean difference.

*average of two groups (mild and moderate depression for Visser et al.; AD and VaD for Jean et al.) calculated

** average scores of colour and animal verbal fluency calculated

Table 26. The results of meta-analysis and heterogeneity tests for all-cause dementia and Alzheimer's disease.

	K-studies	N participants (Dementia/No dementia)	SMD (95% CI)	I^2	Q (df)	References
			All-cause			
Delayed recall (overall)	5	137/491	0.84 (0.64 – 1.05)***	0%	0.15 (4)	Visser et al. Jean et al. Von Gunten et al. Potter et al. Heser et al.
Delayed recall (CERAD)	2	99/391	1.23 (0.43 – 2.03)**	89.98%	9.97 (1)	Potter et al. Heser et al.
Immediate recall (overall)	4	122/453	1.02 (0.63 – 1.41)***	61.87%	7.36(3)	Jean et al. Von Gunten et al. Potter et al. Heser et al.
Immediate recall (CERAD)	2	99/391	1.18 (0.69 – 1.68)***	75.06%	4.01 (1)	Potter et al. Heser et al.
Attention (DRS/Digit Span)	2	44/199	1.17 (0.82 – 1.52)***	0%	0 (1)	Jean et al. Potter et al.
Processing speed	2	45/187	1.23 (0.37 – 2.10)**	81.30%	5.35 (1)	Visser et al. Potter et al.
Language (Verbal Fluency)	4	108/417	0.70 (0.50 – 0.91)***	0%	1.5(3)	Visser et al. Von Gunten et al., Potter et al. Heser et al.
Language (Naming)	3	53/211	0.54 (0.16 – 0.93)**	10.32%	1.97(2)	Jean et al. Von Gunten et al. Potter et al.
Intelligence	3	92/304	0.42 (-0.27 – 1.10)	53.39%	4.28(2)	Jean et al. Von Gunten et al.

						Heser et al.
Construction	3	53/211	0.67 (0.37 – 0.98)***	0%	0.03(2)	Jean et al. Von Gunten et al. Potter et al.
Orientation	3	98/377	1.13 (0.90 – 1.36)***	0%	1.37(2)	Jean et al. Rushing et al. Heser et al.
CERAD Delayed Recognition	2	99/391	1.30 (0.59 – 2.01)***	87.23%	7.83(1)	Heser et al. Potter et al.
			AD			
Delayed recall	3	37/173	1.05 (0.67 – 1.42)***	0%	0.48(2)	Visser et al. Jean et al. Rushing et al.
Immediate recall	2	22/135	1.26 (0.74-1.79)	15.75%	1.19(1)	Jean et al. Rushing et al.
Attention (Jean et al. DRS)	2	22/135	0.66 (-0.002; 1.32)	44.35%	1.80(1)	Jean et al. Rushing et al.
Attention (Jean et al. MMSE)	2	22/135	1.12 (-0.39; 2.62)	87.21%	7.81(1)	Jean et al. Rushing et al.
Processing speed	2	30/143	0.66 (0.26 – 1.07)**	0%	0.17(1)	Visser et al. Rushing et al.
Language (verbal fluency)	2	30/143	0.47 (0.06 – 0.87)*	0%	0.43 (1)	Visser et al. Rushing et al.
Language (naming)	2	22/135	0.55 (-0.13 – 1.23)	47.31%	1.90 (1)	Jean et al. Rushing et al.
Orientation	2	22/135	1.64 (0.67 – 2.62)**	67.89%	3.11(1)	Jean et al. Rushing et al.

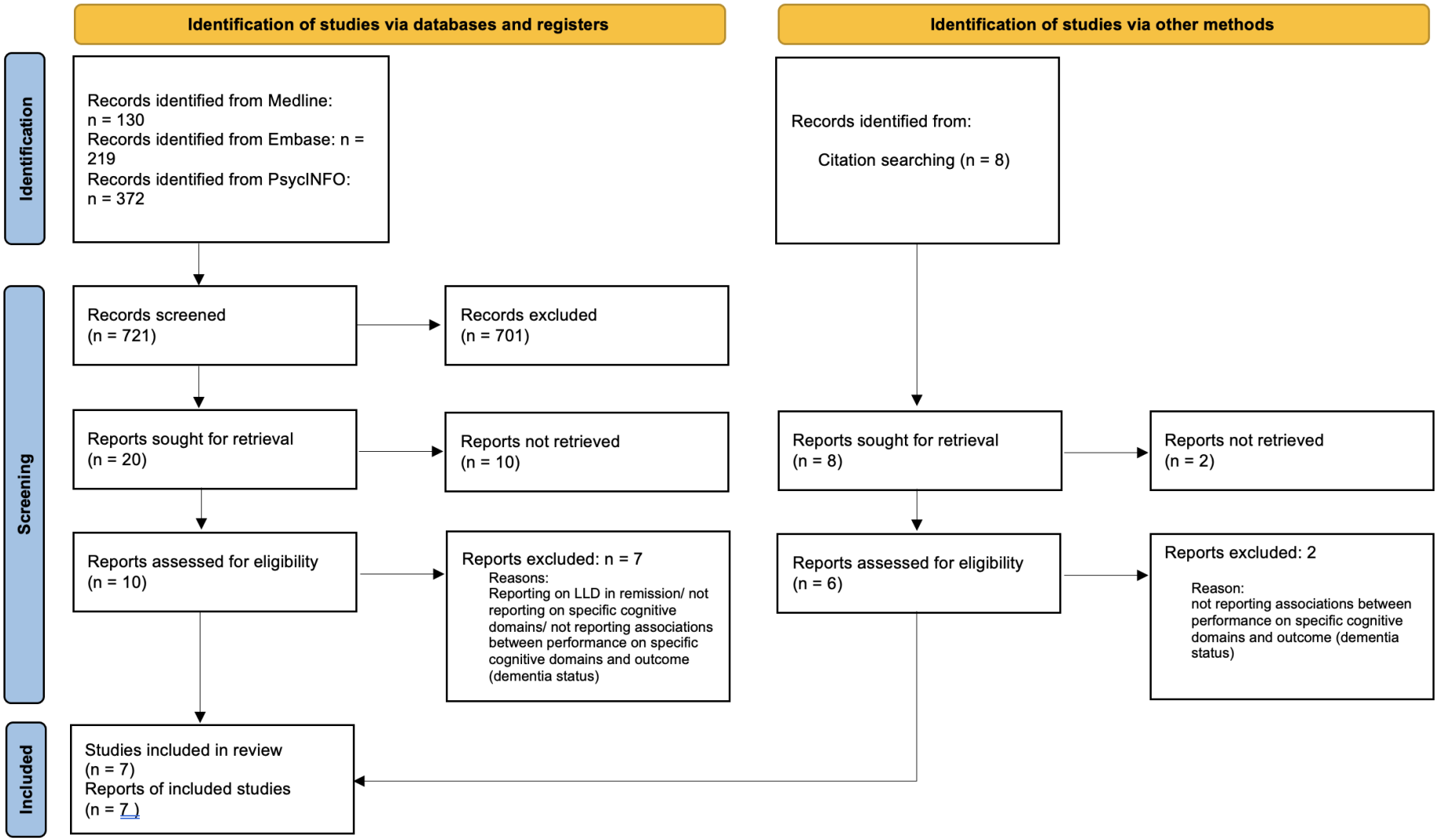


Fig 16. PRISMA flowchart illustrating the article search and screening process for the systematic review and meta-analysis

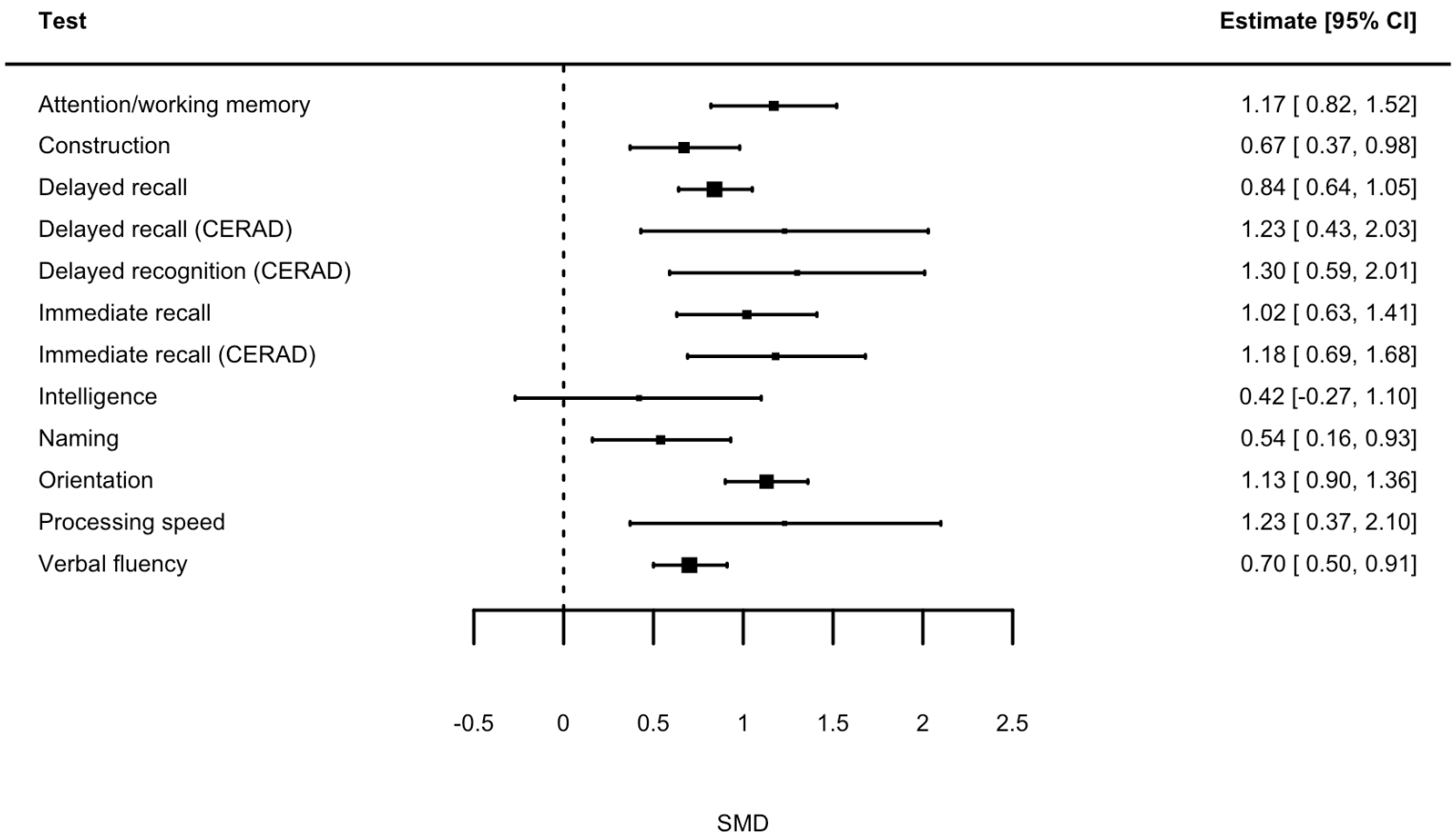


Fig.17 Forest plot showing effect sizes for mean differences in performance on neurocognitive tests at baseline between non-converters and converters to all-cause dementia. LLD patients who did not convert to dementia at follow-up performed significantly better on all tests apart from intelligence.

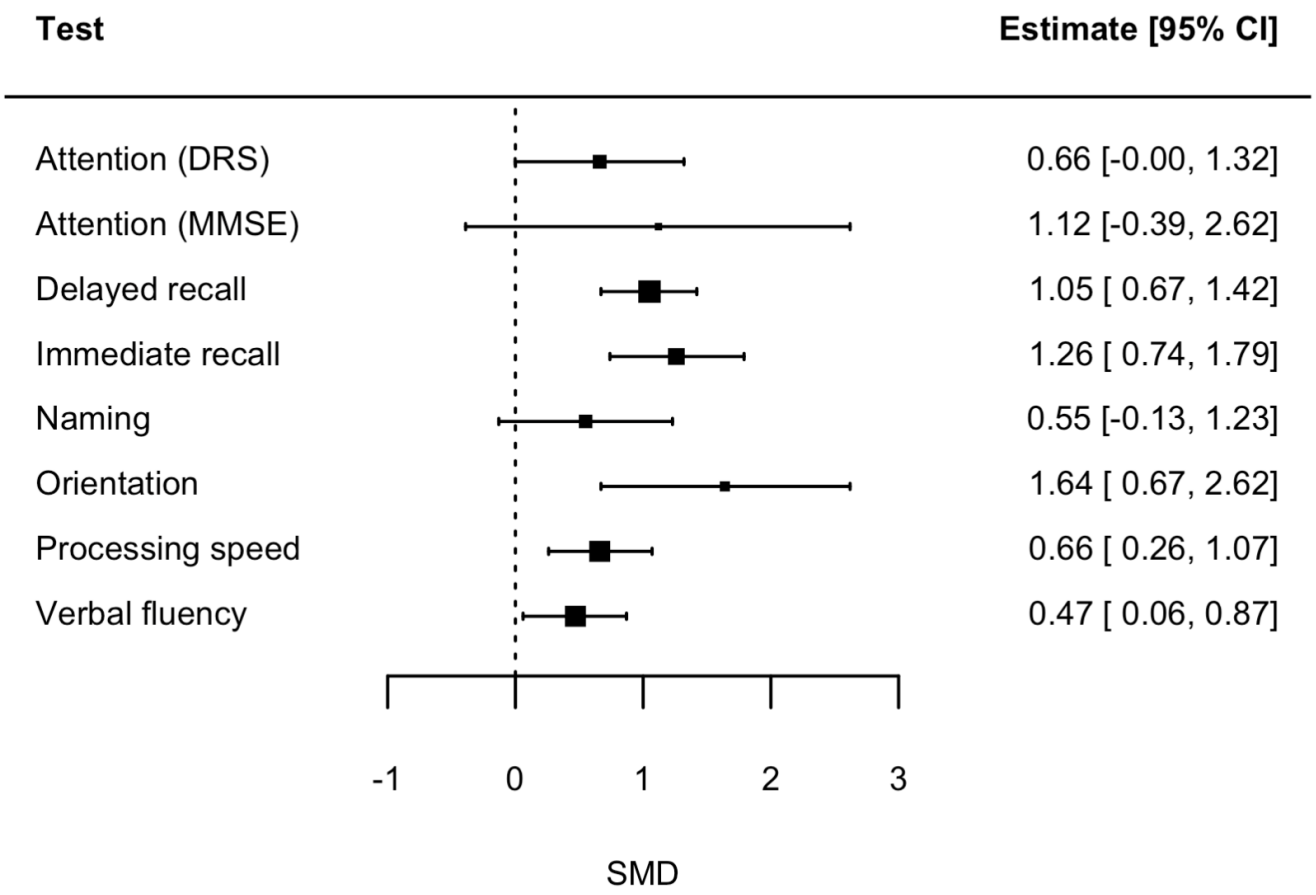


Fig.18 Forest plot showing effect sizes for mean differences in performance on neurocognitive tests at baseline between non-converters and converters to Alzheimer's disease. LLD patients who did not convert to dementia at follow-up performed significantly better on tests of delayed recall, immediate recall, orientation, processing speed, and verbal fluency.

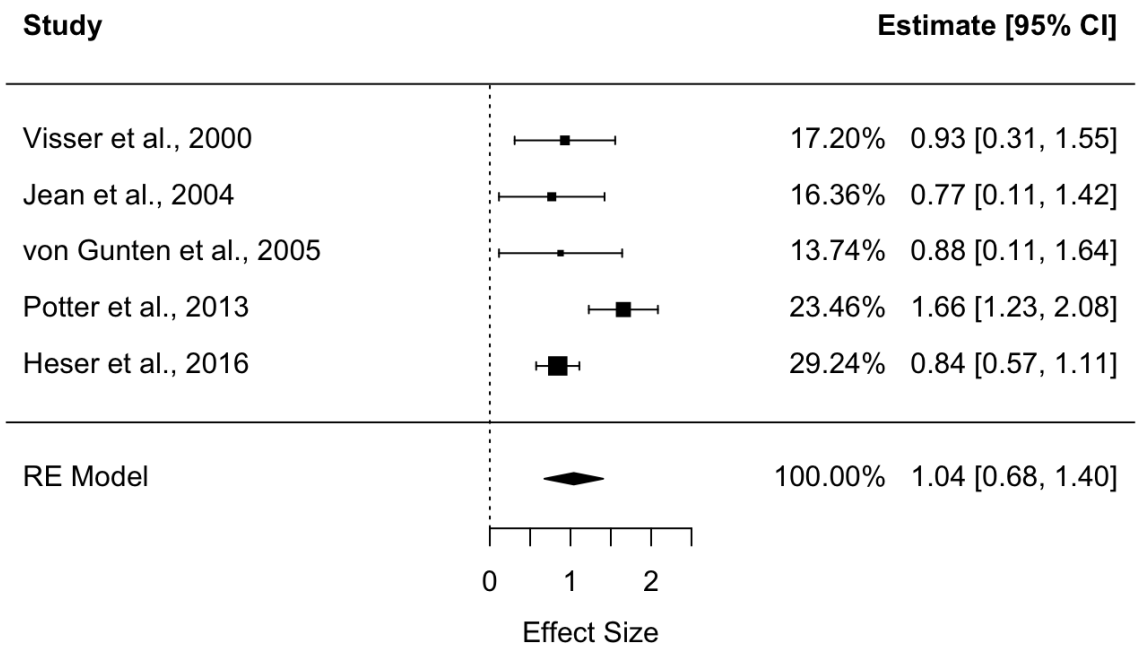


Fig 19. Forest plot showing effect sizes and pooled effect size for mean differences in performance in delayed recall (all tests) between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

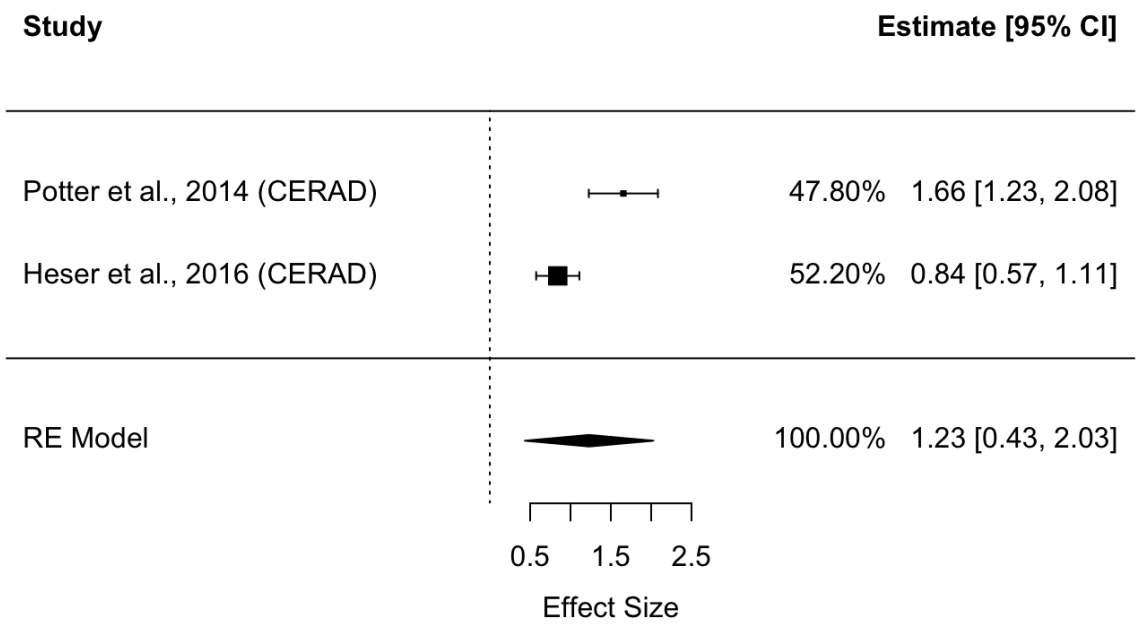


Fig 20. Forest plot showing effect sizes and pooled effect size for mean differences in performance in delayed recall (CERAD) tests between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

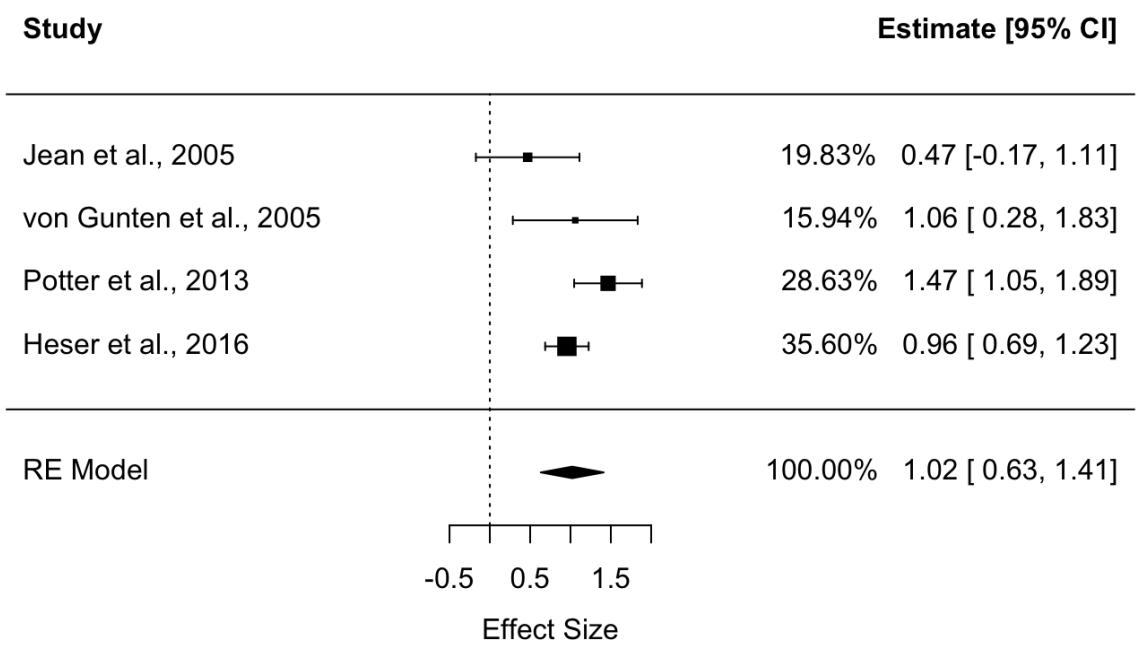


Fig 21. Forest plot showing effect sizes and pooled effect size for mean differences in performance in immediate recall (all tests) between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

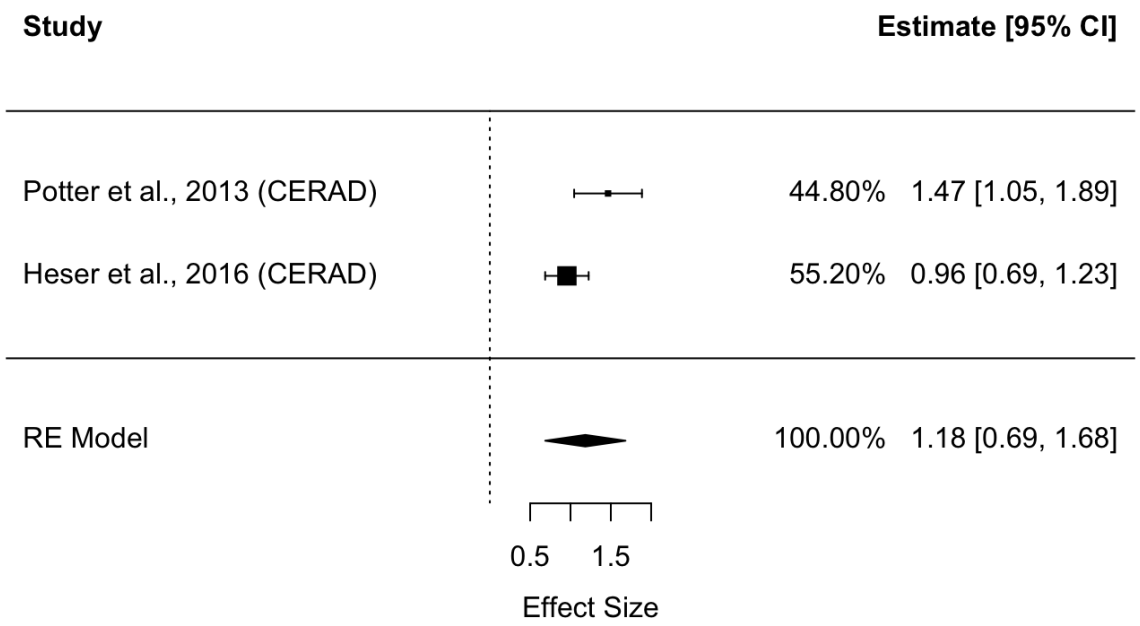


Fig 22. Forest plot showing effect sizes and pooled effect size for mean differences in performance in immediate recall (CERAD tests) between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

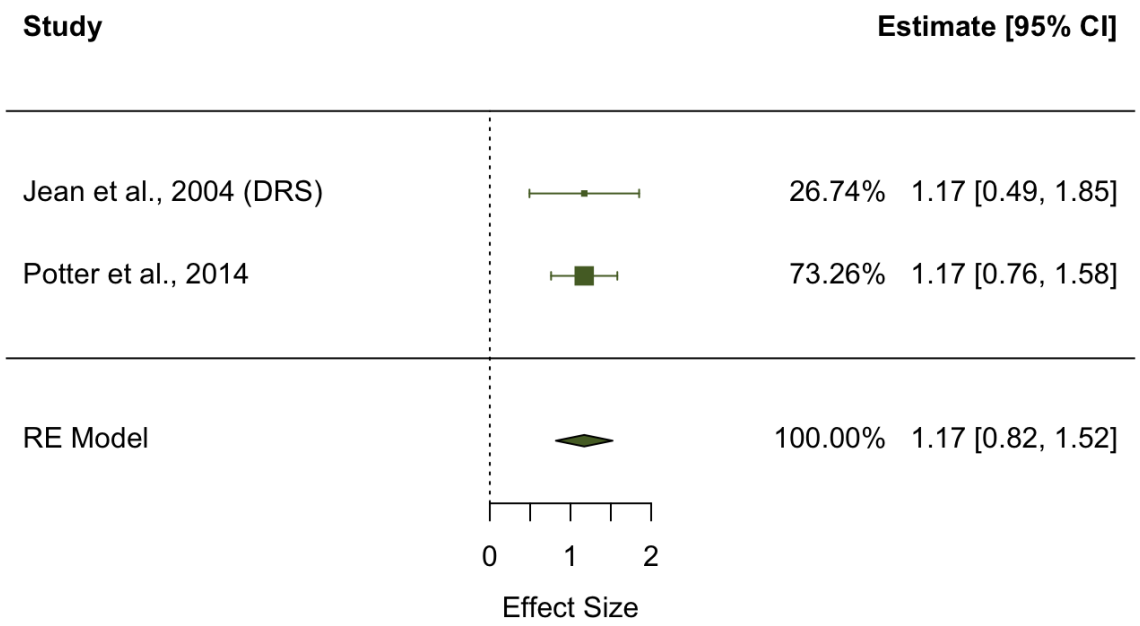


Fig 23. Forest plot showing effect sizes and pooled effect size for mean differences in performance in attention/working memory tests (DRS attention; Digit Span fwd&bwd) between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

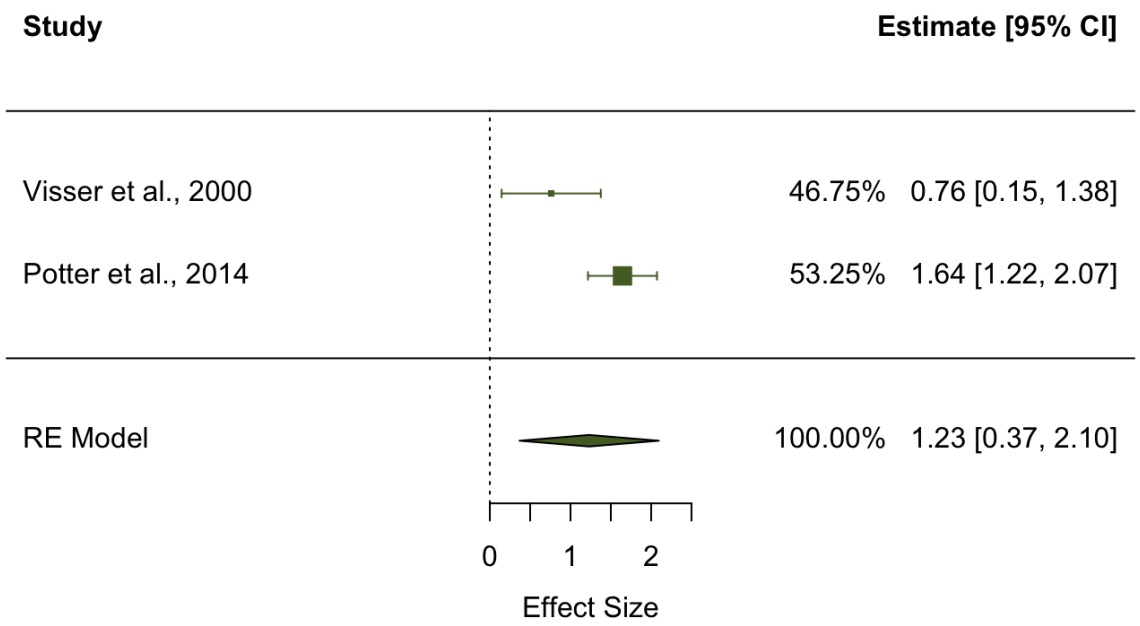


Fig 24. Forest plot showing effect sizes and pooled effect size for mean differences in performance in processing speed tests (MST-L1/SDMT) between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

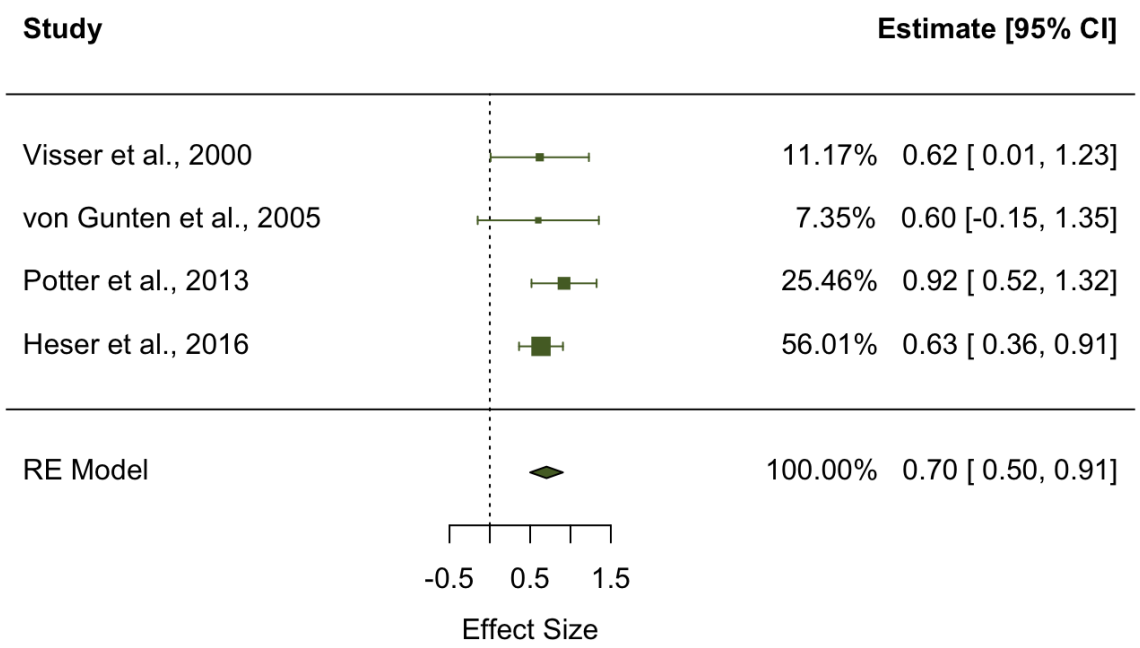


Fig 25. Forest plot showing effect sizes and pooled effect size for mean differences in performance in verbal fluency tests between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

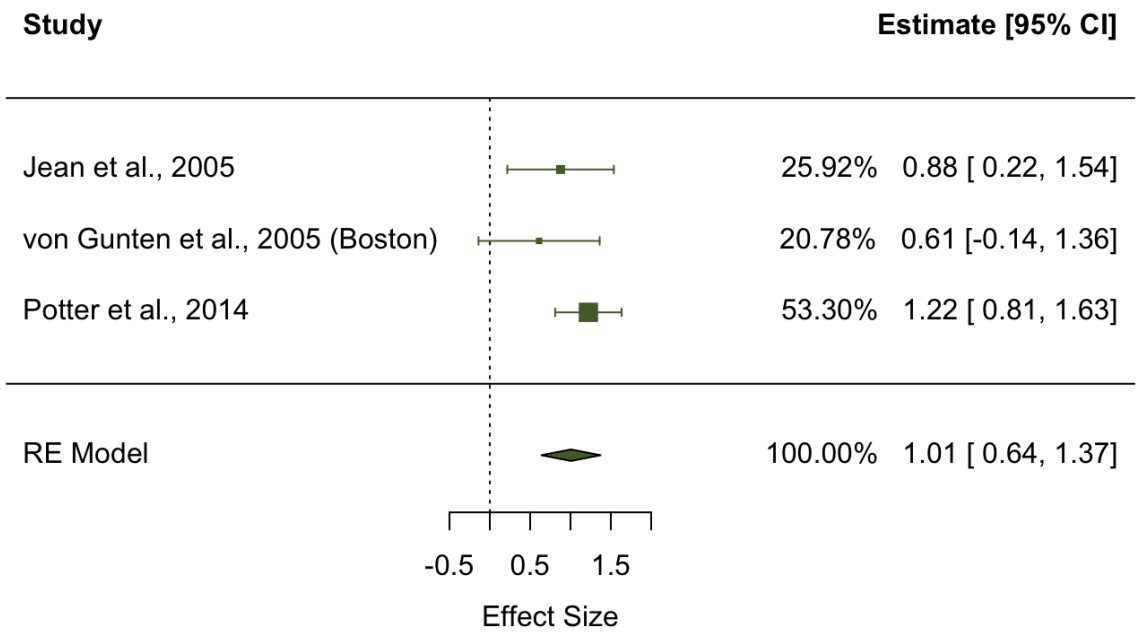


Fig 26. Forest plot showing effect sizes and pooled effect size for mean differences in performance in naming tests between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

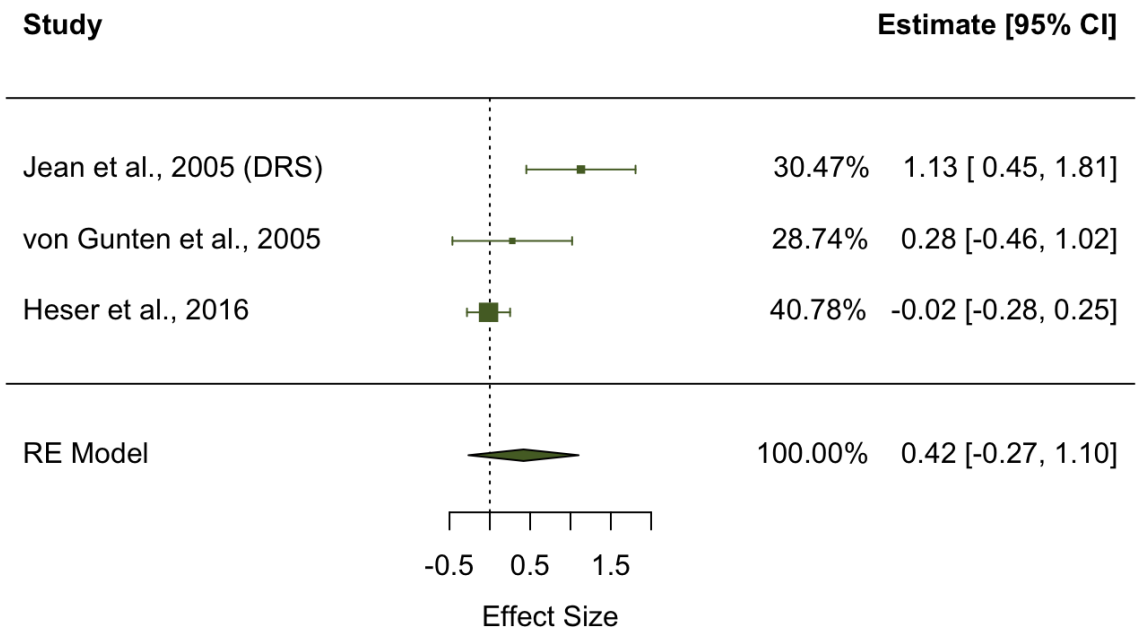


Fig 27. Forest plot showing effect sizes and pooled effect size for mean differences in performance in intelligence tests between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

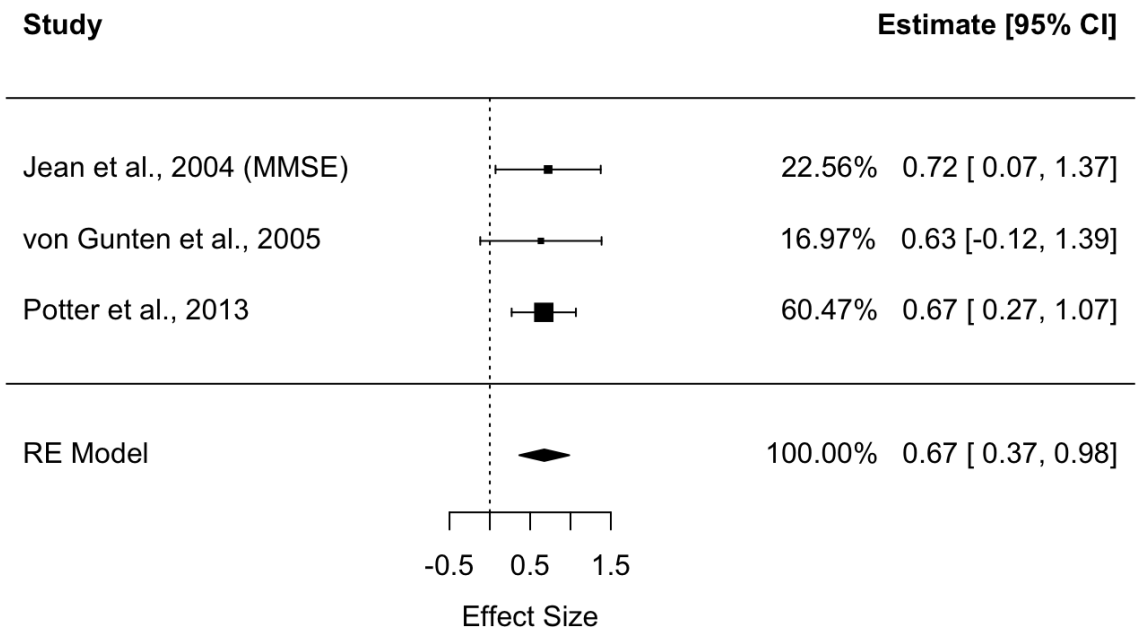


Fig 28. Forest plot showing effect sizes and pooled effect size for mean differences in performance in construction tests between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

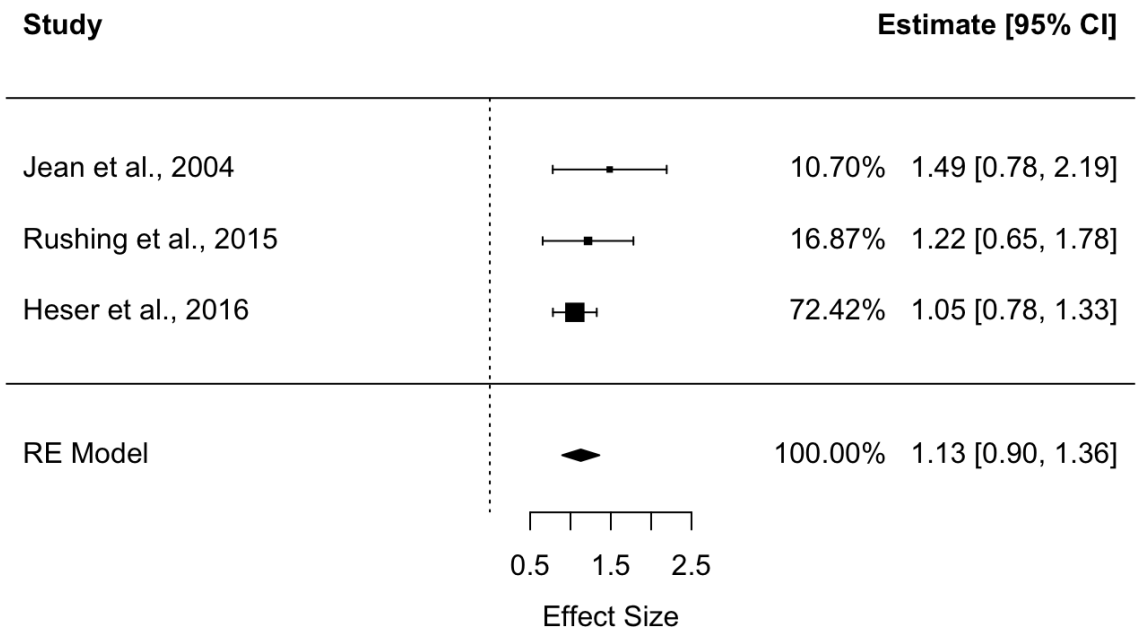


Fig 29. Forest plot showing effect sizes and pooled effect size for mean differences in performance in orientation tests between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

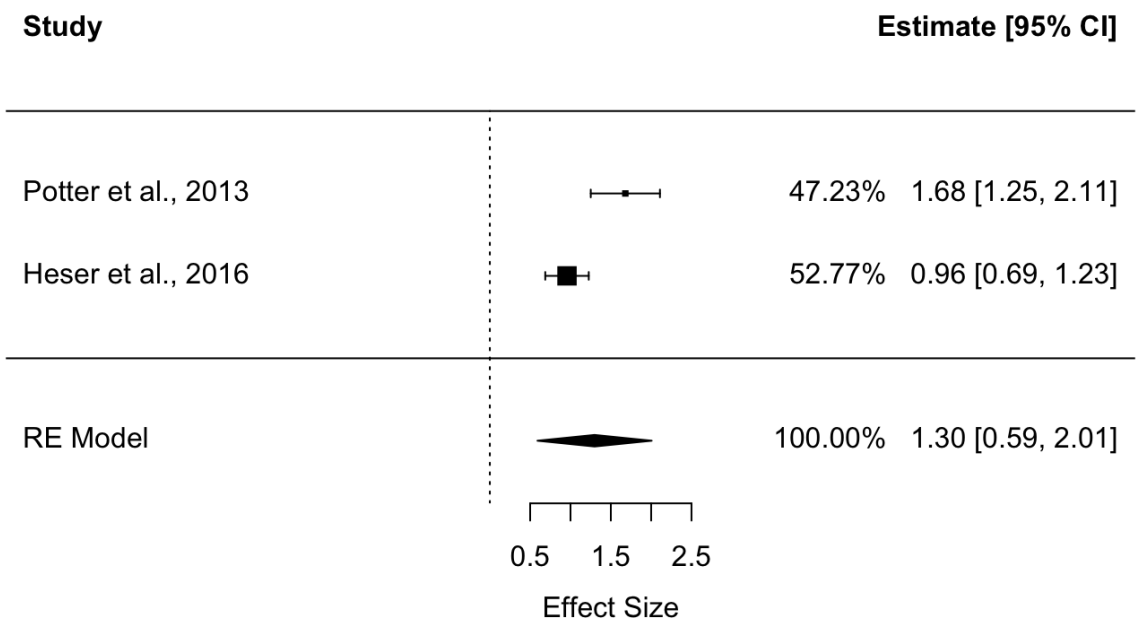


Fig 30. Forest plot showing effect sizes and pooled effect size for mean differences in performance in delayed recognition (CERAD) tests between LLD patients who did not convert to **all-cause dementia** at follow-up and those who did.

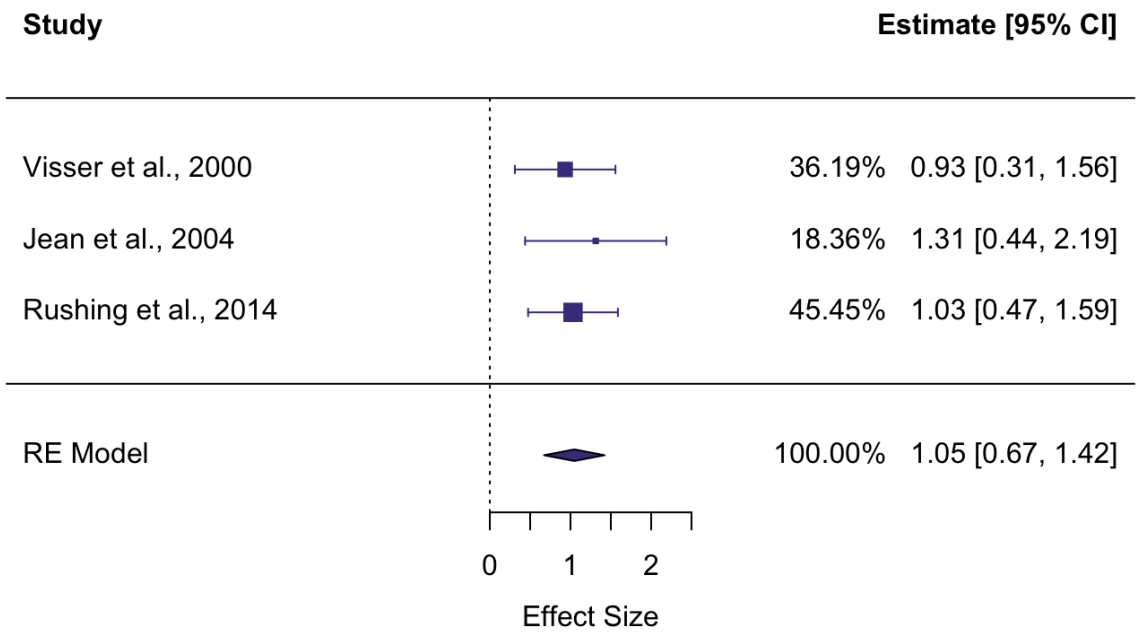


Fig 31. Forest plot showing effect sizes and pooled effect size for mean differences in performance in delayed recall tests between LLD patients who did not convert to **AD** at follow-up and those who did.

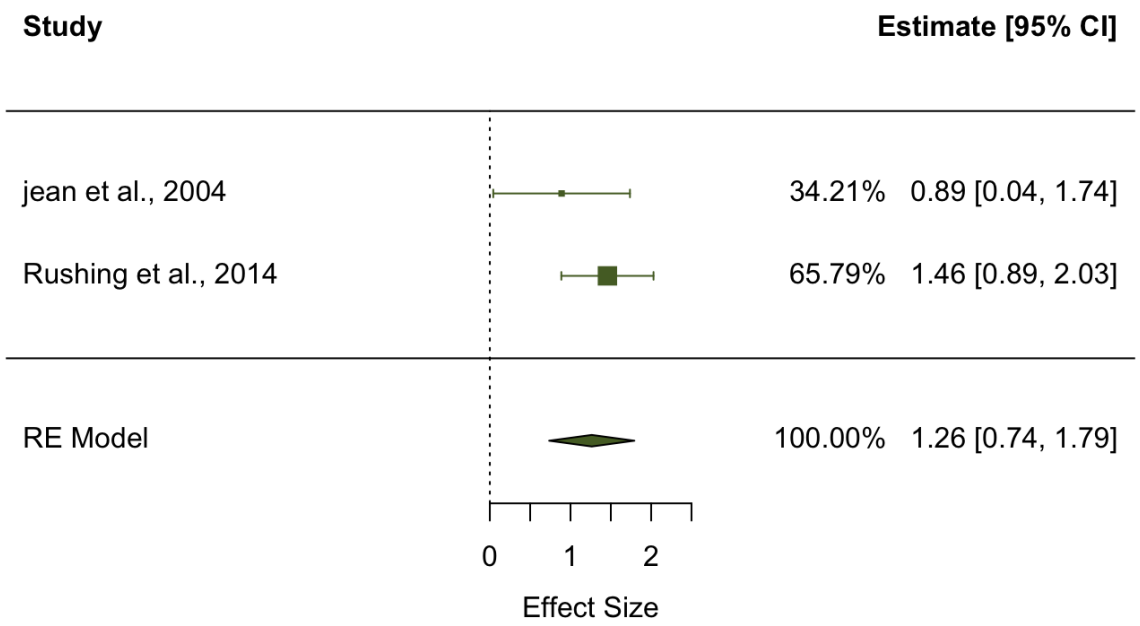


Fig 32. Forest plot showing effect sizes and pooled effect size for mean differences in performance in immediate recall tests between LLD patients who did not convert to **AD** at follow-up and those who did.

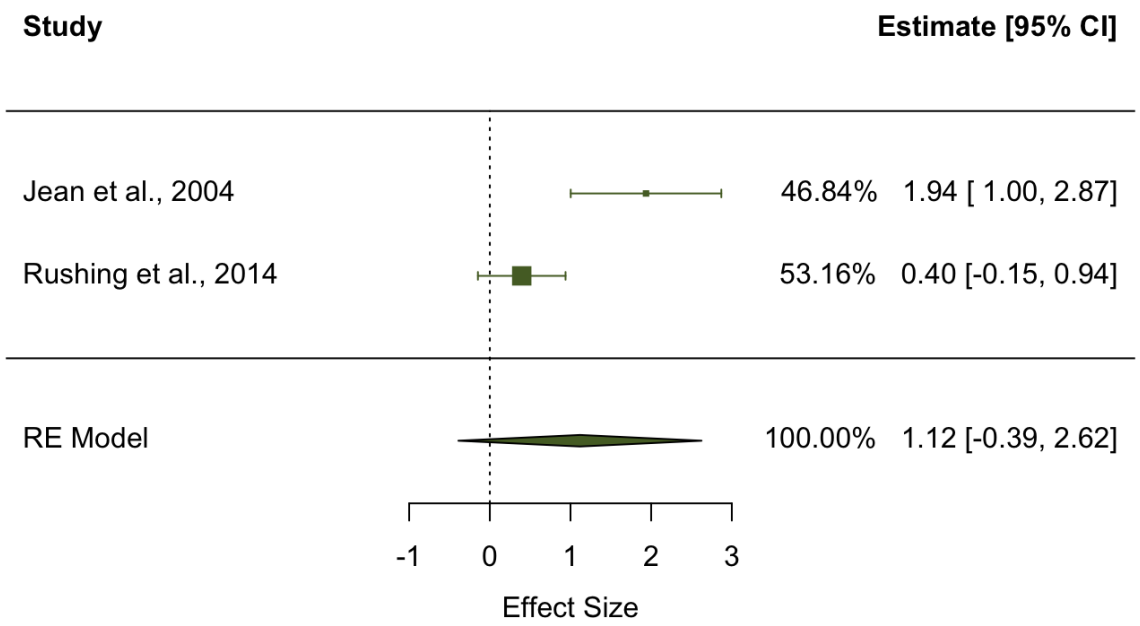


Fig 33a. Forest plot showing effect sizes and pooled effect size for mean differences in performance in attention (Jean et al. – MMSE) tests between LLD patients who did not convert to **AD** at follow-up and those who did.

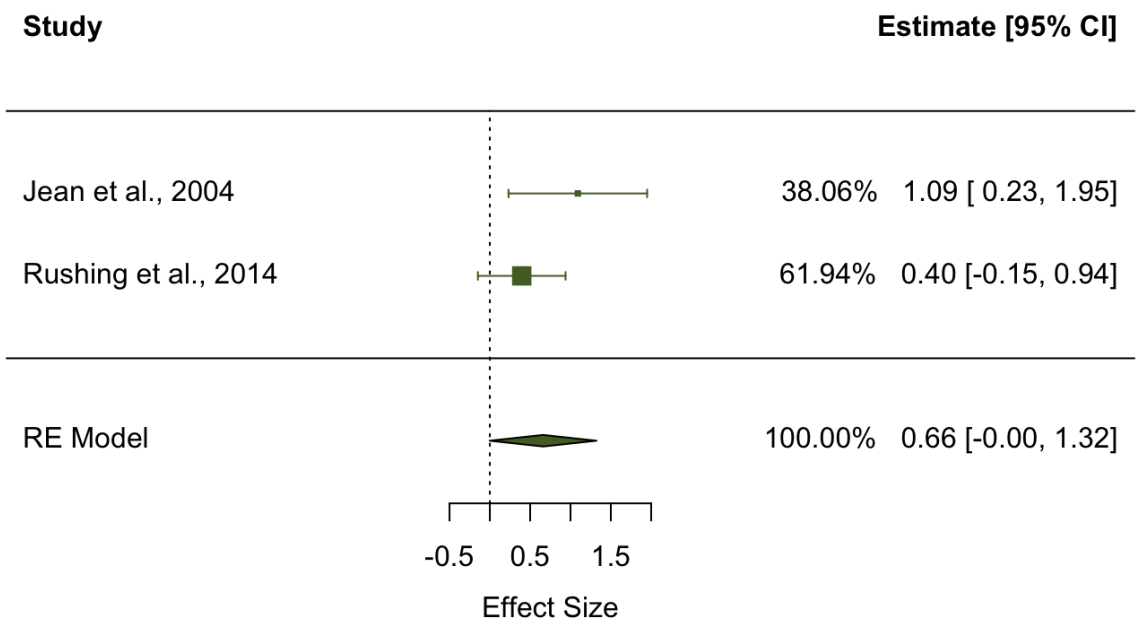


Fig 33b. Forest plot showing effect sizes and pooled effect size for mean differences in performance in attention (Jean et al. – DRS) tests between LLD patients who did not convert to **AD** at follow-up and those who did.

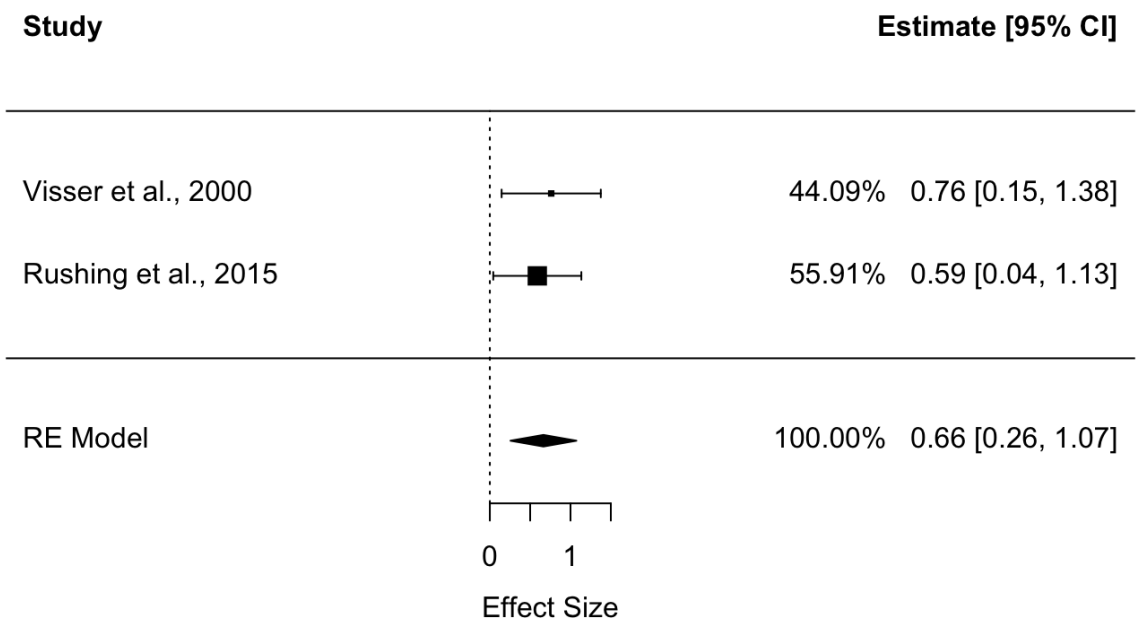


Fig 34. Forest plot showing effect sizes and pooled effect size for mean differences in performance in processing speed (MST-L1/SDMT) tests between LLD patients who did not convert to **AD** at follow-up and those who did.

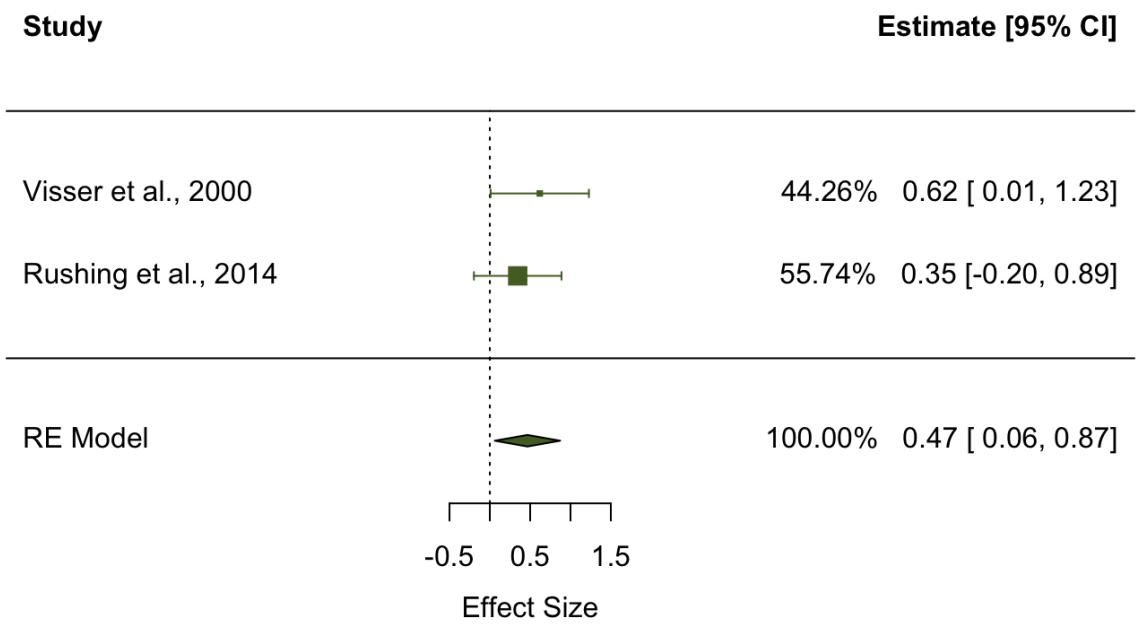


Fig 35. Forest plot showing effect sizes and pooled effect size for mean differences in performance in verbal fluency tests between LLD patients who did not convert to **AD** at follow-up and those who did.

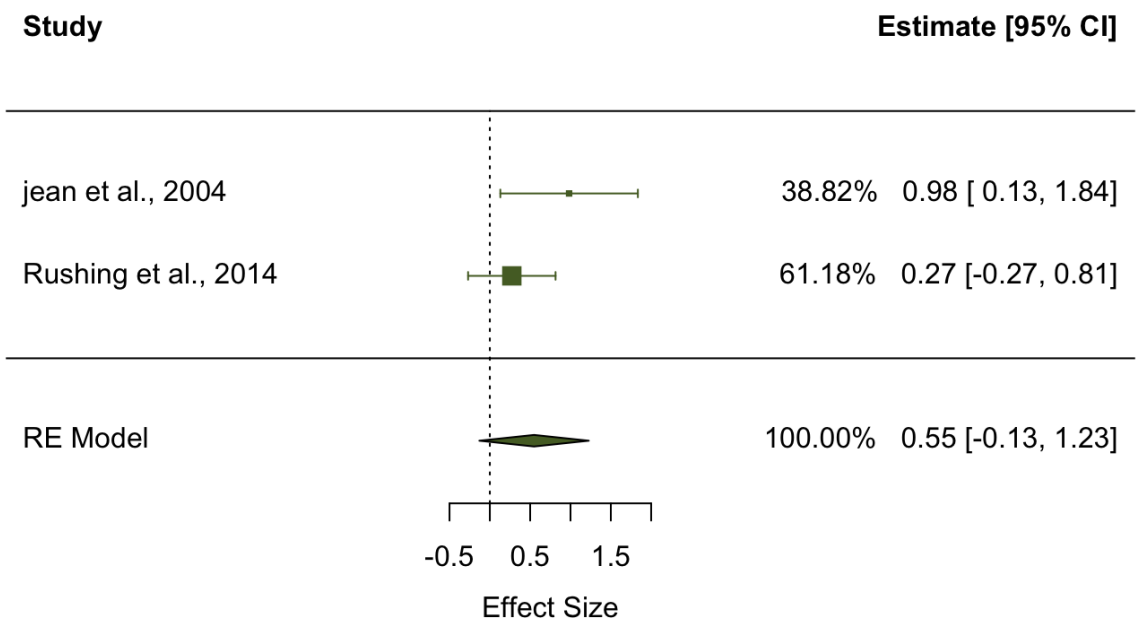


Fig 36. Forest plot showing effect sizes and pooled effect size for mean differences in performance in naming tests between LLD patients who did not convert to **AD** at follow-up and those who did.

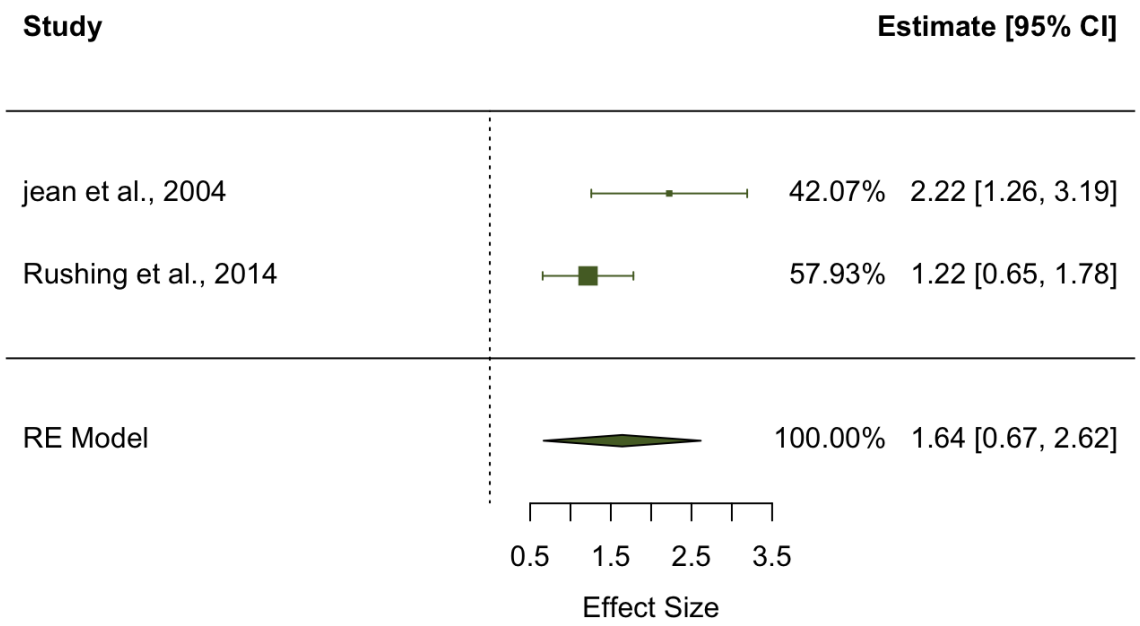


Fig 37. Forest plot showing effect sizes and pooled effect size for mean differences in performance in orientation tests between LLD patients who did not convert to **AD** at follow-up and those who did.

Table 27. The description of individual neurocognitive tests used for the meta-analysis.

Domain	Author	Test	Test description	
Delayed recall	Visser et al.	AVLT Delayed Recall	Fifteen words are presented five times; after each presentation, the subject is asked to reproduce as many words as possible. After 20 minutes, the delayed recall is tested.	Lezak et al., 1985 Brand et al., 1985
	Jean et al.	MMSE delayed recall	The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. After a few minutes, the patient is asked to name the three objects again.	Folstein et al., 1975
	Von Gunten et al.	Free prose delayed recall	A 20-chunk prose recall task	n/r
	Potter et al.	CERAD Delayed Recall		

	Heser et al.		Delayed recall of a 10-item word list	Morris et al., 1989; Welsh et al., 1994
Immediate recall	Jean et al.	MMSE registration	Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct).	Folstein et al., 1975
	Von Gunten et al.	Free prose immediate recall	A 20-chunk prose recall task	n/r
	Potter et al.	CERAD immediate recall	Immediate recall of 3 learning trials of a 10-item word list	Kaplan, Goodglass, & Weintraub, 1978
	Rushing et al.			
	Heser et al.			
Attention/working memory	Jean et al.	MMSE attention	Patients were asked to spell “world” backwards and awarded one point for every correct letter (range 0–5).	Folstein et al., 1975
	Rushing et al.			

Jean et al.	DRS attention	The ATT subscale measures working memory (i.e., forward and backward digit span) and the ability to attend to and execute verbal and visual commands of varied complexity	Mattis, 1973; 1976
Potter et al.	Digit Span (total score)	Ascending: The examiner read a series of numbers and asked the patient to reorder the numbers in ascending order from smallest to largest. Participants were read lists ranging from 2 to 8 numbers and allowed a maximum of two tries at each level. The task was stopped if the patient made two errors at a given	Sair, Welsh-Bohmer, Wagner, & Steffens, 2006; Wechsler, 1981

level or completed eight digits correctly. Scores range from 0 to 14.

Digit Span Backward is a test of working memory and mental tracking which involved presenting a series of digits out loud at a rate of one per second. The patient was then asked to repeat the digits in backward order (range 0–14).

Processing speed	Visser et al.	Time to Complete the Memory Scanning Task Letter 1 (MST-L1)	The subject has to memorize one target letter and cross it out from a sheet containing 24 target letters and 120 nontarget letters.	Brand et al., 1987
	Potter et al.	The Symbol Digit Modalities Test (SDMT)	Patients use a key showing nine number and symbol pairs to write a series of numbers matching their corresponding symbols. The total number of correct responses within 90 seconds is recorded, with a maximum score of 110.	Smith, 1982
	Rushing et al.			
Language (Verbal fluency)	Visser et al.	"Fluency"	Tests the ability to name as many professions or trades as possible within 1 minute	n/r

Von Gunten et al.	Colour&animal fluency (average score)	Naming as many colours/animals as possible within 1 minute	n/r
Rushing et al.	CERAD verbal fluency	Patients were asked to generate words that belonged to a specific category (i.e., animals). The total score was calculated by summing the number of words the subject produced each 15 seconds.	Morris et al., 1989; Welsh et al., 1994
Heser er al.			
Potter et al.	COWAT	Letter fluency is measured as the total number of words the patient is able to produce starting with the letters F, A and S within a time limit of 1 min for each letter. Similarly, category fluency is measured as the	Morris et al., 1989; Welsh et al., 1994

			total number of items named for the two categories “animal” and “clothing”	
Language (Naming)	Jean et al.	MMSE language	Comprehension of a three step command, including naming, repetition, and sentence writing	Folstein et al., 1975
	Von Gunten et al.	CERAD Boston Naming Test	The Boston Naming Test is a measure of confrontation	Morris et al., 1989; Welsh et al., 1994

	Potter et al.		naming ability that contains five high, medium, and low frequency items. The examiner presented patients with a series of black and white drawings and asked them to provide the name of the object. Ten seconds were allowed for each picture. Each correct response, including a correct response after semantic cue, was given one point (range 0–15).	Kaplan, Goodglass, & Weintraub, 1978
	Rushing et al.			
Intelligence	Jean et al.	DRS conceptualization	The CONCEPT subscale assesses abstract concept formation skills and the ability to identify	Mattis, 1973; 1976

			similiarities and differences among sets of objects presented both visually and verbally.	
	Von Gunten et al.	Current intelligence score	A test comprising the interpretation of two proverbs, a similitude question, an alternate verbal fluency task and interpretation of a written and a drawn situation	n/r
	Heser et al.	SISCO (SIDAM) intellectual ability	n/r	n/r
Construction	Jean et al.	MMSE construction	The examiner gives the patient a blank piece of paper and asks him/her to draw the two intersecting pentagons. All 10 angles must be present and two must intersect.	Folstein et al., 1975
	Von Gunten et al.	A 3-	Copying of two 2-D pictures and one	n/g

		item visual construction task	3-D picture	
	Potter et al.	CERAD constructional praxis	Copying of 4 geometric designs	Morris et al., 1989; Welsh et al., 1994
Orientation	Jean et al.	MMSE orientation	Orientation to place was assessed by asking for the state, county, city, floor of building, and address. Temporal orientation was assessed by asking for the year, season, date, day of week, month. Responses to each question were coded 1 (correct) or 0 (incorrect) and then summed (range 0–10).	Folstein et al., 1975
	Rushing et al.			
	Heser et al.	SISCO (SIDAM) orientation	n/r	n/r

Delayed recognition	Potter et al. Heser et al.	CERAD delayed recognition	Delayed recognition/discrimination of target words from nontarget foils presented as part of immediate/delayed recall task	Morris et al., 1989; Welsh et al., 1994

First Author/Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	STROBE SCORE
Rushing et al. (2014)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	95.5%
Potter et al. (2013)	Y	Y	Y	Y	Y	Y	P	Y	P	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	71.6%
von Gunten et al. (2005)	Y	P	Y	Y	N	Y	P	Y	P	N	Y	P	N	P	Y	Y	Y	Y	Y	Y	P	Y	60.1%
Heser et al. (2016)	Y	N	Y	Y	P	P	Y	P	P	N	Y	Y	N	Y	Y	Y	Y	P	P	P	N	N	60.6%
Jean et al. (2005)	Y	Y	Y	Y	Y	Y	Y	Y	P	N	Y	P	Y	N	Y	P	P	P	Y	Y	Y	P	76.2%
Visser et al. (2000)	Y	Y	P	P	Y	Y	Y	Y	P	N	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	P	P	80.7%

Table 28. Quality/Risk of bias assessment of the studies included in the meta-analysis using the STROBE checklist.

Chapter 5. Clinical factors and symptoms of late-life depression associated with progression to dementia: a historical cohort study using electronic health records

Abstract

Background. Late-life depression is one of the factors most consistently associated with higher risk of dementia.

Aims. To investigate clinical factors of late-life depression associated with progression to dementia using retrospective cohort data.

Methods. Data was extracted from the electronic health records of secondary mental healthcare services. Patients (n = 3845) had a diagnosis of major depression at baseline, were free of neurodegenerative disorders, and were followed up for an average of 4.24 years (SD 3.02). Factors associated with increased risk of conversion to dementia were assessed.

Results. Symptoms associated with dementia were irritability ($p<0.001$) and hallucinations ($p=0.009$). Hopelessness was associated with lower risk of developing dementia, although this was no longer significant in sensitivity analysis after excluding patients with baseline cognitive impairment. Scoring high on "Non-accidental self-injury" (reflecting autoaggressive behaviour/suicidal ideation) was a consistent protective factor across all models ($p<0.001$). Higher age ($p<0.001$), physical illness ($p<0.01$) and cognition at baseline ($p<0.001$), as well as antihyperglycaemic ($p<0.01$) and anticoagulant/antiplatelet ($p<0.01$) medication were associated with higher risk of conversion. Recurrent depression, as opposed to first-episode late-onset depression, was univariately associated with lower risk of progression to dementia (HR 0.68, 95%CI 0.59-0.79, $p<0.001$), but this was not significant in a fully adjusted model (HR 0.9, 95%CI 0.76-1.067, $p = 0.1$).

Conclusion. Hallucinations and irritability may distinguish late-life depression from prodromal dementia. Hopelessness and suicidal ideation were linked to lower likelihood of progression to dementia. The role of age of onset of depression is unclear and needs to be investigated in further studies.

5.1 Introduction

5.1.1 Background

Dementia is one of the major causes of disability among the elderly worldwide, and one of the leading healthcare concerns of the 21st century (WHO, 2020). Despite extensive research into the pathogenesis of different types of dementia, the availability of approved treatments remains extremely limited. Therefore, research into modifiable risk factors and early signs of dementia remains crucial (Livingston et al., 2020).

Depression in late life has been strongly linked with progressive cognitive impairment. A number of meta-analyses have shown that cognitively normal people who experience an episode of depression after the age of 60-65 have a higher likelihood of subsequently being diagnosed with dementia compared to the general population (Jorm et al., 2001; Cherbuin et al., 2015; Diniz et al., 2013). Some authors have pointed to the potential of preventing dementia by treating depression (Lykstos et al, 2016; Kessing et al., 2012).

Despite the consistently confirmed association between late-life depression and dementia, the mechanisms linking the two conditions are not straightforward. Depending on the clinical history, number of depressive episodes and proximity of depression to dementia, it can be seen as a risk factor, as a prodromal state, or even as a reaction to emerging cognitive decline. Moreover, depression can be a manifestation of shared underlying pathology with Alzheimer's disease or other kinds of dementia (e.g. "vascular depression", a proposed endophenotype of late-life depression, can be a manifestation of cerebrovascular disease which may also at some point manifest as progressive cognitive decline and vascular dementia). While the exact mechanisms linking depression and dementia are yet to be disentangled, the identification of clinical predictors of incipient dementia in late-life depression appears to be a pressing issue.

Neuropsychiatric symptoms have been investigated by multiple researchers as features of prodromal dementia (Stella et al, 2014). In particular, the syndrome of "mild behavioural impairment" (MBI) has been proposed as a diagnostic construct associated with prodromal stages of dementia in patients without apparent cognitive decline (Ismail et al., 2015; Creese et al., 2019). In addition, a meta-analysis showed that apathy in elderly was associated with a 2-fold increase in risk of subsequent dementia (van Dalen et al., 2018). However, the diagnosis of MBI is made in the absence of major depression, and little is known about the particular symptoms or phenotypes attributable to major depression that could be suggestive of future progression to dementia.

5.1.2 Previous studies addressing symptom profiles/phenotypes of depression predicting dementia or cognitive decline

There have been two studies which reported the effect of the melancholic subtype of depression on cognitive outcome. Do Couto et al. performed a longitudinal study of depressed patients recruited between 1977 and 1984 and followed up for around 20 years. Depression was diagnosed using the Association for methodology and documentation in psychiatry system (AMDP) criteria, and based on initial examination, reevaluated using DSM-5 criteria at follow-up. Dementia was diagnosed using approved criteria and clinician consensus. The study showed that patients with melancholic depression at baseline had an increased risk of all-type dementia. Logistic binary regression analysis showed a significantly increased risk for dementia only in melancholic subjects but not in non-melancholic subjects (adjusted OR 7.72; 95% C.I. 3.18–18.77). The other depression characteristics were not associated with a higher risk for dementia. Notably, the earlier the onset of depression, regardless of sybtype, the higher were the odds of dementia (8.69; 95% C.I. 2.21–34.23 and 4.00; 95% C.I. 1.87–8.60, for those younger than 45 and 60, respectively;Do Couto et al., 2016).

Sachs-Ericsson et al. showed that patients with late-onset melancholic depression exhibited significantly greater cognitive decline than early-onset melancholic patients, after a follow-up of 3 years (Sachs-Ericsson et al. 2014).

However, in a study bv Corsentino et al. where cognitive decline was measured continuously as deterioration on MMSE score, DSM-IV-TR defined melancholic depression was not associated with significantly higher cognitive decline, when controlled for severity of depression and psychomotor symptoms (Corsentino, 2010).

Oudega et al. studied the rates of cognitive decline in patients who had received ECT for geriatric depression. They followed 39 patients for a median of 8 years, and 61,5% of patients demonstrated cognitive decline after follow-up, as defined by Informant Questionnaire of Cognitive Decline in the Elderly (IQ CODE) filled in by a proxy. Interestingly, in this study, psychotic depression was associated with a significantly lower risk of subsequent dementia (Oudega et al., 2015).

A few other studies suggested applying a dimensional approach to characterise late-life depression. A longitudinal study by Lugtenburg et al. identified two factors based on the GMS *(*Geriatric Mental State Schedule) items: the "general depression" factor, comprising core mood symptoms, and the "cognitive/motivational" factor, comprising cognitive and motivational symptoms and excluding core mood symptoms. In the whole sample which included both depressed and non-depressed subjects at baseline, the general depression factor, but not the cognitive/motivational factor, increased the risk of dementia (OR 1.48, 95% CI 1.14-1.92). However after the depressed at baseline patients were excluded from the sample, in the remaining 1725 nondepressed older persons, the cognitive/motivational factor significantly predicted dementia after adjustment for covariates (OR: 1.53, 95% CI: 1.03-2.28), but not anymore after additional adjustment for subjective memory complaints (OR: 1.41, 95% CI: 0.94-2.13). The general depression factor did not significantly predict dementia in nondepressed older persons. These findings suggest that they may indeed be different underlying pathways in the association between depression and dementia (Lugtenburg et al., 2015).

Bartolini et al. followed 222 subjects of who 124 were depressed (DSM-III diagnosis) at baseline for 1 year. The authors used BDI scores to distinguish between three domains of depression corresponding to mood-related, somatic and motivation-related symptoms. The study found that although total BDI scores were similar in depressed subjects who developed dementia vs those who didn't, the subscores differed significantly. The probability of being diagnosed with dementia during follow-up was significantly associated with a motivational BDI subscore above 7 (odds ratio: 3.89, 95% Cl 1.54–9.79; Bartolini et al., 2004).

These results are consistent with those obtained by Berger et al., 1999, and Mossaheb et al.2012, and Turner et al., 2015.

Berger et al., followed 222 patients for 3 years before the diagnosis of AD. Those who developed AD during follow-up had more depressive symptoms at baseline in total, and also showed a dominance of motivation-related symptoms, as assessed by Comprehensive Psychopathological Rating Scale. With respect to the individual motivation-related symptoms, the incident AD patients reported more lack of interest, loss of energy, and concentration difficulties compared with nondemented patients. Although there was no overall group difference in mood-related symptoms, the incident AD group had more thoughts of death than the control subjects. The groups did not differ in terms of sleep disturbance (Berger et al., 1998).

Mossaheb et al. studied an association between particular depression symptoms (a DSM-IV-TR-based questionnaire) with the risk of subsequent development of AD in a sample of 75-year-old patients in the VITA study who were followed up for 5 years. They found that out of 9 symptoms, only "loss of interest" was associated with increased probability of AD (OR = 5.27; 95% CI, 1.62-17.2). This symptom predicted AD with high specificity (97.8) but low sensitivity (10.4; Mossaheb et al., 2012).

Turner et al. focused their research on a population of elderly African-Americans. They examined an association between baseline GDS and CESD scores and cognitive decline measured by an array of neuropsychological tests over a mean of 5 years. Total CESD score did not predict cognitive decline, while total GDS score predicted decline in. semantic and working memory. Among CES-D factors, lack of positive affect (e.g., anhedonia) was related to decline in global cognition, episodic memory and perceptual speed. Similarly for the GDS, anhedonia was associated with decline in semantic memory, and increased negative affect was associated with decline in global cognition, episodic, semantic, and working memory (Turner et al., 2015).

However, finding by Saha et al. did not support the association between risk of dementia and anhedonia. Based on a cohort of 290 participants from the NCODE study, they derived 5 symptom factors, including anhedonia and sadness; suicidality and guilt; appetite and weight loss; sleep disturbance and anxiety and tension. In their analysis, only higher appetite/weight loss factors were associated with increased hazard of AD (HR 1.69, 95% CI: 1.18 – 2.42). Interestingly, when stratified by age of onset, using 60 as a cutoff, the appetite/weight loss factor was no longer significant for any of the groups, although there was a trend for higher HR (1.71 95% CI: 0.93-3.16,, p=.09) in the late-onset group (Saha et al., 2016).

At the same time, Geerlings et al. found that out of 12 depressive symptoms of the Dutch version of GMS, only subjective bradyphrenia (OR 4.56; 95% CI 1.71-12.18**)** and depressed mood, but not loss of interest or appetite/weight-related symptoms, were associated with increased occurrence of AD during follow-up period (Geerlings et al., 2000).

Finally, Johnson et al. performed a big two-staged study where they aimed to identify an endophenotype of depressive patients prone to cognitive decline and cross-validate it in a second independent cohort. The established depressive endophenotype (DepE) consisted of 5 GDS items: "feeling of more memory problems", "feeling downhearted and blue", "feeling worthless", "frequently feel like crying", "trouble concentrating". However, only TARCC was a longitudinal cohort in this study and therefore its data is of higher interest within the scope of this review. DepE scores were significant predictors of AD status (compared to controls) at 12-month follow-up visits (OR 4.02; 95% CI 1.73-9.32; p=0.001), and at 24-month follow-up visits

(OR 3.84, 95% CI 1.13-13.10, p=0.03). When neuropsychological tests were taken into account as a continuous outcome measure (MMSE and CDR-SB change), baseline DepE scores also predicted cognitive decline. In the other non-longitudinal cohort, DepE alone was a significant predictor of AD status as well in both ApoEε4 carriers (OR 2.81, 95% CI 1.2-6.5, p=0.02) and ApoEε4 non-carriers (OR 8.03, 95% CI 3.06-21.08, p<0.001), although the effect was stronger for non-carriers (Johnson et al., 2013).

Electronic health records can be a useful tool for investigating factors contributing to dementia risk, and possibly creating prognostic models(ref). The present study uses retrospective data from the Clinical Record Interactive Search (CRIS) electronic health records system to explore factors associated with conversion from late-life depression to dementia in a sample of elderly patients referred to South London and Maudsley NHS Foundation Trust.

5.2 Methods

5.2.1 Source of data

Data for this study was obtained using the electronic health records of the South London and Maudsley NHS Foundation Trust (SLaM) which cover 1.2 million residents living in four of South London boroughs (Croydon, Lambeth, Lewisham and Southwark; Perera et al., 2016). Since 2006, all records in the system have been fully electronic, with imported legacy systems which included a records system run for several years previously in dementia care. Clinical Record Interactive Search (CRIS) is an application developed for access to anonymized data extracted from these health records. CRIS currently contains records on over 270 000 mental health service users. CRIS was set up in 2008 and has research ethics approval as a database for secondary analysis (Oxford Research Ethics Committee C, reference 18/SC/0372). CRIS has been enhanced by a range of natural language processing (‘text-mining’) applications which extract structured data from text fields, including applications to ascertain pharmacotherapy.

CRIS is linked to other national databases, including HES (Hospital Episode Statistics) and ONS (Office of National Statistics) which were used for the present study (Data linkage service user and Carer Advisory Group Newsletter, 2020). HES includes information about all accident and emergency, hospital admissions and outpatient visits which occur in all public-sector hospitals throughout England. For the purpose of the present study, we obtained HES diagnoses of all participants initially selected through CRIS. We also obtained information about the diagnoses from death certificates available from the ONS Mortality data.

5.2.2 Sample

Using CRIS data, we selected people aged over 65 years who were diagnosed with depression in the period between January 1st, 2008 and March 31st, 2017. Depression was defined in accordance with the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes, both from diagnoses recorded in structured fields and in free text within clinical correspondence, through a bespoke natural language processing algorithm (a detailed explanation of the method is provided in Chapter 2). Further, using CRIS, HES, or ONS data, we registered the diagnoses of dementia occurring within the follow-up period using the same method. Cases with diagnosis of dementia occurring within three months from, or before, the diagnosis of depression, were excluded to avoid overlapping diagnoses. Besides, patients diagnosed with MCI at baseline, as well as schizophrenia, substance abuse, organic brain damage, delirium, Parkinson’s disease, and stroke were excluded from the sample.

Participants were considered as not having dementia by the end of the observation period if they were not diagnosed with dementia on their most recent record of either an outpatient visit (in the CRIS data) or of hospital admission (in the HES data) in the follow-up window ending March 31st, 2017 or at death.. Additionally, patients were not considered to have developed dementia if no diagnosis of dementia was recorded on their death certificate, should they have died in the observation period.

5.2.3 Measurements

Late-life depression

Initial depression diagnoses (the index contact) were determined by the following diagnostic codes from ICD-10 within a primary or secondary diagnosis: F32 (depressive episode), F32.2 (severe depressive episode without psychotic symptoms), F32.3 (severe depressive episode with psychotic symptoms), F33 (recurrent depressive disorder), F33.2 (recurrent depressive disorder, current episode severe without psychotic symptoms), F33.3 (recurrent depressive disorder, current episode severe with psychotic symptoms). Data were also obtained for any depression diagnoses (F32, F33) recorded before the index date. Several characteristics of depression were specified based on ICD-10 codes: recurrent depression, mild/moderate/severe depression, and psychotic depression.

Dementia

Dementia diagnoses were determined by the following diagnostic codes from ICD-10 within a primary or secondary diagnosis: F00 (dementia in Alzheimer’s disease), F01 (vascular dementia), F02 (dementia in other diseases classified elsewhere), F03 (unspecified dementia).

Symptoms of depression

Information about the presence of specific symptoms of depression was obtained from patient records using natural language processing. Data was available for the following symptoms: feeling helpless, feeling hopeless, feeling worthless, anhedonia, poor motivation, apathy, low mood, poor concentration, agitation, irritability, low energy, insomnia, appetite loss, anergia, hallucinations, delusions, and suicidal ideation.

For each symptom, data was available in the form of a binary variable indicating the symptom having been mentioned in the patients record in a 6-months window around the index date, and a discrete variable indicating the number of times the patient mentioned the symptom. In the present analysis, binary measures were used as the main predictor variables.

Covariates

The choice of covariates (listed below) was based on known predictors of dementia from previously published studies, as well as relevant covariates significantly associated with outcome in univariate analyses (Peakman et al., 2020). All models were adjusted for demographic factors: age, gender, ethnicity and marital status ("married"/"single" /"widowed/divorced").

Medication data was available for both psychotropic and general physical medication which the patient was taking within the six-month period around the time of depression diagnosis. Of psychotropic medication, the following categories were available: antidepressant medication (any), SSRI, SNRI, mirtazapine, TCA, and lithium (although lithium was not included in the analysis due to low frequency of use). Somatic medication included the following categories: antihypertensive, anticoagulant/antiplatelet, antilipid, and antihyperglycaemic agents.

Assessing baseline cognition

Baseline cognition was assessed using the cognitive subscale of the Health of the Nation Outcome Scales for older people (HoNOS65+). HONOS65+ is a clinician-rated instrument routinely administered in SLaM services. HoNOS65+ items are rated from 0 (least severe status) to 4 (most severe status); for the purpose of the present analysis, the value for severity of impairment on each subscale was dichotomised into "absent/low" (0-1 on HoNOS65+) and "present/high"(2-4 on HoNOS65+). A study comparing the clinical utility of HONOS65+ with more commonly used scales including MMSE showed that HONOS65+ could be appropriate for assessing clinical outcomes (Spear et al., 2002).

At the same time, the 2018 revision of HONOS65+ mentioned that the previous version of the cognitive scale had had an excessively narrow focus on dementia (James et al., 2018). Our study sample had been assessed with the earlier HONOS65+ version. Therefore, in order to avoid including patients who could have had undiagnosed dementia at baseline, we performed a sensitivity analysis whereby we separately assessed the factors predicting conversion in the sample where patients had no HoNOS65+-defined cognitive decline at baseline. Patients who scored "2" (2-4 according to the original scale) on the "cognitive problems" subscale of HoNOS65+ were excluded in this part of the analysis.

Other HoNOS65+ subscale scores extracted for this analysis were: agitated behaviour, non-accidental self-injury, drug/alcohol problems, hallucinations or delusions, depressed mood, physical illness or disability, activities of daily living (ADLs), living conditions, occupational and recreational activities, social relationships.

5.2.4 Statistical analysis

Univariate analyses of patients' baseline characteristics by outcome status were performed using independent sample t-tests or two-sample Wilcoxon rank-sum (Mann-Whitney) tests according to normality of distribution for continuous variables, and chi-squared test for categorical variables.

Factors associated with shorter time to being diagnosed with dementia were identified using Cox proportional hazards regression. Lowest time from the diagnosis of depression to the diagnosis of dementia in CRIS, HES or ONS systems was used as time function. HoNOS65+ was recoded as a time-varying variable since it violated the proportional hazards assumption.

The effect of each factor was assessed in several models: univariate Cox regression (Model 1), adjusted for all demographic factors and recurrence (Model 2), further adjusted for baseline cognition (Model 3), adjusted for general physical health HoNOS65+ score (Model 4), further adjusted for "non-accidental self-injury" HoNOS65+ score (Model 5) and finally, additionally adjusted for physical medication (Model 6).

The role of depressive symptoms was assessed separately, first in univatiate Cox regression (Model1), then adjusted for all other symptoms (Model 2), further adjusted for demographics(Model 3) and HoNOS65+ scores(Model 4), and the final model included additional adjustment for relevant medication (Model 5). In the whole sample, we also analysed the effects of "symptoms mentioned at least twice", but not in subgroup analyses (see below) to avoid overfitting due to low prevalence of symptoms.

Results are presented as hazard ratios and 95% confidence intervals for factors associated with conversion to dementia.

Missing data

The original dataset contained missing values, predominantly for HONOS65+ subscales (73% complete data). Missing data was identified as MAR in accordance with guidelines presented in Sterne et al. (2009). Multiple imputation was then used to replace missing values. When compared to Cox regression results using complete case analysis, analysis results for MI did not show any substantial difference. Results from complete case analysis are presented in this paper.

Subgroup analysis

Distinguishing between elderly patients and "the oldest old"

The original dataset contained data on patients whose age at baseline varied within a wide range, from 64 up to 103. While the majority of patients (65.9%) were aged between 65 and 80 at the time of depression diagnosis, 34,1% of the sample fell into the "oldest old" category at baseline (Valenzuela et al., 2019; Lai et al., 2018). Therefore we investigated the factors associated with conversion first in the full sample, and further separately in the two subgroups of patients aged between 64-80 and above 80. Associations were analysed using the same models as in the full sample.

5.3 Results

At the initial stage of data preparation, 6509 patients with depression diagnosed between Jan 1, 2008 and March 31, 2017 were identified using CRIS, HES and ONS records. During data cleaning, 2212 cases were excluded as having dementia prior to/within 3 months of diagnosis of depression. Further, 354 observations were excluded as having a baseline comorbid diagnosis that met exclusion criteria (e.g. schizophrenia, organic brain damage, delirium, Parkinson's disease, etc.).

Of the 3845 participants included in the final dataset, the majority were female (63.2%) and of white (British/Irish/other European) ethnicity (82.6%). Median age was 76.8 years (SD 7.74). All patients were depressed at baseline; a fourth (24.8%) were diagnosed as having recurrent depression; 32.2% had moderate depression; 13.2% had mild depression; 11.3% and 4.2% were registered as having severe and psychotic depressive episodes, respectively.

Dementia during follow-up was diagnosed in 1026 (26.5%) patients. Mean follow-up time did differ significantly between non-converters and converters (4.04 vs 4.85, respectively, p<-.001). Half of the patients (49%) died during the course of observation, the other half survived; of those who died during follow-up, dementia was diagnosed in 33% cases, as opposed to 20% in those who survived until the end of the study. Those who developed dementia were older on average (73.66 vs 71.82, p<0.01), more likely to be female (69.3% vs 61.3%, p<0.01) and single (54.3% vs 47.6%, p<0.01). There was also a trend towards converters being less likely to have recurrent depression (25.6% vs 22.9%), although not significant. Tables 26-27 summarise baseline characteristics and the comparison between those who developed dementia at follow-up and those who didn't.

Clinical and demographic factors predicting conversion to dementia

Univariate associations between demographic and clinical factors and the risk of conversion to dementia are presented in Table 2. In Model 1, adjusted for demographics, age and ethnicity (non-white) were associated with increased hazard of conversion, while recurrent depression remained a significant protective factor (HR 0.78; 95% CI 0.67-0.91). However, after adjustment for physical illness, recurrent depression was no longer significantly protective (HR 0.88, 95%CI 0.75;1.04, p = 0.197). In a fully adjusted model, age, cognitive decline, physical illness, problems in daily living, occupational problems remained significant predictors of faster progression, while non-accidental self-injury predicted lower rates of dementia.

Of psychotropic medication, only antidepressants in general (HR 1.24, 95%CI 1.06;1.45, p = 0.007), in particular SSRI(1.23, 95%CI1.09;1.39, p = 0.001), were univariately associated with faster conversion to dementia., anticoagulant/antiplatelet (HR 1.59, 95%CI1.39;1.82, p<0.001), antihypertensive (HR 1.34, 95%CI 1.19;1.5,p<0.001), antihyperglycaemic (HR 1.49, 95%CI 1.23;1.81, p<0.001) and antilipid medication (HR 1.26, 95%CI 1.10;1.43, p= 0.001) were all linked with higher rates of conversion. In the fully adjusted model, both anticoagulant/antiplatelet and antihyperglycaemic remained significantly associated with conversion to dementia (HR 1.32, 95%CI 1.14;1.53, p<0.001; HR 1.38, 95%CI1.11;1.72, p=0.004, respectively; see Table 28.

Symptoms associated with conversion to dementia

Symptoms univariately associated with faster conversion to dementia were: apathy (HR 1.37, 95%CI 1.06-1.78, p = 0.016), irritability (HR1.26, 95%CI 1.09;1.45, p=0.002), appetite loss (HR 1.15, 95%CI 1.02-1.31, p=0.022) and hallucination (HR 1.41, 95%CI 1.15;1.74, p=0.001). At, patients who reported feeling hopeless (HR 0.79, 95%CI 0.69;0.92, p = 0.002) and insomnia (HR 0.78, 95%CI 0.65;0.94, p = 0.008) were less likely to convert to dementia. When adjusted for all other symptoms (Model 2s), the associations remained the same. In a fully adjusted model, hallucination (HR 1.36, 95%CI 1.08-1.71, p=0.009) and irritability (HR 1.38, 95%CI 1.17;1.63, p<0.001) remained predictive of faster conversion, while hopelessness was the only symptom that was associated with lower hazard of conversion (HR 0.73, 95%CI 0.61;0.86). Apathy was no longer significant, yet the trend was sustained (HR 1.31, 95%CI 0.98-1.76, p= 0.076). Insomnia or appetite showed no association in fully adjusted model.

When original symptom measures were replaced with "symptoms mentioned at least twice in clinical notes", associations remained the same, however apathy became a strong predictor of faster conversion (HR 2.07, 95%CI 1.45-2.95, p <0.001).

Predictors of conversion to dementia within the group of patients aged between 65-80

With the ample restricted to patients aged between 65 and 80, there were 2,507 patients diagnosed with depression at baseline. The majority (60.9%) were female, of white ethnicity(78.94), and widowed/divorced (44.03%). In this subsample, 517 (20.6%) patients converted to dementia during follow-up. In the fully adjusted model, irritability was associated with higher likelihood of conversion (HR 1.57, 95%CI 1.26; 1.95, p<0.001), along with older age, HoNOS65+ cognitive impairment at baseline, physical illness, anticoagulant/antiplatelet and anti hyperglycaemic medication. Hallucination showed a non-significant trend (HR 1.34, 95%CI 0.99;1.83, p=0.061). Hopelessness was associated with lower likelihood of conversion (HR 0.66; 95% CI 52;0.83, p<0.001), along with HoNOS65+ self-injury score.

Predictors of conversion to dementia within the group of patients aged 80 or above

There were 1,338 patients who belonged in the "oldest old" category, with age at baseline ranging between 80 and 103 years (mean 85.73, SD 4.26). Among this group, 67.7% were female, 13% were of non-white ethnicity, and the majority (834, 61.4%) were widowed or divorced. First-onset depression at baseline was diagnosed in 1215(81.9%) patients, and 401(30.9%) of patients scored 2 or higher on HoNOS65+ "cognitive problems" subscale, indicating present cognitive impairment.

Dementia at follow-up was diagnosed in 509(38%) of the patients. In a fully adjusted model, the only factors significantly associated with faster conversion were older age and cognitive problems at baseline, while non-accidental self-injury was linked to lower hazard of conversion. No symptoms significantly predicted conversion, although agitation showed a trend (HR 1.23, 95%CI 0.99;1.52, p= 0.06). Recurrence of depression was not a significant factor after full adjustment.

Sensitivity analysis: predictors of conversion to dementia in patients with normal cognition at baseline

As mentioned above, we performed a sensitivity analysis by excluding patients who scored 2 or higher on HoNOS65+ scale. There were 2644 participants with complete data on baseline cognitive problems. They were followed up for an average of 2.99 years (ranging from 3 months to 11.3 years). Full characteristics of the subsample are presented in Tables 29-30.

In a fully adjusted model, faster conversion to dementia was predicted by higher age, poor physical health, as well as by taking antihyperglycaemic and anticoagulant/antiplatelet medication (HR 1.5, 95%1.16-1.96; HR 1.25, 95%CI 1.044 – 1.5, respectively). Patients who scored high on HoNOS65+ "self-injury" subscale were less likely to convert to dementia during follow-up (HR 0.57, 95%CI 0.43-0.77).

Among the symptoms of depression, in the full model, only **irritability** and **hallucination** remained significantly predictive of faster progression (HR 1.25, 95%CI 1.03-1.51; HR 1.52, 95%CI 1.17-1.97, respectively). Hopelessness was a significant protective factor when adjusted for other symptoms (HR 0.79; 95%CI 0.66-0.94), but not in the fully adjusted model (HR 0.89; 95%CI 0.70 – 1.12).

5.4 Discussion

This study analysed the relationship between depression in the elderly and incident dementia using a cohort derived from the electronic health records of the South London and Maudsley NHS Foundation Trust (SLaM). All patients were diagnosed with major depression by a clinician at baseline and had no diagnosis of MCI/dementia on inclusion. Sensitivity analysis was performed on a cohort of patients who did not have any cognitive decline at baseline, as ascertained by scoring "0" or "1" on the 4-item HoNOS65+ "cognitive problems" subscale.

All-cause dementia during follow-up was diagnosed in 23.9% of the sample. The rate of conversion was 19.4% in patients aged between 65 and 80, and 32.66% in patients aged 80 or above. These figures are significantly higher than the population average, the general prevalence of dementia in the UK being estimated at 7.1% for people aged above 65 (specifically 7.2% in England, and at 20% for people aged over 80 (Wittenberg et al., 2019; $\chi^2 = 1107.8$, $p<0.001$; $\chi^2 = 90.7$, $p<0.001$). This indirectly confirms that depressed patients are more likely to develop dementia, as demonstrated by numerous studies previously.

More than half of the patients in our sample converted to dementia within 3 years of follow-up, and 78% converted by 5 years. There hasn't been an established timeline regarding what constitutes depressive symptoms prodromal to dementia as opposed to independent conditions, and previous studies have reported varying time windows, from 37.4 months to 7-8 years **(**Amieva et al., 2008; Devier et al., 2010; Almeida et al., 2017; Tapiainen et al., 2017). Thus, it is not possible to conclusively attribute the cases of depression in our cohort to prodromal dementia, but it is likely that the majority (78%) which converted within 5 years were in fact prodromal cases.

We aimed to investigate whether late-onset depression was more likely to progress to dementia as opposed to recurrent episodes. Indeed, in univariate analyses, as well as in the model adjusted for demographics and baseline cognition, recurrent depression was associated with a significantly lower likelihood of conversion. However, when further adjusted for HoNOS65+ subscale of "disability associated with physical illness", recurrence lost significance as a protective factor. This is likely due to the true confounding effect of physical illness, where non-recurrent – and therefore late-onset - depression is secondary to disabling physical illness.

Scoring 2 or above on HoNOS65+ "cognitive problems" scale was consistently associated with at least a 2-fold increase in likelihood of conversion (HR 2.21, 95%CI 1.8; 2.72), and an even higher hazard in patients aged 80 or above (HR 2.65; 95%CI 2.061;3.40, $p<0.001$). Out of 520 patients who scored 2 or above on HoNOS65+ cognitive problems scale, 246 (47%) converted to dementia, of them 201(82%) within the first three years. This indicates that HoNOS65+ may be a useful tool in identifying late-life depression prodromal to dementia.

Interestingly, one of the most consistent findings across all models was that scoring 2 or above on HoNOS65+ "non-accidental self-injury" subscale was associated with significantly lower likelihood of conversion to dementia. This was consistent with the validation study findings which showed that the "non-accidental self-injury" subscale distinguished patients with dementia from those with depression. Only the highest score (4) on this subscale assumes the presence of actions directed at self-harm, while scoring "2" or "3" rather reflects having suicidal or auto-aggressive thoughts. While suicidal ideation is not uncommon in dementia (Draper et al., 1998), and some studies showed that executive function, attention and memory may be impaired in depressed non-demented elderly patients with suicidal ideation (Dombrovski et al., 2008; Guiral et al., 2014), it appears that suicidal ideation/self-harm are more specific for actual depressive episodes rather than prodromal dementia. When assessed as an individual symptom, suicidal ideation was not a factor in the finally adjusted model, but univariate models demonstrated a trend for lower likelihood of conversion for suicidal

ideation mentioned at least once recorded in text (HR 0.85, 95%CI 0.72-1.01, p=0.067), and a significantly "protective" effect when mentioned at least twice(HR 0.74, 95%CI 0.59;0.93, p=0.009).

Several studies have investigated the question of whether specific subtypes of depression are associated with increased likelihood of conversion to dementia. A study by Do Couto et al. proved that patients with melancholic depression had higher risk of progression to dementia (Do Couto et al., 2016). Another study reported that increased risk for AD was predicted by appetite loss/weight loss which is a core symptom of melancholic depression (Saha et al., 2016). This could support the risk factor mechanism, since one of the proposed explanations for this mechanism is the glucocorticoid cascade leading to hippocampal atrophy, and it is melancholic depression that has been specifically linked to glucocorticoid abnormalities. However, another study showed no association between melancholic late-life depression and cognitive decline on MMSE. Besides, one more study showed that patients with late-onset melancholic depression exhibited greater cognitive decline compared to those with early-onset melancholic depression, which is not consistent with the accumulating hippocampal damage pathway. We did not find evidence to support the hypothesis that patients with symptoms commonly associated with melancholic depression (i.e. appetite loss or insomnia) could be more likely to progress to dementia. In univariate analyses, insomnia and appetite showed significant yet opposite effects, and neither were significant in a fully adjusted model.

Depressive symptoms most consistently associated with conversion were irritability and hallucination. Hallucination and irritability constitute the symptoms of mild behavioural impairment, a condition which has been tightly linked to prodromal stages of dementia and has been described as a "transitional state between normal ageing and dementia" - however, the diagnosis of MBI assumes that the symptoms are not better explained by other conditions, including major depression (Hwang et al., 2004). Our study shows that in patients with diagnosed depression as well, these two symptoms can predict conversion to dementia. Agitation, on the other hand, was only a marginally significant predictor in patients aged above 80.

The symptom associated with having a "protective" effect in the full sample was feeling hopeless. Despite one previous study reporting hopelessness as one of the most common neuropsychiatric symptoms in MCI (Hwang et al., 2004), this symptom was significantly more prevalent in non-converters (according to exploratory χ^2 associations), and was associated, in all models, with lower hazard of conversion in the whole sample and in patients aged below 80, but not in those above 80. This may indicate that the more "endogenous" affective symptoms are more likely to be features of depression rather than dementia prodrome; on the other hand, patients with emerging cognitive decline may be more likely to be alexithymic and fail to verbalise their feeling of hopelessness.

Our study has several limitations. First, the data did now allow to account for the effect of education, one of the most common factors predicting cognition in the elderly (despite being reflected indirectly by the index of multiple deprivation; Caamaño-Isorna et al., 2006; Xu et al., 2016)**.** Besides, despite having excluded patients with a history of stroke, Parkinson's disease and organic brain conditions, we could only account for the confounding effect of physical illness by using the "Problems related to physical illness/disability" HoNOS65+ score, which reflects disability related to physical conditions rather than the presence of physical conditions. Data on cerebrovascular disorders and diabetes was incomplete. In all of the models, among the strongest and most consistent predictors of conversion were taking anticoagulant/antiplatelet and antihyperglycaemic medication. A study investigating the association between types of antihyperglycaemic medication and dementia showed that while metformin had a protective effect, insulin increased risk of dementia (Bohlken et al., 2018). Similarly, the effect of anticoagulant/antiplatelet medication is not simple either: while oral anticoagulants reduced the risk of dementia in several cohorts, mainly by reducing the risk of strokes, the same wasn't demonstrated for antiplatelet treatment, and combination of OAC and antiplatelet agents increased the risk of dementia (Monghon et al., 2020; Ding et al., 2018; Chen et al., 2018). Therefore, unfortunately, it is not possible to distinguish whether in our sample these variables represented the effect of the medication itself or the underlying conditions.

5.5 Conclusion

We found that patients with recurrent depression were less likely to progress to dementia, however this association was not significant after adjustment for all covariates, therefore it is not possible to conclude with certainty whether age of onset plays a role in the association between depression and dementia. Melancholic depressive symptoms were not linked to higher risk of conversion. Symptoms predicting conversion were hallucination and irritability, while "feeling hopeless" and "non-accidental self-injury" (autoaggressive/suicidal ideation) were associated with lower likelihood of conversion during follow-up. Historical cohort studies using electronic health records can be a useful tool in identifying predictors of dementia.

	Dementia (n=1026)		No dementia (n=2,819)		
	Mean	**SD**	**Mean**	**SD**	**p-value**
Age	73.66	7.23	71.82	7.45	<0.001
Follow-up time	4.24	3.02	4.03	3.03	<0.001
IMD	27.19	11.47	26.55	12.05	0.28

Table 29a. The comparison of baseline characteristics between patients with dementia and no dementia at follow-up (full sample; continuous measures)

		Dementia (n=1026)		No dementia (n=2,819)			
		N	%	N	%	χ^2	p-value
Gender	Female	709	69.10	1,719	61	21.2	<0.001
	Male	317	30.90	1,099	39		
Ethnicity	White	819	80.85	2,253	83.29	3.06	0.08
	Other	194	19.15	452	16.71		
Marital status	Married	283	28.91	896	34.66	15.37	<0.001
	Widowed/Separated	539	55.06	1,237	47.85		
	Single	157	16.04	452	17.49		
Recurrent depression	1 vs 0	231	22.51	701	24.87	2.27	0.13
Severe depression	1 vs 0	100	9.75	332	11.78	3.11	0.078
Psychotic depression	1 vs 0	36	3.51	118	4.19	0.89	0.34

Table 29b. The comparison of baseline characteristics between patients with dementia and no dementia at follow-up (full sample; categorical measures

	Overall sample (n=3845)		Dementia (n=1026)		No dementia (n=2,819)			
Symptom	N positive	%	N positive	%	N positive	%	χ^2	p-value
Feeling helpless	500	13.0	113	11	387	13.73	4.9	0.027
Feeling hopeless	1120	29.1	241	23.49	879	31.18	21.56	<0.001
Feeling worthless	418	10.9%	97	9.45	321	11.39	2.90	0.089
Anhedonia	594	15.4	146	14.23	448	15.89	1.59	0.21
Poor motivation	1484	38.6	386	37.62	1098	38.95	0.56	0.45
Apathy	216	5.6	61	5.95	155	5.50	0.28	0.59
Low mood	2409	62.7	851	82.94	2409	85.46	3.68	0.055
Concentration difficulty	1394	36.3	367	35.77	1027	36.43	0.14	0.71
Agitation	1211	31.5	334	32.55	877	31.11	0.73	0.39
Irritability	848	22.1	246	23.98	602	21.36	3.0	0.083
Low energy	1291	33.6	323	31.48	968	34.34	2.75	0.97
Insomnia	536	13.9	131	12.77	405	14.37	1.6	0.2
Appetite loss	1982	51.5	535	52.14	1447	51.33	0.2	0.66
Anergia	117	3.0	20	1.95	97	3.44	5.67	0.017
Hallucination	344	8.9	102	9.94	242	8.58	1.7	0.19
Delusion	573	14.9	162	15.79	411	14.58	0.87	0.35
Suicidal ideation	740	19.2	161	15.69	579	20.54	11.37	<0.001

Table 30. The comparison of the prevalence of depression symptoms between patients with dementia and no dementia at follow-up (full sample)

	Unadjusted HR's for each predictor (Model 1)	Model 2 (adjusted for demographic factors and recurrence)	Model 3 Model 2+ baseline cognition	Model 4 Model 3+ HoNOS65+ physical illness	Model 5 Model 4+ HoNOS65+ physical illness and non-accidental self-injury	Model 6 Model 6+ medication
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Age (per year increment)	1.08 (1.07-1.09)***	1.08 (1.07-1.08)***	1.07(1.06-1.08)***	1.07 (1.06 – 1.08)***	1.06 (1.06-1.08)***	1.06(1.05-1.07)***
Female gender	1.15(1.00-1.31)*	1.02 (0.89-1.17)	1.03(0.89-1.18)	1.03 (0.88 – 1.19)	0.88(0.85-1.16)	1.044(0.89-1.22)
Non-white ethnicity	1.15(0.98-1.34)	1.31(1.11-1.54)**	1.3(1.06-1.47)**	1.24 (1.04 – 1.48)*	1.21(1.011-1.44)*	1.12(0.93-1.34)
Being widowed	1.28(1.11-1.48)**	1.01(0.87-1.17)	1.01(0.87-1.17)	1.06 (0.90 – 1.25)	1.08(0.92-1.27)	1.049(0.89-1.24)
Recurrent depression	0.68(0.59-0.79)***	0.78(0.67-0.91)**	0.79(0.68-0.92)**	0.88 (0.75 – 1.04)	0.89(0.75-1.048)	0.9(0.76-1.067)
Baseline cognition	2.96(2.46-3.57)***	———	2.34(1.93-2.84)***	2.23 (1.83 – 2.72)***	2.26(1.85-2.75)***	1.35(1.085-1.69)
Physical illness	1.61(1.4-1.86)***	———	———	1.34 (1.16 – 1.56)***	1.35(1.16-1.57)***	1.25(1.06-1.46)**
Non-accidental self-injury	0.57(0.45-0.72)***	———	———		0.61(0.47-0.78)***	0.61(0.48-0.79)***
Antihyperglycaemic medication	1.49(1.23-1.81)***	———	———		———	1.35(1.085-1.69)**
Anticoagulant/antiplatelet medication	1.34(1.19-1.52)***	———	———		———	1.3(1.11-1.51)**

Table 31. Clinical predictors of progression from late-life depression to dementia: results from Cox proportional regression models; *** p<0.001; ** p<0.01; *p<0.05

	Dementia (n=632)		No dementia (n=2,012)		
	Mean	**SD**	**Mean**	**SD**	**p-value**
Age		7.28	75.72	7.57	<0.001
Follow-up time	5.16	2.86	4.17	3.06	<0.001
IMD	26.17	11.6	26.24	11.9	0.97

Table 32a. The comparison of baseline characteristics between patients with dementia and no dementia at follow-up (Sensitivity analysis: no cognitive impairment at baseline; continuous measures)

		Dementia (n=632)		No dementia (n=2,012)			
		N	%	N	%	χ^2	p-value
Gender	Female	438	69.3	1229	61.1	13.94	<0.001
	Male	194	30.7	783	38.9		
Ethnicity	White	517	82.5	1648	84.9	1.42	0.23
	Other	110	17.5	303	15.1		
Marital status	Married	183	30	645	34.3	6.602	0.037
	Widowed/Separated	330	54.2	906	48.2		
	Single	96	15.8	328	17.5		
Recurrent depression	1 vs 0	148	23.4	495	24.6	0.37	0.55
Severe depression	1 vs 0	67	10.6	242	12.0	0.95	0.33
Psychotic depression	1 vs 0	25	3.96	86	42.7	0.12	0.73

Table 32b. The comparison of baseline characteristics between patients with dementia and no dementia at follow-up (Sensitivity analysis: no cognitive impairment at baseline; categorical measures)

	Overall sample (n=2644)		Dementia (n=632)		No dementia (n=2012)			
Symptom	**N positive**	**%**	**N positive**	**%**	**N positive**	**%**	**χ^2**	**p-value**
Feeling helpless	371	14.0	74	11.7	297	14.7	3.72	0.053
Feeling hopeless	876	33.1	175	27.7	701	34.8	11.1	<0.001
Feeling worthless	319	12.1	66	10.4	253	12.6	2.06	0.15
Anhedonia	448	16.9	96	15.2	352	17.5	1.49	0.22
Poor motivation	1124	42.5	262	41.5	862	42.8	0.38	0.54
Apathy	150	5.7	30	4.7	120	5.9	1.71	0.19
Low mood	2395	90.6	552	87.3	1783	88.6	0.75	0.38
Concentration difficulty	1067	40.4	245	38.8	822	40.9	0.87	0.35
Agitation	893	33.8	213	33.7	680	33.8	0.0019	0.96
Irritability	635	24	159	25.2	476	23.7	0.59	0.44
Low energy	991	37.5	228	36.1	763	37.9	0.7	0.4
Insomnia	405	15.3	93	14.7	312	15.5	0.23	0.63
Appetite loss	1505	56.9	359	56.8	1,146	56.9	0.0047	0.95
Anergia	86	3.3	11	1.7	75	3.7	6.03	0.014
Hallucination	253	9.6	69	10.9	184	9.1	1.75	0.19
Delusion	430	16.3	114	18.0	316	15.7	1.92	0.17
Suicidal ideation	582	22.0	113	17.9	469	23.3	8.26	0.004

Table 33. The comparison of the prevalence of depression symptoms between patients with dementia and no dementia at follow-up (full sample)

Chapter 6. Longitudinal associations between depressive symptoms, anxiety and performance across four cognitive domains in the older age: results from the 3-year follow-up of the PROTECT cohort

Abstract

Objective: To investigate associations between depressive symptoms, anxiety symptoms, and performance across four cognitive domains over a 3-year follow-up period.

Methods: A longitudinal prospective cohort (PROTECT) was used to investigate the relationship between depressive symptoms, anxiety symptoms and cognitive function over time. The sample size included 22,277 participants without dementia or MCI at baseline; 8,693 participants had data on all four timepoints (baseline + 3 years of follow-up). Mean age at baseline was 61.73 (IQR 56.52 - 67.16). Depressive symptoms were measured by the PHQ-9 and anxiety by the GAD-7. Paired Associate Learning (PAL), Verbal Reasoning (VR), Spatial Working Memory (SWM) and Digit Span (DS) were used as measures of episodic memory, language, executive function and working memory, respectively. All measures were collected annually using an on-line platform. Latent growth curve (LGCM) models were run; stratified analysis by history of depression was also conducted.

Results

Depressive symptoms were associated with worse longitudinal performance on DS (β = -.037, p<0.001), PAL (β =*-0.020, p<0.05),* and *VR* (β = -0.53, p<0.001) . Anxiety symptoms were independently associated with worse longitudinal functioning on SWM (β = -0.017; p=0.018), DS (β = -0,022, p<0.05), and VR (β = -0.27; p<0.001). The effect of depressive symptoms on PAL performance and lost significance after stratification by history of depression. Longitudinal effects of both depressive and anxiety symptoms on VR function were more prominent in participants who reported a history of depression. The associations between depressive symptoms and DS performance were reciprocal, as confirmed by several models. However, when "clinically significant depressive symptoms" (PHQ-9≥8) were assessed in CLPMs, only depression predicted worse performance on DS (β = -.16, p<0.001).

Conclusion The study found significant longitudinal associations between depressive symptoms, anxiety symptoms, and worse performance in DS, SWM and VR.

6.1 Introduction

Geriatric depression represents a serious healthcare problem, affecting around 3% of elderly people in the general population and up to 7% in outpatient medical settings **(**Reynolds et al., 1996; Birrer et al., 2004; Mahmoud et al., 2016). One of the key challenges presented by patients with geriatric depression is associated cognitive decline. About 30% of elderly patients with severe depressive symptoms were shown to also have cognitive impairment in a birth cohort study (Arve et al., 1999). While a certain degree of cognitive deterioration can be seen as part of normal ageing, in patients with late-life depression (LLD), decline in cognitive functioning was shown to be accelerated (John et al., 2018). Furthermore, LLD has been consistently associated with higher likelihood of subsequent manifestation of dementia compared to the general population, and has been listed among the potentially modifiable risk factors for dementia in the latest Lancet Commission on Dementia (Livingston et al., 2020).

Despite evidence supporting the link between LLD and cognitive decline, currently, the exact mechanisms of this association are not clear. Plausible mechanisms include depression acting as a risk factor, i.e., increasing the biological vulnerability to cognitive impairment; depression being a manifestation of a prodromal stage of dementia, and also depressive symptoms occurring as a reaction to emerging cognitive deficits (Butters et al., 2008). Studies examining the temporal relationship between depressive symptoms and cognitive impairment have not been able to clarify the exact nature of the association in relation to these potential mechanisms.

Research into the association between depression and cognitive decline is further complicated by the fact that cognition is a broad term, encompassing a range of domains such as episodic memory, executive functions including working memory, verbal fluency, processing speed, and visuospatial skills, which might not be affected at the same time (Harvey et al., 2019). A number of studies have demonstrated that elderly depressed patients perform worse on tests of executive functioning, working memory and processing speed (some studies attribute the latter two domains to executive functioning) compared to non-depressed ones. This impairment may persist even when the depressive symptoms are in remission and be associated with worse response to medication (Nakano et al., 2008; Barch et al., 2012). However, results are not consistent across studies with some research showing no such impact of LLD on episodic memory (Lohman et al., 2014; Jayaveera et al., 2016; Klojčnik et al., 2017; Wilson et al., 2018).

A previous study by Desai et al., using 1-year follow-up data from the PROTECT cohort, demonstrated that depressive symptoms at baseline were associated with worse functioning on measures of Verbal Reasoning, Paired Associate Learning, Digit Span and Spatial Working Memory at follow-up, and that the relationship with the latter two domains was reciprocal, such that impaired function at baseline predicted worse depressive symptoms at follow-up (Desai et al., 2020).

Using the PROTECT cohort, the present chapter seeks to investigate the following:

6.1.1 Objectives

1. To explore cross-sectional associations between symptoms of depression, anxiety and cognition on four cognitive domains at baseline
2. To explore the role of age of onset of depression on cognitive performance at baseline
3. To investigate the longitudinal relationship between depressive symptoms, anxiety symptoms and cognition on four cognitive measures over three years of follow-up
4. To examine whether there's a difference in the longitudinal associations between depressive, anxiety symptoms and cognitive performance between patients with and without a history of depression

6.2 Methods

6.2.1 Study Design and Participants

Longitudinal data from the on-going Platform for Research Online to investigate Genetics and Cognition in Ageing Study (www.protectstudy.org.uk) were used. PROTECT comprises a large community-based cohort of participants who were cognitively healthy at baseline.

6.2.2 Data Collection

Participants were recruited by media campaign full details of which have been published previously. Inclusion criteria were being a UK resident, aged 50+, with a working command of English and access to the Internet via a computer. Participants self-reporting a pre-existing diagnosis of dementia at baseline were excluded; participants were further excluded from the present analysis if they reported having MCI, Parkinson's disease, or a history of stroke. Baseline data collection commenced in November 2015 with on-going follow-up data collected annually. The current study utilised baseline data plus data from the first three waves of data collection. The PROTECT study received ethical approval from the London Bridge NHS Research Committee (Ref: 13/LO/1578).

6.2.3 Covariates

Demographic characteristics, including age, sex, ethnicity, education level, and employment, were collected at baseline. Height and weight were also collected at baseline and used to derive BMI scores, as well as information on physical health and diagnosed medical conditions.

6.2.4 Mental Health Measures

Mental health symptoms were measured at baseline and each subsequent follow-up wave. Depressive symptoms were measured using the 9-item Patient Health Questionnaire (PHQ-9) scale. This questionnaire has been shown to be valid and reliable (Kroenke et al., 2001). Scores range from 0 to 27 with higher scores indicating higher levels of depression symptomology. Clinically relevant depressive symptoms were defined as a score of ≥8 on the PHQ-9, which has shown to be the optimal cut-off score for a diagnosis of depression (Manea et al., 2012). Anxiety symptoms were measured using the 7-item Generalised Anxiety Disorder (GAD-7) questionnaire. The GAD-7 has also been found to have good validity and reliability. This inventory captures anxiety symptoms on a range of scores between 0 and 21, with higher scores indicating higher anxiety levels. Clinically relevant anxiety was defined as a score of ≥8 this cut off score has been shown to have good sensitivity and sufficient specificity in a recent meta-analysis (Plummer et al., 2016).

Variables categorising participants based on past depression history were created using a set of self-report questions. The key questions used to establish a positive history of depression were "Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row"; and "Have you ever had a time in your life lasting two weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure?", as well as "Have you ever been diagnosed with one of the following conditions?" where depression was the first option. A participant was classified as having had a history of depression if they answered "yes" to having been diagnosed with depression, and "yes" to at least one of the first two questions addressing core symptoms (according to DSM criteria, either of the core symptoms must be present for a diagnosis of depression). Only participants who answered "no" to all three questions were classified as having no history of depression.

To investigate the impact of age-of-onset of depression a subgroup of participants aged 60+ was selected and divided into five groups: (1) never-depressed (ND), (2) history of depression with late onset and clinically significant depressive symptoms at baseline ("LOD-d"), (3) history of depression with late onset and symptoms in remission at baseline ("LOD-r") , (4) history of depression with early/midlife (<55) onset and clinically significant depressive symptoms at baseline ("EOD-d"), (5) history of depression with early/midlife onset and symptoms in remission at baseline ("EOD-r").

6.2.5 Cognitive Measures

Traditional cognitive tests were adapted for online completion and found to be valid and reliable (Wesnes et al., 2017). A battery of four cognitive measures was completed at each testing occasion. The four measures comprised: Paired Associate Learning (PAL), Verbal Reasoning (VR), Spatial Working Memory (SWM) and Digit Span (DS). A detailed description of this cognitive battery has been previously reported (See Chapter on Methods). In brief, the PAL is a test of episodic memory and is found to be particularly sensitive to deficits in new learning; values (post-winsorising) ranged from 2 to 7. The test has been found sensitive to deficits seen in memory and learning in MCI and preclinical AD (Fowler et al., 2010; Bondi et al., 2009). VR is a measure of general intelligence based on Baddely's Grammatical Reasoning Test (Baddeley, 1968); values ranged from 11 to 54. The SWM is a self-ordered search task that is sensitive to deficits in executive function (Owen et al., 1990); values raged from 4 to 12. The DS is a measure of attention and working memory (Lezak et al., 2012); values ranged from 4 to 12.

6.2.6 Statistical analysis

6.2.6.1 Descriptive statistics

Key outcome variables were assessed for normality of distribution using histograms and Q-Q plots, and by listing extreme values which exceeded three standard deviations away from the mean. Assumptions of linear modelling were violated for scores on the PHQ-9 and GAD-7, therefore analyses including these variables were bootstrapped using 1000 bootstrap draws. Due to a large number of outliers on measures of cognition, cognitive variables were winsorised (i.e. outliers were replaced with the mean score +/− 2.5 SD).

Univariate associations between demographic characteristics and cognitive performance were analysed using independent sample t-tests and Mann-Whitney U tests for parametric and non-parametric distributions of continuous outcomes, respectively, or $\chi 2$ tests for comparing proportions.

6.2.6.2 Cross-sectional (baseline) associations

Cross-sectional associations were analysed using multiple linear regression; the outcome variables were baseline values of VR, DS, PAL and SWM. The assumption of independence of observations was checked using the Durbin-Watson statistic and multicollinearity was excluded by inspecting correlation coefficients and Tolerance/VIF values. Heteroscedasticity was assessed using scatterplots of predicted residuals, and the Breusch-Pagan / Cook-Weisberg test.

All baseline regression models were adjusted in a stepwise manner: for GAD score (Model 1), further for all other cognitive domains (Model 2), for demographics (Model 3), and finally for BMI and physical health (Model 4).

6.2.6.2.1 Baseline cognitive performance across groups based on mental health history

To investigate baseline associations between groups based on mental health history and cognitive performance, univariate analyses were performed using one-way ANOVA with Bonferroni adjustment for multiple comparisons, or Bonferroni-adjusted Dunn's test if equal variances assumptions was violated. Adjusted analyses were performed using one-way ANCOVA with Bonferroni adjustment for multiple comparisons, and further verified using linear regression with dummy-coded variables for levels of "history of depression".

6.2.6.3 Cross-Lagged Panel Model Analysis of the association between depression/anxiety at baseline and cognitive performance at Year 3

Longitudinal associations between measures of cognition and depression were investigated using bootstrapped SEM cross-lagged panel models. Each analysis was performed in three stages: as univariate models assessing unadjusted cross-lagged associations between PHQ-9 or GAD-7 score and one of the cognitive measures (Model 1), as a model including PHQ-9, GAD-7 scores, and all four cognitive measures (Model 2), and finally a model further adjusted for demographics, BMI and physical health (Model 3).

Model fit was assessed using the chi-square ($\chi 2$) statistic and the ratio of the $\chi 2$ to degrees of freedom (DF). The $\chi 2$/DF ratio below 2 or 3 is considered acceptable fit (Arbuckle & Wothke, 1999). Other parameters used for the assessment of model fit were the Comparative Fit Index (CFI; Bentler, 1990) and the Root Mean Square Error of Approximation (RMSEA; Browne & Cudeck, 1992). Values of CFI over 0.90 and of RMSEA below 0.05 indicate good fit.

The analysis of the longitudinal association between binary measures of "clinically significant" depression and anxiety was performed using GSEM models assuming Bernoulli distribution for binary variables of depression/anxiety and Gaussian distribution for cognitive measures, and using the same three steps as described above.

6.2.6.4 Four-Wave Cross-Lagged Panel Models analysing the relationship between depression/anxiety and cognitive performance on each of the four domains

In the next step of the analysis, we performed four-wave cross-lagged panel models, which allows to assess lagged effects across all four time points, autoregressive effects, as well as the correlation of error terms at T1, T2 and T3. As a first step, four-wave CLPMs were performed separately for the associations between depressive symptoms or anxiety symptoms and one of the four cognitive measurements. Wald statistic was used to analyse the stability of cross-lagged effects over time.

As a second step, a four-wave CLPM incorporating anxiety, depressive symptoms, and all four cognitive measures was performed, also using first unconstrained and then constrained cross-lagged effects. This model was adjusted for age and gender. Model fit was assessed as described in 2.6.3.

6.2.6.5 Latent growth curve models

As a final step, the relationship between depressive symptoms, anxiety symptoms and four measures of cognition across four waves of measurement was analysed using latent growth curve models (LGCM), with latent variables representing intercept and slope for each of the variables. First, six separate growth curve models were constructed for depressive symptoms, anxiety, DS, PAL, SWM and VR. An example of such model for PHQ-9 scores shown in Figure 8. The intercept of these models was set as the first wave of measurement.

The full model included all six latent growth curves (depressive symptoms, anxiety, as well as the intercepts and slopes for all four cognitive measures), allowing all intercepts and slopes to intercorrelate. In addition, the model was adjusted for age and gender. Model fit was assessed as described in 6.3.6.3.

6.2.6.6 Longitudinal cognitive performance across groups based on mental health history

To analyse whether there is a difference in longitudinal cognitive performance between never-depressed and previously depressed participants, the sample was stratified into participants with and without past history of depression; standard cross-lagged models (as described in 6.3.6.3) and LGMs (as described in 2.6.5) were performed in the stratified sample.

6.2.7 Missing data

6.2.7.1 Baseline

After excluding participants with a history of stroke and diagnoses of MCI and Parkinson's disease, the number of participants with complete cognitive data at baseline was 22,277. Demographic data (age, sex) were available for 22,256(99.9%) of those; and data on education, ethnicity and employment status was available for 21,929 (98.4%) of those.

Depression and anxiety scores were available for 20809 (93.4%) and 20,713(92.9%) people, respectively. Missingness on depression scores was predicted by lower scores on DS, VR, SWM, by education level, and also marginally by age (p=0.053); missingness on anxiety scores was predicted by lower scores on SWM, VR, and by higher age.

Information on BMI (after values below 15 and above 50 were dropped as corresponding to either extremely low weight or extreme morbid obesity and therefore likely representing errors) was available for 21444 participants (96.3%) at baseline. Missingness on BMI was predicted by performance on SWM and VR.

For cross-sectional analysis of baseline associations, missing data on depression, anxiety and BMI was completed using multiple imputation.

6.2.7.2 Follow-up

Cognitive performance data at years 1-3 was available for 15,334 (68.8%); 11,410 (51.2%) and 8,693(39%), respectively. Comparison of baseline characteristics between patients with complete and incomplete 3-year follow-up data is presented in Table 1. In brief, subjects who dropped out by year 3 had worse baseline performance on all four cognitive tests, and higher depression and anxiety scores.

Longitudinal analyses relying on SEM models were performed using the full information maximum likelihood (FIML) method, which allowed for the use of all available data without imputation.

6.3 Results

6.3.1 Descriptive statistics

Most participants were female (73.9%); median age at baseline was 61.7 years (IQR 56.5-67.2). Most participants were white (98.1%) and had an undergraduate degree or above (52.1%); half of participants were retired at the time of enrolment (50.7%).

The vast majority of participants did not have even mild depressive symptoms at baseline (median PHQ9 score 2, IQR 0-4). However, 1540 participants (7.4%) had clinically significant depressive symptoms at baseline. Clinically significant anxiety was reported by 732(3.5%) participants for cut-off 8.

Median BMI value was 25.2 (IQR 22.7-28.3); 5,024 (24.3%) participants reported having been diagnosed with hypertension, 938 (4.3%) with hypercholesterinaemia, 924 (4.3%) with some form of heart disease, 804 (3.7%) with diabetes. All of these conditions were associated with worse cognitive performance; hypertension and heart disease were independent predictors of worse performance on all cognitive domains.

Full descriptive statistics for the whole sample are reported in Table 31.

		Whole sample	Complete follow-up	Incomplete follow-up	P-value (for comparison between subjects with complete and incomplete FU data)
Numerical measures					
Age	Median, IQR	61.73 (56.52 - 67.16)	62.37(57.24- 67.50)	61.42(56.15- 66.95)	<0.001
BMI	Median, IQR	25.16(22.71- 28.34)	24.80(22.52 - 27.90)	25.34(22.86-28.59)	<0.001
DS	Mean, (SD)	7.33(1.39)	7.40(1.33)	7.28(1.42)	<0.001
PAL	Mean, (SD)	4.47(.77)	4.52(.72)	4.44(.79)	<0.001
SWM	Mean, (SD)	7.36(2.35)	7.59(2.09)	7.22(2.49)	<0.001
VR	Mean, (SD)	31.40(9.05)	32.37(8.76)	30.83(9.18)	<0.001
PHQ-9	Median (Min-Max)	2(0-27)	2(0-25)	2(0-27)	<0.001
GAD-7	Median (Min-Max)	0(0-21)	0(0-21)	0(0-21)	<0.001
Categorical measures (N, %)					
Gender	Male	5,809(26.10)	2,046(24.66)	3,763(26.96)	<0.001
	Female	16,447(73.90)	6,252 (75.34)	10,195(73.04)	
Ethnicity	White	21,504(98.06)	8,171(98.47)	13,333(97.81)	0.001
	Other	425(1.94)	127 (1.53)	298(2.19)	
Education	Secondary	3,516 (16.03)	1,138 (13.71)	2,378 (17.45)	<0.001
	Post-Secondary	2,574 (11.74)	952 (11.47)	1,622 (11.90)	
	Vocational Qualification	4,412 (20.12)	1,677 (20.21)	2,735 (20.06)	
	Undergraduate Degree	7,056(32.18)	2,779 (33.49)	4,277 (31.38)	
	Post-graduate Degree	3,628 (16.54)	1,436 (17.31)	2,192 (16.08)	
	Secondary	3,516 (16.03)	1,138 (13.71)	2,378 (17.45)	
Employment	Employed(full-time)	4,352 (19.85)	1,317 (15.87)	3,035 (22.27)	<0.001
	Employed(part-time)	3,535 (16.12)	1,335 (16.09)	2,200 (16.14)	
	Self-employed	2,265 (10.33)	809 (9.75)	1,456 (10.68)	
	Retired	11,111 (50.67)	4,642 (55.94)	6,469 (47.46)	
	Unemployed	666 (3.04)	195 (2.35)	471 (3.46)	
PHQ-9≥8	1 vs 0	1,540 (7.40)	490 (6.08)	1,050 (8.23)	<0.001
GAD-7≥8	1 vs 0	732 (3.53)	226 (2.80)	506 (4.00)	<0.001
Previous depression	1 vs 0	5,307 (35.38)	1,848 (32.05)	3,459 (37.47)	<0.001
Hypertension	1 vs 0	5,024 (24.34)	1,953 (23.62)	3,071 (24.82)	0.049
Heart disease	1 vs 0	924 (4.29)	317 (3.83)	607 (4.57)	0.009
Diabetes	1 vs 0	804 (3.73)	241 (2.91)	563 (4.24)	0.009

Table 34. Baseline characteristics of the whole sample, participants with complete and incomplete follow-up data.

6.3.2 Baseline associations between cognition, depression and anxiety: PHQ9 and GAD7 scores

In univariate models, higher depressive symptoms were associated with worse performance on DS (β = -.024, p<0.001), SWM (β = -.039, p=0.023) and much more weakly with PAL (β = -.007, p<0.001), while higher anxiety scores were associated with worse performance on DS (β = -.023, p<0.001), SWM (β = - 0.064, p<0.001), PAL (β = - 0.011, p<0.001) as well as VR(β = -.063, p=0.012).

In a model including both GAD7 and PHQ9 scores, the association with DS was only significant for depressive symptoms (β = -.025, p<0.001); however, the association with PAL (β = -.007, p<0.001), SWM (β = -.053, p<0.001) and VR (β = -.088, p = 0.005) scores only remained significant for anxiety. Surprisingly, after adjusting for anxiety, depressive symptoms were mildly positively associated with VR performance.

In models fully adjusted for the remaining three cognitive test scores, demographics, BMI, and physical health, depressive symptoms were negatively associated with performance on DS (β = -0.021, p<0.001) and PAL (association with PAL became significant after adding BMI in the model; β= -0.005, p=0.019), and positively with VR (β = 0.1, p<0.001). Anxiety remained significantly negatively associated with VR (β = -.76, p=0.034). SWM scores were only negatively associated with GAD-7 scores. Fully adjusted models are illustrated in Fig.15a-d.

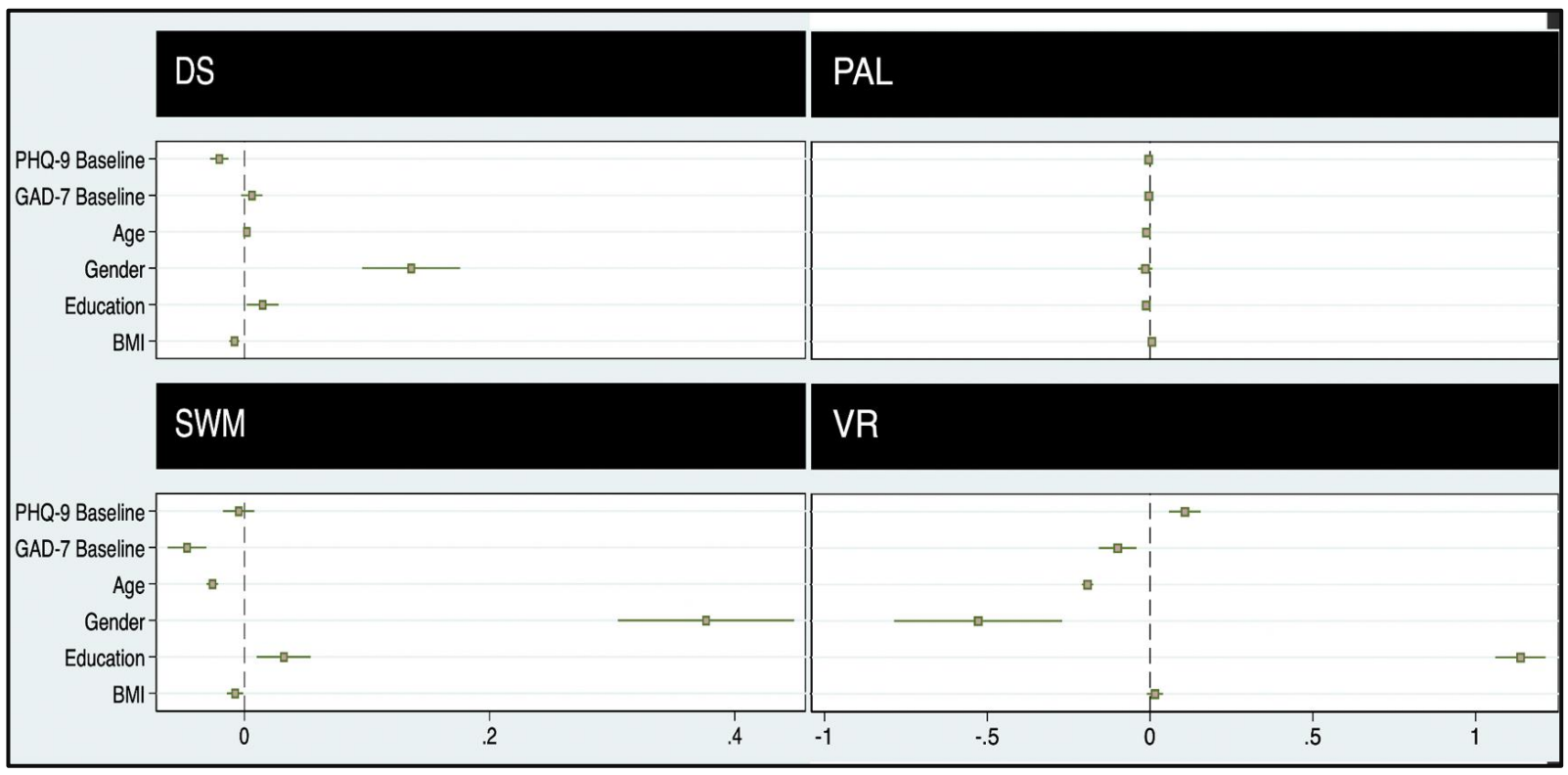


Fig. 15a-d. Baseline associations between PHQ-9 and GAD-7 scores and performance on cognitive domains (fully adjusted model). The coefficients for three other cognitive domains (all significant at p<0.001), ethnicity, hypertension and heart omitted for illustration purposes.

6.4.2.1 Baseline associations between cognition, depression and anxiety: clinically significant depressive/anxiety symptoms (PHQ9/GAD7 ≥8)

When categorical measures of "clinically significant depressive symptoms" were analysed as a predictor, univariately, depression was a significant predictor of worse performance on DS (β = -.24, p<0.001), PAL (β = -.079, p<0.001) and SWM (β -.042, p<0.001). Clinically significant anxiety symptoms were associated with worse performance on all four domains at high levels of significance (p<0.001).

In a model including both clinically significant depression and anxiety, DS, SWM and PAL were significantly negatively associated with both – although DS was more strongly associated with depression (β = -.22, p<0.001 for depression vs. β = -.13, p<0.001 for anxiety) , while SWM with anxiety (β = -.28, p<0.001 for depression vs. β = -.54, p<0.001 for anxiety).

In fully adjusted models, depression was associated with worse performance on DS (β = -0.15, p <0.001), PAL (β = -0.054, p =0.007), and SWM (β = -0.21, p =0.001). Anxiety was independently associated with worse SWM (β = -0.41, p <0.001) and VR (β = -0.76, p =0.034) scores. Fully adjusted associations are illustrated in Fig. 16a-d.

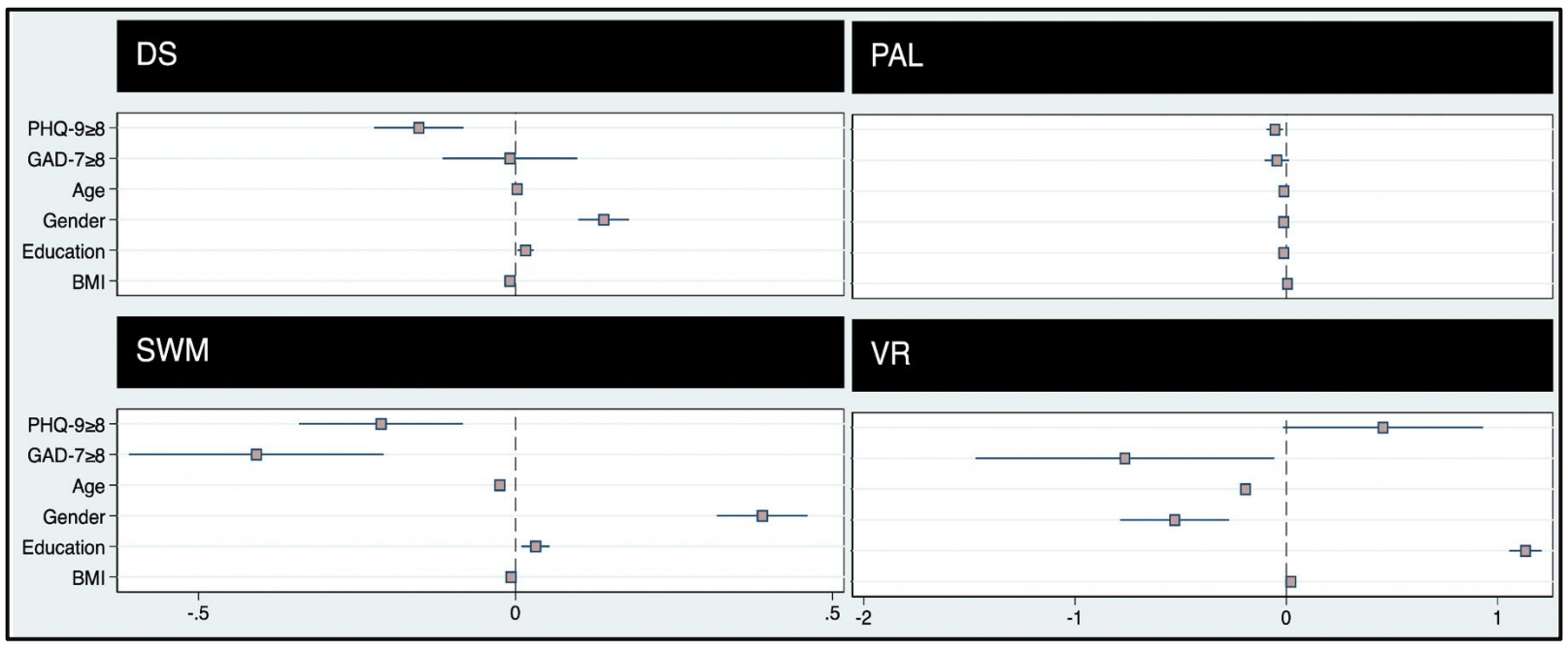


Fig. 38a-d. Baseline associations between clinically significant depressive and anxiety symptoms and performance on cognitive domains (fully adjusted model). The coefficients for three other cognitive domains (all significant at p<0.001), ethnicity, hypertension and heart disease not included for illustration purposes.

6.3.3 The effect of history of depression on cognitive performance at baseline

In order to investigate the role of history of depression in the association between depression in late life and cognitive performance, we limited the sample to those aged 60 or above (to match the criterion of "late-onset depression"). Of those, sufficient information about mental health history was available for 8,567 participants. They were divided into five groups as described above: never depressed, including not depressed (PHQ9≤8) at baseline (n = 5,788); late onset (age 60 or above) and depressed at baseline (n = 112), late onset, remission at baseline (n = 107), early or midlife onset (age <60), depressed at baseline (n=336); and early-onset in remission at baseline (n = 2,224). Descriptive statistics and comparison of demographic characteristics between the groups are presented in Table 32.

There were significant differences between the groups for all four cognitive measures.

Participants with EOD-d performed worse on DS than never-depressed participants (β = -.31, p<0.001 in a fully adjusted model), and EOD-r participants (β = -.22, p=0.006 in a fully adjusted model). The same was observed for SWM performance (β = -.41, p=0.001; β = -.27, p=0.037, respectively).

EOD-d participants also performed worse on PAL compared to ND participants (β = -.10, p=0.009 in a fully adjusted model). Interestingly, EOD-r participants performed much better on VR compared to ND participants (β = 1.41, p<0.001). Associations from fully adjusted models are presented in Fig.17.

		Never-depressed (n = 5,788)[a]	Late-onset (PHQ-9≥8)[b]	Late-onset, remitted (PHQ-9<8)[c]	Early-onset (PHQ-9≥8)[d]	Early-onset, remitted (PHQ-9<8)[e]	
Numerical measures							
Age	Median(IQR)	66.31(63.03- 70.19)	65.81(62.82-69.43)	68.89(65.71- 72.26)	64.50(62.26- 68.34)	65.17(62.49- 68.78)	[a] vs [c]/[a] vs [d]/[a] vs [e]/[b] vs [c]/[c] vs [d]/[d] vs [e]: p<0.001 [b] vs [d] : p<0.05
BMI	Median(IQR)	24.93(22.67 - 27.69)	27.34(23.47- 30.36)	25.98(23.42 - 29.13)	27.34(23.89 - 31.62)	25.35(22.85 - 28.60)	[a] vs [b]/[a] vs [d]/[a] vs [e]/[d] vs [e] :p<0.001 [a] vs [c]/[b] vs [e]/[c] vs [d] :p<0.05
PHQ-9	Median(IQR)	1(0-2)	9.5(8-11)	3(1-4)	10(9-13)	2(1-4)	[b] vs [d] : p<0.01*
GAD-7	Median (IQR)	0 (0-1)	4(2-6)	0.5(0-3)	5(3-9)	0(0-3)	[b] vs [d] :p<0.001*
Categorical measures (N, %)							
Gender	Male	2,121 (36.67)	46 (41.07)	37 (34.58)	67 (19.94)	417 (18.75)	[a] vs [d]/[b] vs [d]/[a] vs [e]/[b] vs [e]/[c] vs [e] :p<0.001 [c] vs [d] :p<0.01
	Female	3,663 (63.33)	66 (58.93)	70 (65.42)	269 (80.06)	1,807 (81.25)	
Ethnicity	Non-White	91 (1.58)	1 (0.89)	3 (2.83)	6 (1.80)	27 (1.21)	n/s
	White	5,683 (98.42)	111 (99.11)	103 (97.17)	328 (98.20)	2,196 (98.79)	
Education	Secondary	1,039 (17.99)	28 (25.00)	34 (32.08)	66 (19.76)	353 (15.88)	[c] vs [e] :p<0.001 [a] vs [c]/[a] vs [e] :p<0.01 [c] vs [d] :p<0.05
	Post-Secondary	639 (11.07)	14 (12.50)	7 (6.60)	49 (14.67)	253 (11.38)	
	Vocational Qualification	1,125 (19.48)	28 (25.00)	22 (20.75)	64 (19.16)	484 (21.77)	
	Undergraduate Degree	1,884 (32.63)	24 (21.43)	30 (28.30)	94 (28.14)	668 (30.05)	
	Post-graduate Degree	853 (14.77)	13 (11.61)	9 (8.49)	54 (16.17)	382 (17.18)	
	Doctorate	234 (4.05)	5 (4.46)	4 (3.77)	7 (2.10)	83 (3.73)	
Employment	Employed(full-time)	392 (6.79)	12 (10.71)	3 (2.83)	34 (10.18)	130 (5.85)	[a] vs [d]/[a] vs [e]/[d] vs [e] :p<0.001 [a] vs [b]/[a] vs [c] :p<0.01 [b] vs [c]/[b] vs [e]/[c] vs [d]/[c] vs [e] :p<0.05
	Employed(part-time)	553 (9.58)	13 (11.61)	11 (10.38)	45 (13.47)	269 (12.10)	
	Self=employed	420 (7.27)	14 (12.50)	4 (3.77)	24 (7.19)	184 (8.28)	
	Retired	4,369 (75.67)	70 (62.50)	84 (79.25)	218 (65.27)	1,614 (72.60)	
	Unemployed	40 (0.69)	3 (2.68)	4 (3.77)	13 (3.89)	26 (1.17)	
Hypertension	1 vs 0	1,635 (29.71)	41 (39.42)	41 (42.27)	94 (30.82)	610 (29.68)	[a] vs [c]/[c] vs [e] :p<0.01 [a] vs [b]/[b] vs [e]/[c] vs [d] :p<0.05
Heart disease	1 vs 0	352 (6.11)	11 (9.82)	11 (10.38)	18 (5.42)	140 (6.32)	n/s
Diabetes	1 vs 0	245 (4.25)	8 (7.14)	4 (3.77)	24 (7.23)	119 (5.37)	[a] vs [c]/[a] vs [e] :p<0.05

Table 35. The comparison of baseline clinical and demographic characteristics between groups based on history of depression. Comparison of depressive and anxiety symptoms severity is presented only for the two groups with clinically significant depressive symptoms.

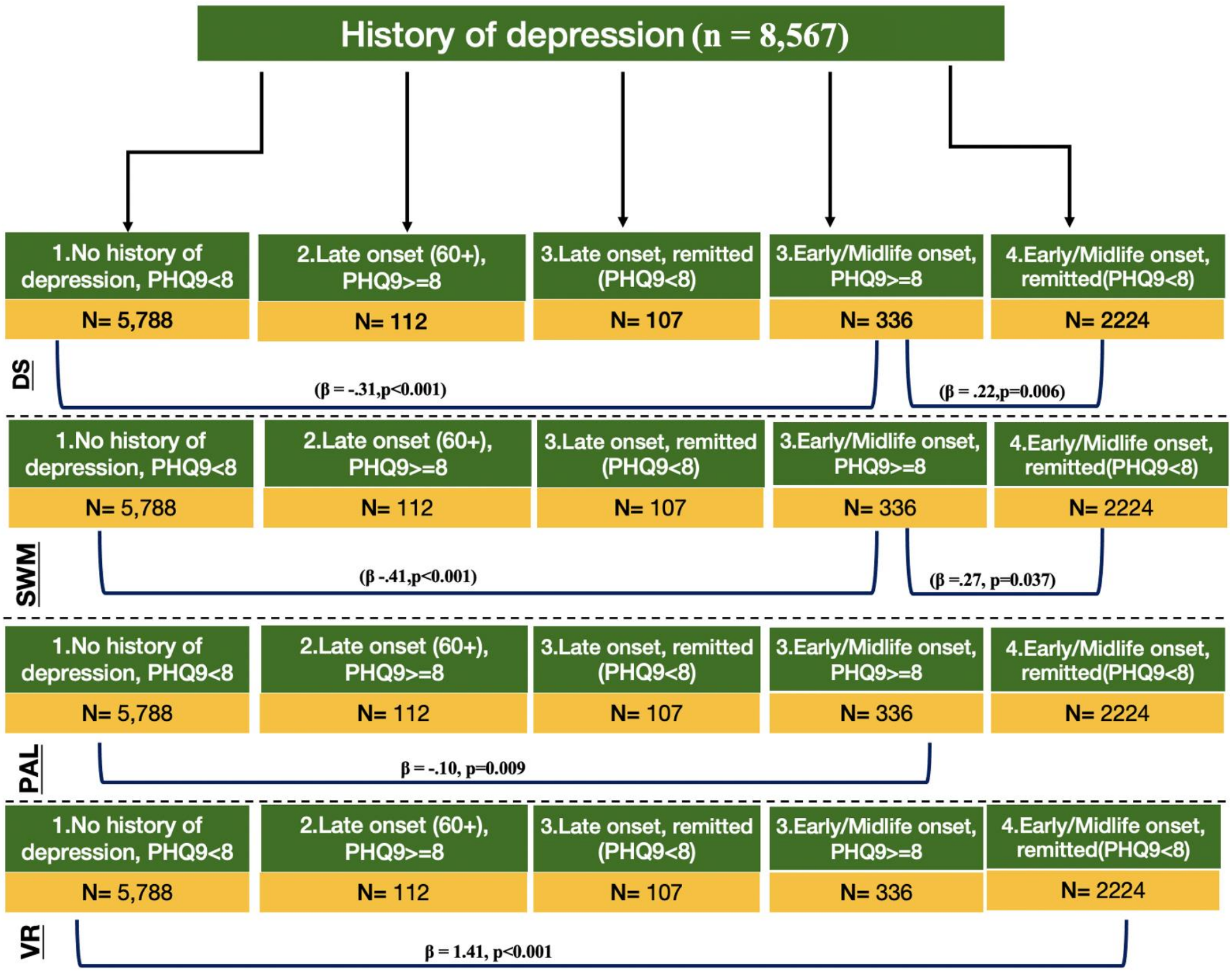


Fig.39. Associations that remained significant after adjustment for demographics, other cognitive domains, and anxiety; all coefficients are presented for comparison of a group of higher order vs group of lower order (e.g. 2 vs 1)

6.3.4 Standard three-year cross-lagged panel models

6.3.4.1 PHQ-9 and GAD-7 scores

Unadjusted cross-lagged panel models (Model 1) were just identified. In these models, baseline depressive symptoms predicted poorer performance at year three on DS (β = -.019, p<0.001), SWM (β = -.026, p<0.001), PAL(β = -.008, p=0.003) and VR (β = -.096, p<0.001).

The association between depressive symptoms and DS and SWM scores was reciprocal, and the effect of cognition on depressive symptoms was stronger than the opposite (poorer DS and SWM performance predicted higher PHQ-9 score: β = -.066, p=0.003; β = -.032, p=0.021, respectively).

Higher anxiety scores and performance on DS, SWM, and PAL also had a reciprocal relationship, however no association was observed for VR (see Table 33).

The model incorporating the effects of both anxiety and depression and all four cognitive measures (Model 2) had a good fit ($\chi2$ = 0.8.99, p = 0.11; RMSEA = 0.006, CFI = 1.000). In this model, only depressive symptoms, not anxiety, predicted worse performance on DS (β = -.022, p<0.001), SWM (β = -.024, p=0.005), and VR (β = -.12, p<0.001). Depressive and anxiety symptoms were both predicted by worse DS performance at baseline (β = -.056, p=0.013; β = -.041, p=0.034). The model is presented in Fig.4a.

Finally, the fully adjusted model (Model 3) also had a good fit ($\chi2$ = 11.32, p = 0.13; RMSEA = 0.005, CFI = 1.000). Baseline depressive symptoms predicted worse performance on all four domains at follow-up. No effect of anxiety on longitudinal cognitive performance or reciprocal associations were observed (See Fig.18).

	Model 1(unadj.)				**Model 2**				**Model 3**			
	β	**SE**	**95% CI**	**p-value**	***β***	**SE**	**95% CI**	**p-value**	***β***	**SE**	**95% CI**	**p-value**
PHQ-9 (0) → DS(3)	**-.019**	**.0034**	**-.026; -.012**	**<0.001**	**-.022**	**.0044**	**-.031; -.014**	**<0.001**	**-.018**	**.004**	**-.026; -.009**	**<0.001**
DS(0) →PHQ-9 (3)	**-.066**	**.023**	**-.11; -.021**	**0.004**	**-.054**	**.024**	**-.10; -.0074**	**0.023**	-.044	.024	-.09; .003	0.069
PHQ-9(0) → PAL(3)	**-.0076**	**.0025**	**-.012; -.0027**	**0.002**	-.0063	.0035	-.013; .00055	0.071	**-.008**	**.0034**	**-.015; -.0015**	**0.017**
PAL(0) → PHQ-9(3)	-.078	.043	-.163; .0074	0.073	-.031	.048	-.12; .062	0.51	-.037	.048	-.13; .057	0.44
PHQ-9(0) → SWM(3)	**-.026**	**.0069**	**-.039; -.012**	**<0.001**	**-.024**	**.0087**	**-.041; -.0073**	**0.005**	**-.020**	**.0085**	**-.037; -.0034**	**0.019**
SWM(0) → PHQ-9(3)	**-.032**	**.015**	**-.062; -.0028**	**0.032**	-.016	.016	-.048; .015	0.31	-.010	.016	-.042; .022	0.53
PHQ-9(0) → VR(3)	**-.096**	**.024**	**-.143; -.048**	**<0.001**	-.12	.032	-.19; -.061	<0.001	**-.096**	**.032**	**-.16; -.034**	**0.003**
VR (0) →PHQ-9(3)	-.0043	.0035	-.011; .0026	0.22	.0011	.0038	-.0064; .0087	0.77	.0034	.004	-.0043; .011	0.39
GAD-7(0) → DS(3)	**-.013**	**.0041**	**-.021; -.0047**	**0.002**	.0048	.0053	-.0057; .015	0.371	.0011	.0054	-.0094; .012	0.83
DS(0) →GAD-7 (3)	**-.067**	**.021**	**-.11; -.026**	**0.001**	**-.047**	**.021**	**-.087; -.0036**	**0.033**	-.040	.022	-.082; .0019	0.061
GAD-7(0) → PAL(3)	**-.0070**	**.0031**	**-.013; -.00093**	**0.024**	.00086	.0043	-.0075; .0092	0.84	-.0032	.0043	-.012; .005	0.45
PAL(0) → GAD-7(3)	**-.094**	**.041**	**-.18; -.013**	**0.024**	-.044	.044	-.13; .043	0.32	-.061	.046	-.151; .028	0.18
GAD-7(0) → SWM(3)	**-.021**	**.0084**	**-.037; -.0042**	**0.014**	-.0027	.011	-.024; .018	0.80	-.014	.010	-.034; .0064	0.18
SWM(0) → GAD-7(3)	**-.034**	**.013**	**-.060; -.0082**	**0.010**	-.022	.014	-.049; .0061	0.13	-.021	.014	-.049; .0074	0.148
GAD-7(0) → VR(3)	-.024	.030	-.082; .035	0.432	**.086**	**.039**	**.0099; .16**	**0.027**	.018	.039	-.058; .094	0.64
VR (0) →GAD-7(3)	-.0033	.0031	-.0093; .0027	0.284	.00014	.0033	-.0063; .0066	0.97	-.0008	.0034	-.0076; .0059	0.81

Table 36. Cross-lagged panel models of the three-year associations between depressive symptoms, anxiety and the four cognitive measures. Model 1 represents unadjusted associations between either depressive symptoms or anxiety and one of the four cognitive measures; Model 2 represents the model including all cognitive measures and both depressive and anxiety symptoms; Model 3 is further adjusted for demographics, BMI and physical health.

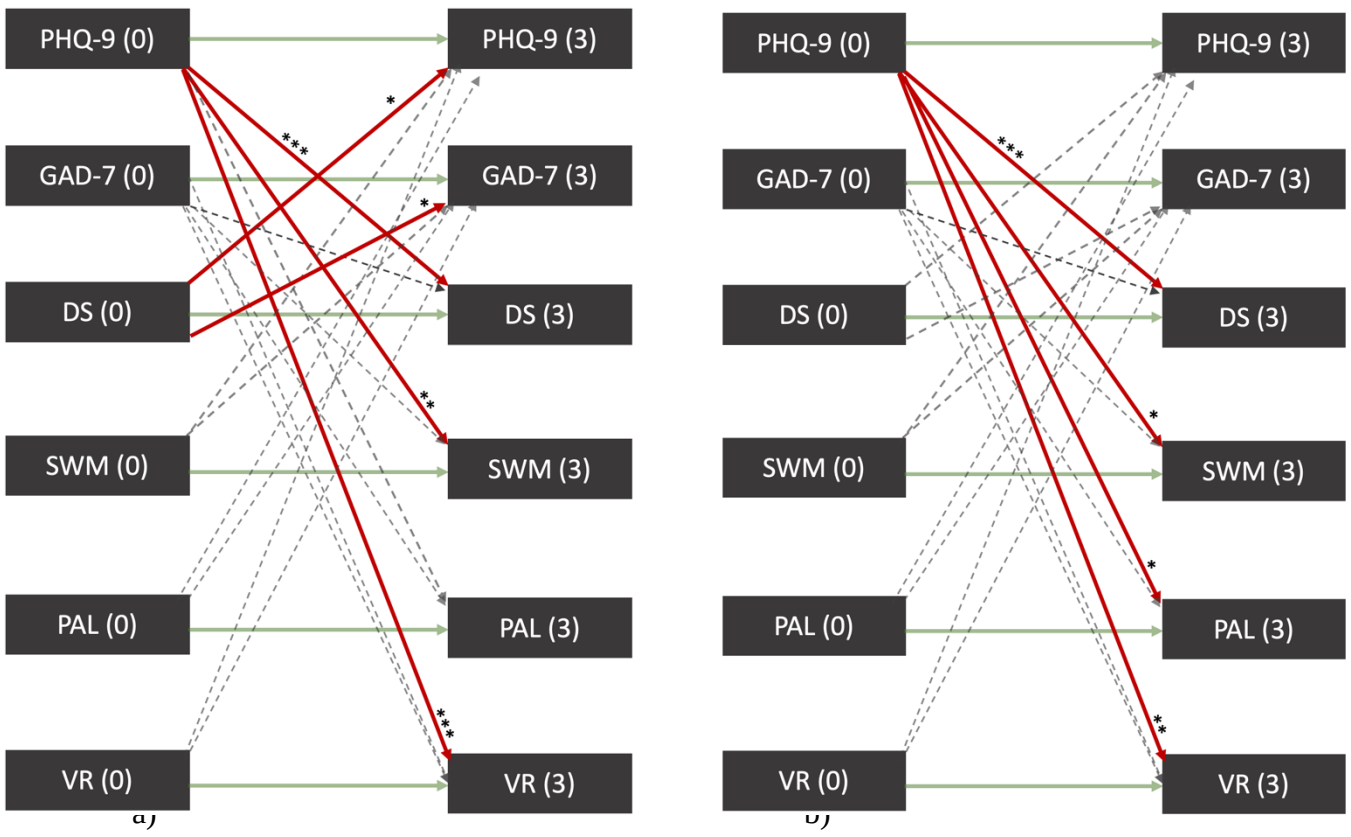


Fig.40. Cross-lagged 3-year associations between depressive symptoms, anxiety symptoms, and four cognitive measurements: a) mutually adjusted; b) further adjusted for demographics, BMI and physical health. Strong mutual associations were observed for depression and anxiety, and between all four measures of cognition; they're not presented for clarity.

→ significant negative associations.

→ significant positive associations.

- - ► non-significant associations

*** p<0.001| ** p< 0.01| *p<0.05

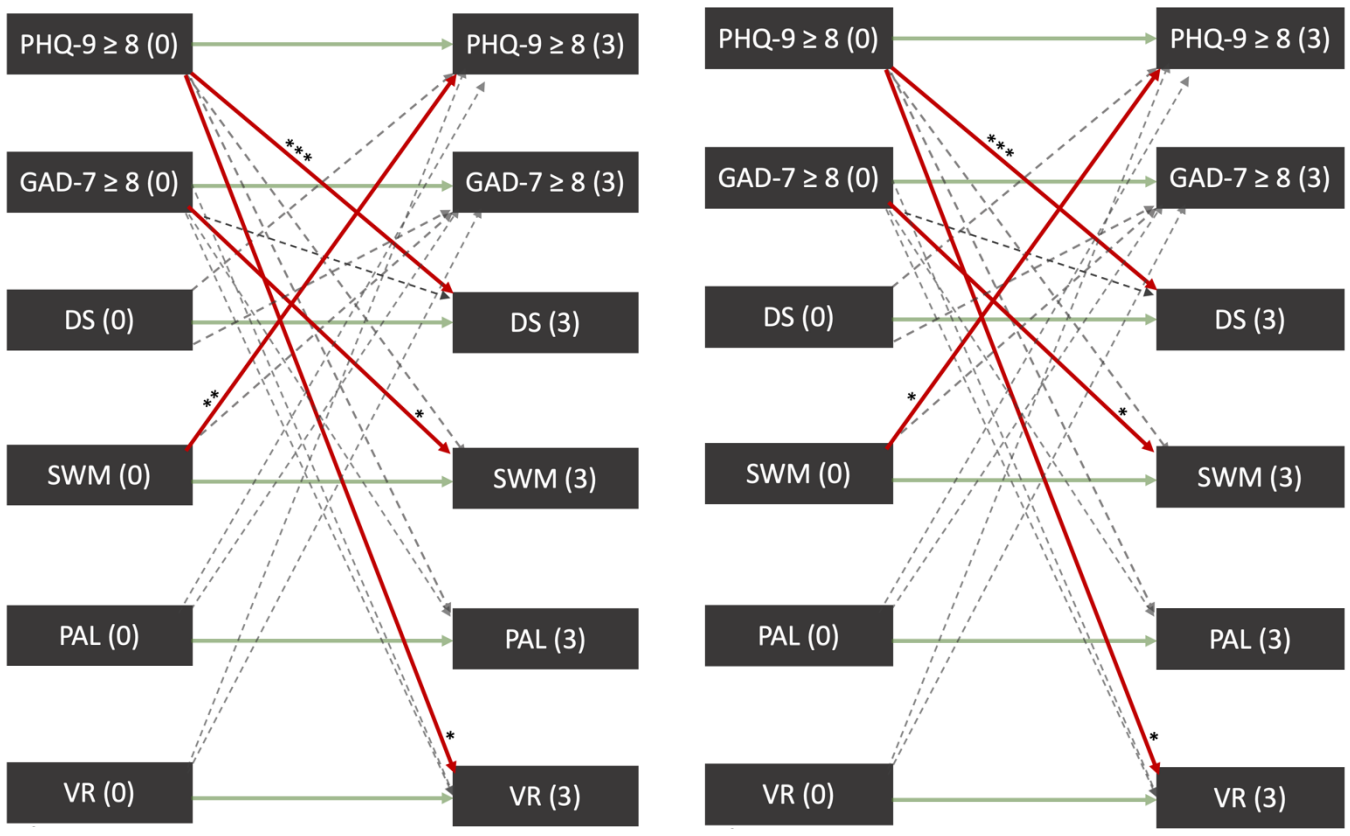
6.3.4.2 Clinically significant depressive (PHQ90≥8) and anxiety (GAD-7≥8) symptoms

Clinically significant depression (PHQ-9≥8) at baseline predicted worse performance on DS (β = -.19, p <0.001), SWM (β = -.23, p=0.006) and VR (β = -.89, p=0.002) but not PAL. Clinically significant anxiety (GAD-7≥8) predicted worse DS (β = -.013 p=0.035) and SWM (β = -.37, p=0.002) performance; at the same time, worse DS and SWM scores predicted anxiety at follow-up (β = -.12, p=0.007; β = -.007, p=0.009).

The results of Model 2, incorporating both clinically significant anxiety and clinically significant depression along with the four cognitive measures, are presented in Table 34 and Fig.19. In the fully adjusted model, only clinically significant depression at baseline predicted worse performance on DS (β = -.17, p=0.001) and VR (β = -.78, p=0.012). Interestingly, however, only clinically significant anxiety symptoms predicted worse performance on SWM at follow-up (β = -.33, p=0.011). At the same time, better SWM performance was associated with lower likelihood of having depression at follow-up (See Table 34; Fig. 19b).

	Model 1(unadj.)				Model 2				Model 3			
	β	*SE*	*95% CI*	*p-value*	*β*	*SE*	*95% CI*	*p-value*	*β*	*SE*	*95% CI*	*p-value*
PHQ-9≥8(0) → DS(3)	**-.187**	**.043**	**-.27; -.10**	**<0.001**	**-.18**	**.046**	**-.27; -.086**	**<0.001**	**-.16**	**.047**	**-.25; -.066**	**0.001**
DS(0) → PHQ-9≥8(3)	-.064	.036	-.134; .006	0.073	-.060	.041	-.14; .020	0.144	-.038	.042	-.12; .044	0.37
PHQ-9≥8(0) → PAL(3)	-.048	.031	-.11; .014	0.13	-.020	.033	-.085; .045	0.54	-.052	.033	-.12; .013	0.12
PAL(0) → PHQ-9≥8(3)	-.042	.066	-.17; .087	0.52	.052	.076	-.097; .20	0.50	.016	.078	-.13; .17	0.84
PHQ-9≥8(0) → SWM(3)	**-.23**	**.084**	**-.39; -.065**	**0.006**	-.14	.090	-.31; .039	0.13	-.16	.090	-.34; .017	0.076
SWM(0) → PHQ-9≥8(3)	**-.061**	**.021**	**-.10; -.018**	**0.005**	**-.064**	**.023**	**-.11; -.018**	**0.007**	**-.058**	**.024**	**-.10; -.011**	**0.015**
PHQ-9≥8(0) → VR(3)	**-.88**	**.28**	**-1.44; -.33**	**0.002**	**-.68**	**.31**	**-1.28; -.078**	**0.027**	**-.71**	**.31**	**-1.31; -.11**	**0.02**
VR (0) → PHQ-9≥8(3)	-.0026	.0055	-.013; .008	0.63	.0047	.0062	-.0074; .017	0.45	.0045	.0064	-.0081; .017	0.49
GAD-7≥8(0) → DS(3)	**-.13**	**.062**	**-.25; -.0090**	**0.035**	-.00022	.067	-.13; .13	0.99	-.011	.067	-.14; .12	0.87
DS(0) → GAD-7≥8 (3)	-.12	.047	-.22; -.033	0.007	-.081	.053	-.19; .022	0.12	-.073	.054	-.18; .032	0.18
GAD-7≥8 (0) → PAL(3)	-.068	.045	-.16; .020	0.13	-.015	.048	-.11	.079	-.042	.048	-.14; .051	0.38
PAL(0) → GAD-7≥8 (3)	-.11	.084	-.27; .056	0.20	-.017	.098	-.21; .18	0.87	-.063	.010	-.26; .13	0.53
GAD-7≥8 (0) → SWM(3)	**-.071**	**.027**	**-.12; -.018**	**0.009**	**-.27**	**.13**	**-.53; -.017**	**0.036**	**-.33**	**.13**	**-.59; -.081**	**0.010**
SWM(0) → GAD-7≥8 (3)	**-.37**	**.12**	**-.60; -.14**	**0.002**	-.048	.03	-.11; .011	0.11	-.045	.031	-.10; .015	0.14
GAD-7≥8 (0) → VR(3)	-.29	.41	-1.08; .51	0.48	.29	.45	-.58; 1.16	0.51	-.002	.44	-.87; .86	0.99
VR (0) → GAD-7≥8 (3)	-.0051	.007	-.019; .0086	0.47	.0064	.008	-.0093; .022	0.42	.0021	.0082	-.014; .018	0.80

Table 37. Cross-lagged panel models of the three-year associations between clinically significant depressive symptoms, clinically significant anxiety and the four cognitive measures. Model 1 represents unadjusted associations between either clinically significant depressive symptoms or anxiety and one of the four cognitive measures; Model 2 represents the model including all cognitive measures and both clinically significant depressive and anxiety symptoms; Model 3 is further adjusted for demographics, BMI and physical health.



a) ***b)***

Fig.41. Cross-lagged 3-year associations between clinically significant depressive symptoms (PHQ-9≥8), anxiety symptoms (GAD-7≥8), and four cognitive measurements: a) mutually adjusted; b) further adjusted for demographics, BMI and physical health. Strong mutual associations were observed for depression and anxiety, and between all four measures of cognition; they're not presented for clarity.

→ significant negative associations.

→ significant positive associations.

– – ► non-significant associations

*** p<0.001| ** p< 0.01| *p<0.05

6.3.5. Four-wave cross-lagged panel models

The full four-wave cross-lagged panel model had a good fit ($\chi2 = 95.63$; $p = 0.054$; RMSEA = 0.004, CFI = 1.000). Wald test indicated that the lagged effects were time-variant ($p<0.001$ for each effect); therefore, the model with unconstrained time-lagged effects is presented. It can be seen that the relationship between depressive symptoms and worse cognitive functioning is mostly explained by reciprocal associations across the first 2 waves, similarly for anxiety. In the full model (Fig.7), only PHQ-9 scores negatively predicted DS, PAL, SWM functioning at year 1, and VR at years 1 and 2. At the same time, DS performance at baseline predicted worse depressive and anxiety symptoms at year 2, and SWM predicted worse depressive symptoms at year 1, but not at any later wave. Anxiety alone predicted worse PAL functioning at year 1. Significant negative covariances, especially in the first two years, point to cross-sectional associations.

The parameter estimates from the full four-wave cross-lagged model are presented in Table 35.

	Outcome at Year 1						**Outcome at Year 2**						**Outcome at Year 3**					
Predictors	**DS**	**PAL**	**SWM**	**VR**	**PHQ-9**	**GAD-7**	**DS**	**PAL**	**SWM**	**VR**	**PHQ-9**	**GAD-7**	**DS**	**PAL**	**SWM**	**VR**	**PHQ-9**	**GAD-7**
	β (SE)						***β (SE)***						***β (SE)***					
DS (0/1/2)	.56(.0062)***	.085(.0037)***	.090(.012)***	.29(.035)***	**-.064(.016)*****	-.016(.014)	.98(.013)***	-.008(.0075)	-.041(.019)*	.053(.051)	-.016(.022)	.006(.020)	.96(.014)***	.022(.011)*	-.0023(.019)	-.10(.058)	.013(.026)	-.038(.022)
PAL (0/1/2)	.13(.010)***	.30(.0077)***	.26(.024)***	.46(.068)***	-.0094(.029)	**-.059(.025)***	-.035(.014)*	.97(.039)***	.37(.10)***	.18(.28)	.067(.039)	.046(.035)	.039(.039)	.95(.035)***	-.11(.069)	.20(.26)	.027(.046)	.062(.039)
VR (0/1/2)	.016(0010)***	.0075(.00064)***	.024(.0019)***	.85(.0057)***	-.0045(.0026)	**-.0045(.0022)***	-.002(.0059)	.00057(.0011)	-.0050(.0023)*	.99(.0078)***	.0057(.0030)	.0034(.0027)	.0011(.0014)	-.0019(.00094)*	-.00093(.0024)	1.03(.0085)***	-.00041(.0033)	-.0023(.0028)
SWM	.032(.0035)***	.046(.0025)***	.42(.0079)***	.16(.022)***	**-.026(.0095)****	**-.039(.0081)*****	.0008(.0014)	.0074(.010)	.90(.028)***	.11(.072)	.0067(.012)	-.0071(.011)	-.0092(.0053)	.0061(.0082)	.99(.028)***	-.12(.067)	-.014(.016)	-.0032(.013)
PHQ-9	**-.011(.0030)*****	**-.0056(.0022)***	**-.030(.0062)*****	**-.058(.018)*****	.60(.0091)***	.19(.0079)***	-.005(.0035)	-.0087(.0057)	.00005(.0074)	**-.045(.019)***	.97(.028)***	-.023(.025)	-.00092(.0039)	-.0046(.0032)	-.014(.0082)	-.034(.022)	.95(.031)***	.0076(.021)
GAD-7	-.0008(.0036)	**-.0048(.0023)***	-.012(.0073)	-.0046(.022)	.14(.011)***	.46(.0095)***	-.00024(.0041)	.0084(.0054)	.0063(.0088)	.011(.023)	.054(.037)	1.07(.032)	-.0029(.0045)	.0066(.0038)	.0097(.0096)	.026(.026)	-.030(.038)	.86(.026)***

Table 38. Four-wave cross-lagged associations between depressive symptoms, anxiety symptoms, and four cognitive measures. Significant associations of interest are presented in bold/darker shade. *** p<0.001; ** p<0.01; * p<0.05

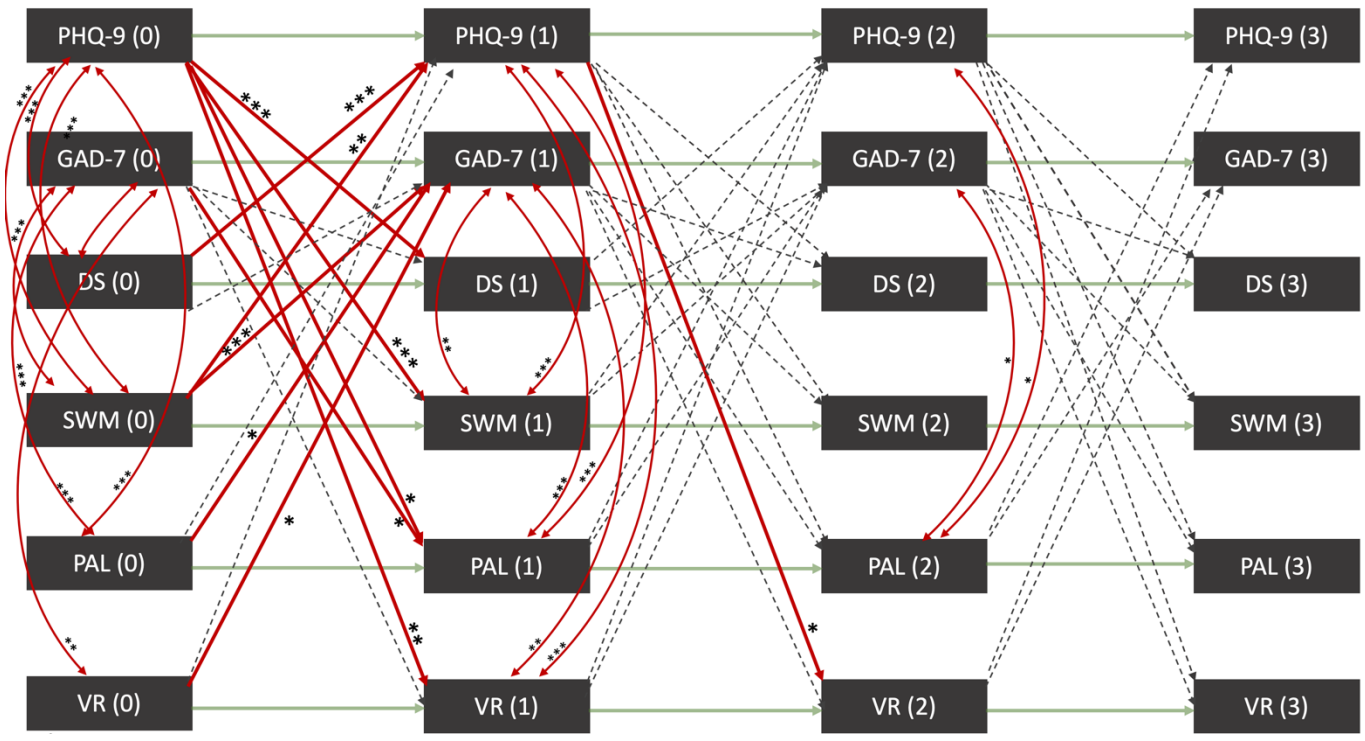


Fig.42. Four-wave cross-lagged between depressive symptoms, anxiety symptoms, and four cognitive measurements. Strong mutual associations were observed for depression and anxiety, and between all four measures of cognition; they're not presented for clarity.

→ significant negative associations or negative covariances.

→ significant positive associations or positive covariances.

- - ► non-significant associations

*** p<0.001| ** p< 0.01| *p<0.05

6.3.6 Latent growth curve models

Individual latent growth curve models were fitted for each longitudinally measured variable of affective symptoms and cognitive performance. Not all LGCMs had a very good fit according to the $\chi 2$/DF ratio, although the RMSEA and CFI indicated an adequate fit for each model. An example of an individual LGCM is presented in Fig.21.

The full model did have a good fit *($\chi 2(142)$* = 172.9, p= 0.04, RMSEA = 0.003, CFI = 1.000). The full model adjusted for age and gender had a worse fit compared to the unadjusted full model, but still adequate ($\chi 2$ (206) = 704.94, p<0.001; RMSEA = 0.011; CFI = 0.997). Age and gender had significant effects on the model, and correlations between the unadjusted and adjusted model differed substantially, therefore the results of the adjusted model are presented here. The results of the full model before adjustment for age/gender are presented in Table 13 and Fig. 13 in Supplementary materials.

Elements of the adjusted full LGCM are presented in Fig.22a-d (the whole model has been split in 4 parts for presentation clarity). Initial levels of depressive symptoms were significantly positively correlated with the slope (β = .12, p=0.010), indicating that participants with higher initial levels of depressive symptoms also had a steeper increase in depressive symptoms during follow-up. The opposite was observed for anxiety (β = -.49, p=0.001), DS, PAL and SWM scores (β = -.028, p<0.001; β = -.089, p=0.001; β = -.052, p=0.021). The opposite, however, was observed for VR performance, where a positive correlation between the intercept and the slope was present (β = 1.52, p<0.001). Intercepts and slopes of cognitive performance measures were all significantly positively correlated. Similarly, intercepts and slopes of the two affective measures were positively correlated (p<0.001 for both). The correlations observed in individual LGMs were generally identical. The coefficients of the full adjusted model are presented in Table 36.

The intercept of depressive symptoms was significantly negatively correlated with all four cognitive measures (p<0.001 for all), indicating that higher initial depressive symptoms were associated with worse initial cognitive performance. Besides, the intercept of depressive symptoms was negatively correlated with the slope of DS, PAL and VR (β -.037; p<0.001; β -.020; p=0.010; β = -.53, p< 0.001, respectively); the correlation with SWM slope was marginally significant(β = -.042, p=0.051) – suggesting that higher initial depressive symptoms were predictive of decrease in cognitive performance. Reciprocally, the intercept for DS was negatively correlated with the slope of depressive symptoms (β = *-.032, p=0.018).* The slope of depressive symptoms was mildly yet significantly negatively correlated with the slope of PAL (β = -.006, p=0.042).

Anxiety intercept was independently negatively associated with the intercepts of all four cognitive domains, as well as with the slopes of DS and VR. The slope of anxiety wasn't correlated with any of the intercepts of cognitive tests; however, only the slope of anxiety, not depressive symptoms, was negatively correlated with the slope of SWM (β = -.016; p=0.018).

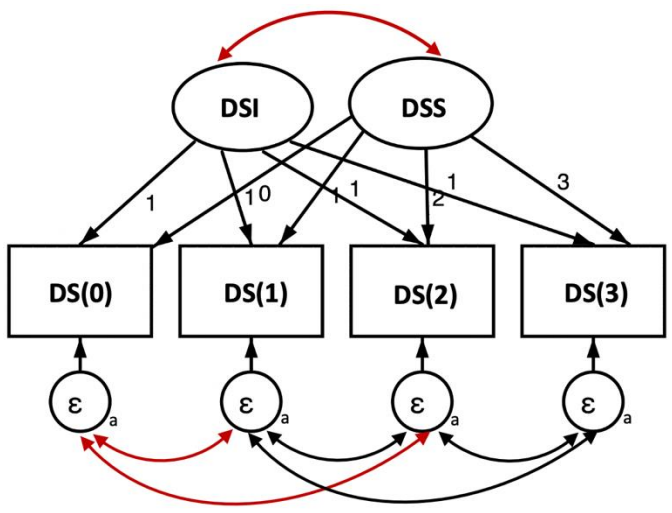
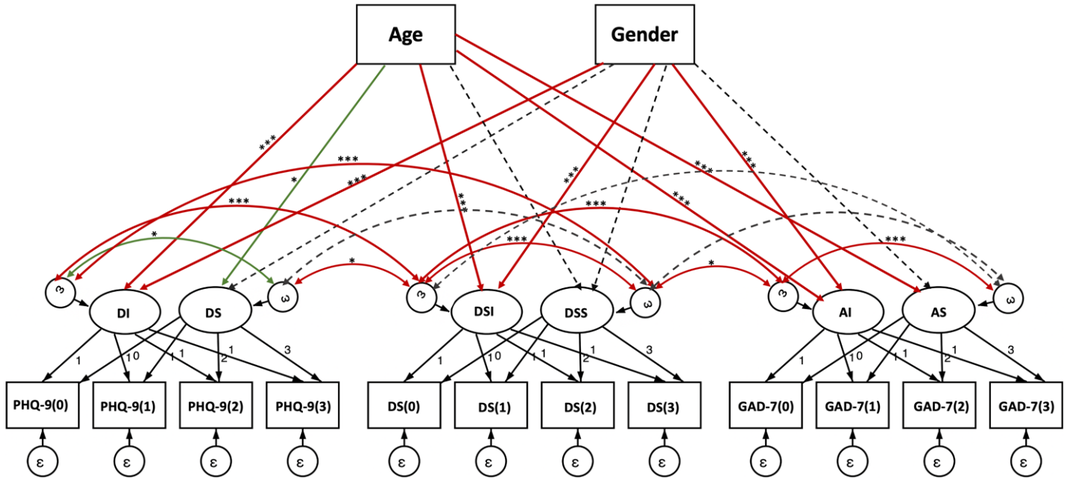
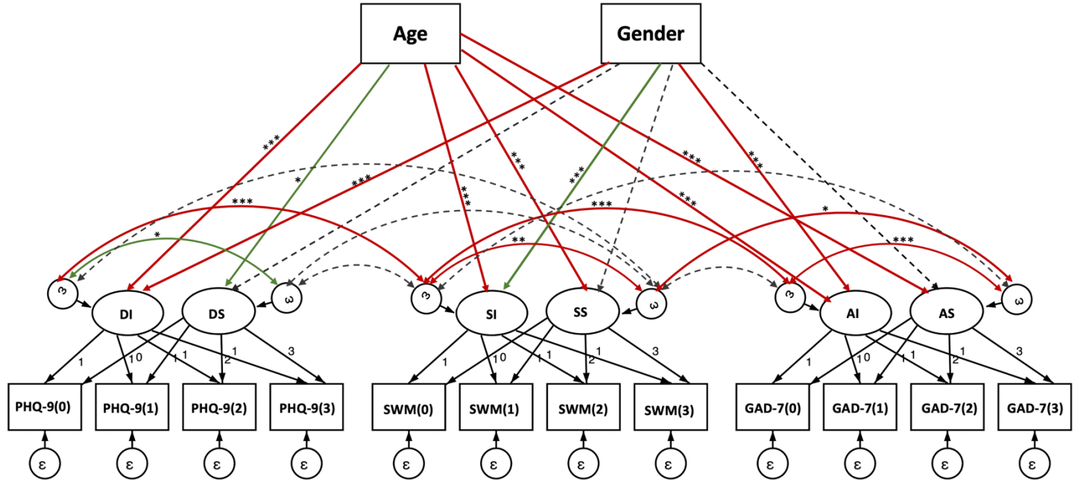


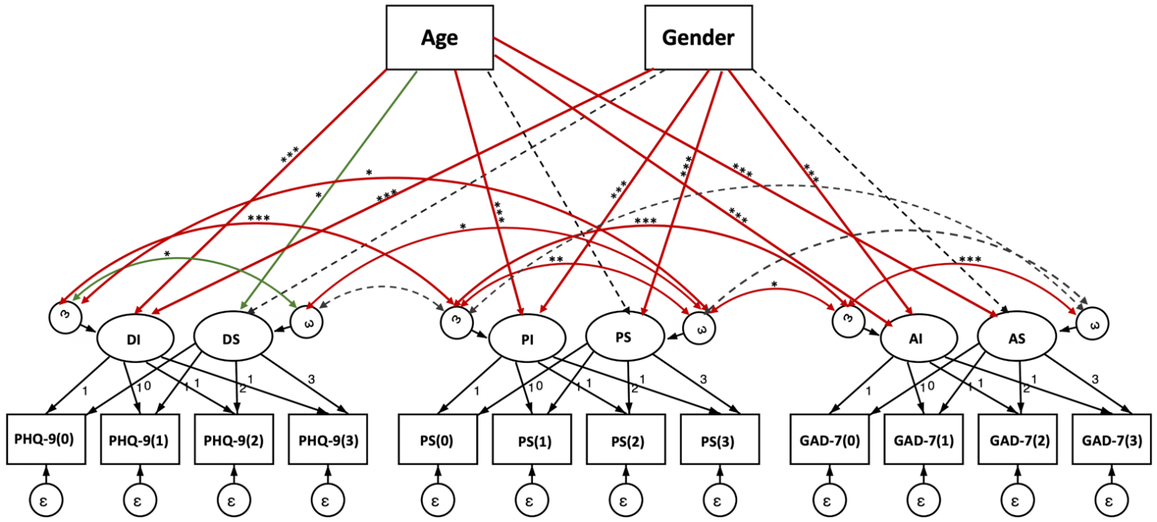
Fig.43. Individual latent growth curve for Digit Span; DSI – Digit Span intercept, DSS – Digit Span Slope. Red arrows indicate significant negative covariances. Model fit: $\chi 2(1) = 3.65$, $p = 0.056$; RMSEA = 0.011, CFI = 1.000).



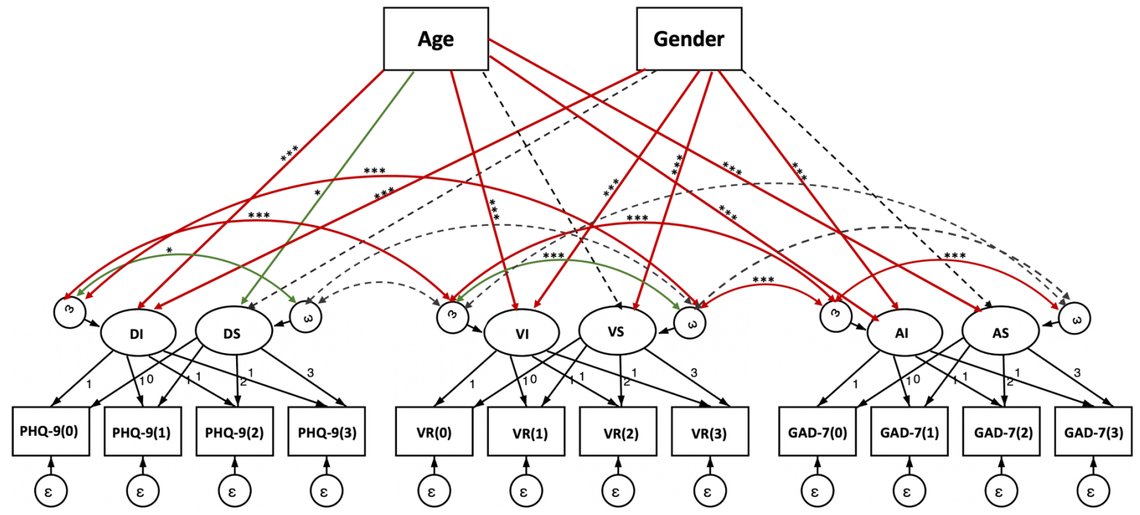
a)



c)



b)



d)

Fig.44a-d Latent growth curve model of anxiety, depressive symptoms and (a) DS (b) PAL (c) SWM (d) VR performance with time-invariant predictors (Age and Gender). For clarity, the growth curve for only one cognitive measure is shown in each graph. DI/DS = depression intercept/ slope; AI/AS = anxiety intercept/anxiety slope; DSI/DSS = Digit Span intercept/slope; PI/PS = Paired Associates Learning intercept/slope; SI/SS = Spatial Working Memory Intercept/Slope; VI/VS = Verbal Reasoning intercept/slope.

significant negative associations or negative covariances.

significant negative associations or negative covariances.

non-significant associations or covariances

*** p<0.001| ** p< 0.01| *p<0.05

		Depressive symptoms		Anxiety symptoms		DS		PAL		SWM		VR	
		Intercept	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*
Age		**-.049*** **	**.0036***	**-.040*** **	-.00090	**-.022*** **	-.00076	**-.022*** **	-.00042	**-.054*** **	**-.0041*** **	**-.32*** **	**-.023*** **
Gender		**-.27*** **	-.020	**-.33*** **	.0011	**.17*** **	-.0052	**.030** **	**-.019** **	**.41*** **	.0058	.22	**-.41*** **
Depressive symptoms	*Intercept*												
	Slope	**0.12***											
Anxiety symptoms	*Intercept*	**4.32*** **	.050										
	Slope	**.71*** **	**.16*** **	**-0.49*** **									
DS	*Intercept*	**-.32*** **	**-.032***	**-.20*** **	-0.012								
	Slope	**-.037*** **	.0027	**-.022***	.0030	**-0.028*** **							
PAL	*Intercept*	**-.16*** **	.0093	**-.13*** **	-.0055	**0.32*** **	**-.011*** **						
	Slope	**-.020***	**-.0064***	-.012	.00014	-.0013	**.0087*** **	**-.0089** **					
SWM	*Intercept*	**-.61*** **	-0.012	**-0.60*** **	-.0071	**0.63*** **	.014	**0.49*** **	.0074				
	Slope	-.043	-.0028	.031	**-0.017***	-.011	**.0087** **	**-.026*** **	**.014** ** *	**-0.052***			
VR	*Intercept*	**-1.07*** **	-0.13	**-1.25*** **	-.027	**4.06*** **	**-.082** **	**1.90*** **	**-.072** **	**5.16*** **	**-.25*** **		
	Slope	**-.53*** **	-.025	**-.27*** **	-.017	**0.18*** **	**.073*** **	**.11*** **	**.053** ** *	**.43*** **	**.13*** **	**1.52*** **	-

Table 39. Unstandardized regression coefficients and correlations between depressive symptoms, anxiety symptoms and four cognitive measures

6.4.6 The role of history of depression: three-year associations between depressive symptoms, anxiety and cognitive performance

The comparison of baseline characteristics between participants with and without a history of depression is presented in Table 37.

		History of depression (N = 5,307)	No history of depression (N = 9,691)	
Numerical measures				
Age	Median, IQR	60.87(55.94 - 65.84)	62.27(56.88- 67.70)	<0.001
BMI	Median, IQR	25.78(23.09 - 29.57)	24.95(22.71 - 27.87)	<0.001
DS	Mean, (SD)	7.24(1.37)	7.40 (1.38)	<0.001
PAL	Mean, (SD)	4.45(.77)	4.50(.75)	<0.001
SWM	Mean, (SD)	7.23(2.34)	7.49(2.30)	<0.001
VR	Mean, (SD)	32.13(8.99)	31.23(8.95)	<0.001
PHQ-9	Median, IQR	3(1-6)	1(0-3)	<0.001
GAD-7	Median, IQR	1(0-4)	0(0-1)	<0.001
Categorical measures (N, %)				
Gender	Male	921 (17.35)	3,162 (32.64)	<0.001
	Female	4,386 (82.65)	6,525 (67.36)	
Ethnicity	White	5,212 (98.30)	9,498 (98.17)	0.559
	Other	90 (1.70)	177 (1.83)	
Education	Secondary	1,585 (16.38)	830 15.65	<0.001
	Post-Secondary	1,095 (11.32)	649 12.24	
	Vocational Qualification	1,873 (19.36)	1,165 21.97	
	Undergraduate Degree	3,279 (33.89)	1,583 29.86	
	Post-graduate Degree	1,493 (15.43)	914 17.24	
	Doctorate	350 (3.62)	161 3.04	
Employment	Employed(full-time)	1,946 (20.11)	1,060 (19.99)	**<0.001**
	Employed(part-time)	1,415 (14.63)	994 (18.75)	
	Self-employed	977 (10.10)	542 (10.22)	
	Retired	5,114 (52.86)	2,465 (46.49)	
	Unemployed	223 (2.30)	241 (4.55)	
PHQ-9≥8	1 vs 0	902 (17.41)	192 (2.01)	<0.001
GAD-7≥8	1 vs 0	434 (8.46)	77 (0.80)	<0.001
Hypertension	1 vs 0	1,259 (25.25)	2,234 (23.92)	0.078
Heart disease	1 vs 0	230 (4.36)	411 (4.26)	0.776
Diabetes	1 vs 0	245 (4.64)	327 (3.39)	<0.001

Table 40. The comparison of baseline characteristics between participants with and without a history of depression.

6.3.6.1 Standard cross-lagged panel models

In standard cross-lagged models, we observed substantial differences between participants with and without a history of depression. Results of unadjusted models (Model 1) and models including only cognitive and affective measurements (Model 2) are presented in Tables 38-39. In a fully adjusted model (Model 3), depressive symptoms only predicted worse performance on DS tasks in patients without a history of depression; similarly, for PAL. Anxiety symptoms were predicted by worse DS scores (see Table 38, Fig.23a).

At the same time, poorer SWM and VR was only predicted by higher depressive symptoms in patients without a history of depression, although for SWM, was not significant in a fully adjusted model (See Table 39, and Fig.23b). In patients with a history of depression, more severe anxiety was predicted by worse PAL scores.

	Model 1(unadj.)*				**Model 2****				**Model 3*****			
	β	SE	95% CI	p-value	β	SE	95% CI	p-value	β	SE	95% CI	p-value
PHQ-9 (0) → DS(3)	***-.021***	***.0078***	***-.037; -.0061***	***0.006***	***-.031***	***. .0088***	***-.048; -.014***	***<0.001***	***-.028***	***.0088***	***-.045; -.011***	***0.002***
DS(0) → PHQ-9 (3)	***-.053***	***.024***	***-.10; -.0062***	***0.027***	*-.048*	*.027*	*-.10; -.0039*	*0.070*	*-.043*	*.027*	*-.095; .0092*	*0.11*
PHQ-9(0) → PAL(3)	***-.014***	***.0057***	***-.025; -.0027***	***0.015***	*-.011*	*.0063*	*-.023; .0010*	*0.073*	***-.013***	***.0063***	***-.025; -.00054***	***0.041***
PAL(0) → PHQ-9(3)	*-.029*	*.044*	*-.11; .058*	*0.52*	*.0093*	*.050*	*-.088; .11*	*0.85*	*.0026*	*.050*	*-.095; .10*	*0.96*
PHQ-9(0) → SWM(3)	*-.0090*	*.015*	*-.038; .020*	*0.54*	*-.018*	*.016*	*-.051; .015*	*0.29*	*-.017*	*.017*	*-.049; .016*	*0.32*
SWM(0) → PHQ-9(3)	*-.00076*	*.015*	*-.030; .029*	*0.96*	*.014*	*.016*	*-.017; .046*	*0.38*	*.017*	*.016*	*-.014; .049*	*0.29*
PHQ-9(0) → VR(3)	*-.033*	*.051*	*-.13; .067*	*0.52*	*-.095*	*.058*	*-.21; .019*	*0.10*	*-.074*	*.057*	*--.19; .039*	*0.20*
VR (0) → PHQ-9(3)	-.0053	.0036	-.012; .0018	0.14	*-.0048*	*.0040*	*-.013; .0029*	*0.22*	*-.0026*	*.0041*	*-.011; .0056*	*0.53*
GAD-7(0) → DS(3)	*.0038*	*.0091*	*-.014; .022*	*0.67*	*.021*	*.010*	*.00034; .041*	*0.046*	*.016*	*.010*	*-.0043; .036*	*0.12*
DS(0) → GAD-7 (3)	***-.064***	***.021***	***-.11; -.022***	***0.003***	***-.057***	***.023***	***-.10; -.011***	***0.015***	***-.054***	***.024***	***-.10; -.0084***	***0.02***
GAD-7(0) → PAL(3)	*-.010*	*.0067*	*-.023; .0031*	*0.13*	*-.0018*	*.0075*	*-.016; .013*	*0.81*	*-.008*	.0074	-.023; .0061	0.25
PAL(0) → GAD-7(3)	*-.043*	*.039*	*-.12; .033*	*0.27*	*-.0040*	*.044*	*-.089; .081*	*0.93*	*-.026*	.044	-.11;060	0.55
GAD-7(0) → SWM(3)	*.014*	*.017*	*-.020; .048*	*0.42*	*.023*	*.020*	*-.016; .061*	*0.25*	*.0072*	*.020*	*-.031; .046*	*0.72*
SWM(0) → GAD-7(3)	*.0089*	*.013*	*-.017; .035*	*0.51*	*.023*	*.014*	*-.0048; .051*	*0.10*	*.021*	*.014*	*-.006; .050*	*0.12*
GAD-7(0) → VR(3)	*.12*	*.060*	*-.0019; .23*	*0.054*	***.18***	***.069***	***.054; .32***	***0.006***	*.093*	*.068*	*-.040; .23*	*0.17*
VR (0) → GAD-7(3)	*-.0059*	*.0032*	*-.0012; .00035*	*0.064*	*-.0045*	*.0035*	*-.011; .0023*	*0.20*	*-.0057*	*.0036*	*-.013; .0015*	*0.12*

Table 41. Cross-lagged panel models of the three-year associations between clinically significant depressive symptoms, clinically significant anxiety and the four cognitive measures in participants without a history of depression. Model 1 represents unadjusted associations between either clinically significant depressive symptoms or anxiety and one of the four cognitive measures; Model 2 represents the model including all cognitive measures and both clinically significant depressive and anxiety symptoms; Model 3 is further adjusted for demographics, BMI and physical health.
*Model was just identified; ** χ^2= 2.215; p=0.70; RMSEA = 0.000; CFI = 1.000; *** χ^2 = 8.67, p=0.19, RMSEA = 0.007 CFI = 1.000

	Model 1(unadj.)*				Model 2				Model 3			
	β	SE	95% CI	p-value	β	SE	95% CI	p-value	β	SE	95% CI	p-value
PHQ-9 (0) → DS(3)	***-.013***	***.0055***	***-.024; -.0023***	***0.017***	*-.013*	*.0074*	*-.028; .0010*	*0.069*	*-.0095*	*.0075*	*-.024; .0052*	*0.21*
DS(0) → PHQ-9 (3)	*.027*	*.061*	*-.092; .15*	*0.65*	*.075*	*.067*	*-.056; .21*	*0.26*	*.095*	*.067*	*-.036; .23*	*0.15*
PHQ-9(0) → PAL(3)	*-.0064*	*.0040*	*-.014; .0015*	*0.11*	*-.0012*	*.0053*	*-.012; .0092*	*0.82*	*-.0033*	*.0054*	*-.014; .0073*	*0.54*
PAL(0) → PHQ-9(3)	*-.19*	*.11*	*-.41; .035*	*0.099*	*-.22*	*.13*	*-.47; .029*	*0.084*	*-.23*	*.13*	*-.48; .022*	*0.073*
PHQ-9(0) → SWM(3)	***--.033***	***.011***	***-.055; -.011***	***0.003***	***-.031***	***.015***	***-.060; -.0018***	***0.038***	*-.028*	*.015*	*-.057; .019*	*0.67*
SWM(0) → PHQ-9(3)	-.058	.038	-.13; .017	0.13	*-.036*	*.041*	*-.12; .043*	*0.37*	*.040*	*.040*	*-.12; .039*	*0.33*
PHQ-9(0) → VR(3)	***-.17***	***.038***	***-.25; -.10***	***<0.001***	***-.16***	***.051***	***-.26; .065***	***0.001***	***-.13***	***.051***	***-.23; -.032***	***0.01***
VR (0) → PHQ-9(3)	*-.0040*	*.0095*	*-.023; .015*	*0.68*	*.0038*	*.011*	*-.017; .025*	*0.72*	*.0028*	*.011*	*-.018; .024*	*0.79*
GAD-7(0) → DS(3)	*-.011*	*.0067*	*-.024; .0015*	*0.082*	*.0021*	*.0088*	*-.015; .019*	*0.81*	*-.0015*	*.0089*	*-.019; .016*	*0.87*
DS(0) → GAD-7 (3)	*.055*	*.052*	*-.047; .16*	*0.29*	***.12***	***.057***	***.0066; .23***	***0.038***	***.13***	***.057***	***.014; .24***	***0.027***
GAD-7(0) → PAL(3)	***-.0096***	***.0048***	***-.019; -.00017***	***0.046***	*-.0047*	*.0064*	*-.017; .0078*	*0.46*	-.0060	.0064	-.018; .0065	0.35
PAL(0) → GAD-7(3)	***-.21***	***.098***	***-.40; -.014***	***0.036***	***-.22***	***.11***	***-.43; -.0067***	***0.043***	***-.25***	***.11***	***-.46; -.034***	***0.023***
GAD-7(0) → SWM(3)	*-.025*	*.013*	*-.051; .0012*	*0.062*	*.0046*	*.018*	*-.030; .040*	*0.80*	*-.0019*	*.018*	*-.037; .033*	*0.91*
SWM(0) → GAD-7(3)	***-.071***	***.033***	***-.14; -.0073***	***0.029***	-.036	.041	-.12; .043	0.37	*-.056*	*.034*	*-.12; .011*	*0.10*
GAD-7(0) → VR(3)	***-.12***	***.045***	***-.20; -.027***	***0.01***	.021	.061	-.098; .14	0.73	*-.021*	*.061*	*-.14; .098*	*0.73*
VR (0) → GAD-7(3)	*-.0033*	*.0082*	*-.020; .013*	*0.68*	.0038	.011	-.017; .025	0.72	*-.0035*	*.0092*	*-.022; .015*	*0.71*

Table 42. Cross-lagged panel models of the three-year associations between clinically significant depressive symptoms, clinically significant anxiety and the four cognitive measures in participants with a history of depression. Model 1 represents unadjusted associations between either clinically significant depressive symptoms or anxiety and one of the four cognitive measures; Model 2 represents the model including all cognitive measures and both clinically significant depressive and anxiety symptoms; Model 3 is further adjusted for demographics, BMI and physical health.
*Model was just identified; ** χ^2= 2.215; p=0.70; RMSEA = 0.000; CFI = 1.000; *** χ^2 = 7.66; p=0.26; RMSEA = 0.007; CFI = 1.000

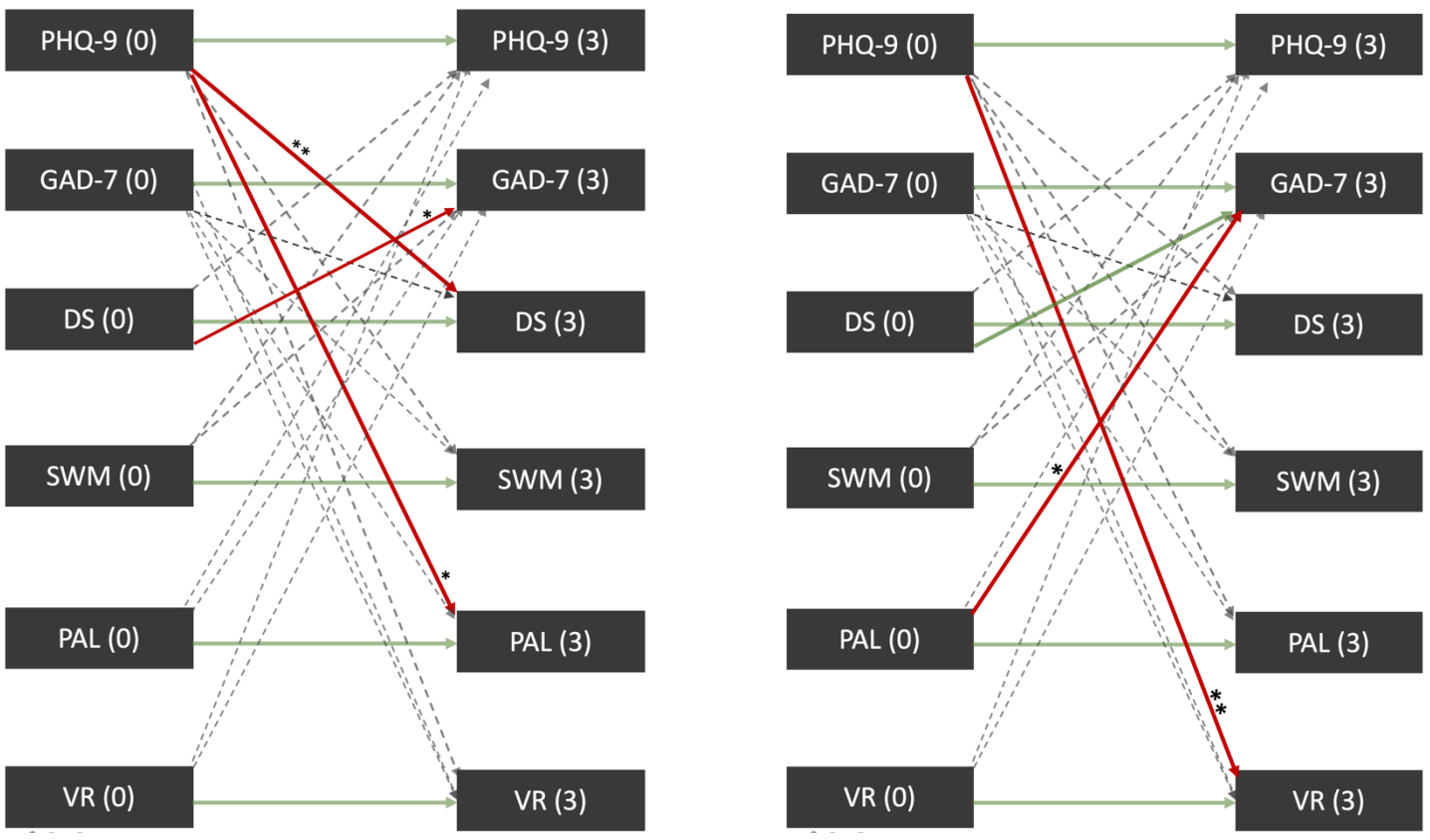


Fig.45a-b. *Cross-lagged 3-year associations between depressive symptoms, anxiety symptoms, and four cognitive measurements; fully adjusted model: a) in participants with no history of depression; b) in participants with a history of depression. Strong mutual associations were observed for depression and anxiety, and between all four measures of cognition; they're not presented for clarity.*

→ significant negative associations.

→ significant positive associations.

- - ► non-significant associations

*** p<0.001| ** p< 0.01| *p<0.05

6.3.6.2. Latent growth curve models

Both models, in participants with and without a history of depression, had a good fit ($\chi2(199) = 432.37$, $p < 0.001$, RMSEA = 0.011, CFI = 0.997; $\chi2(199) = 354.51$; $p<0.001$; RMSEA = 0.012; CFI = 0.996, respectively).

Interestingly, in participants with a history of depression, the correlation between anxiety symptoms and depressive symptoms was much higher than in those without a history of depression (7.77,p<0.001 vs 1.22, p<0.001 for intercept covariance, see Tables 40-41 for other covariances).

In both groups, depression symptoms intercept was negatively correlated with the intercept for the performance on DS; the correlation was stronger in patients with a history of depression (β = -.13, p<0.001; β = -.50, p<0.001). However, similarly to what was observed in the cross-lagged model, only in patients with no history of depression, depressive symptoms intercept was negatively correlated with the slope of DS performance (β = -.02, p=0.036).

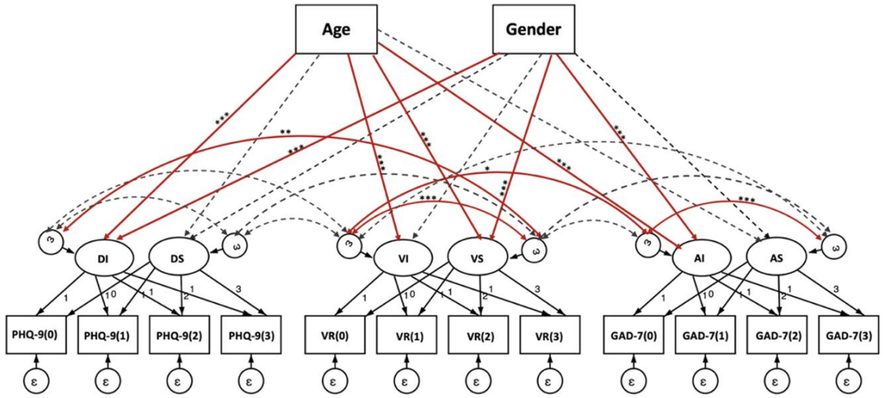
The negative covariance between anxiety slope and SWM slope, observed in the overall model, was only significant for participants without a history of depression (β = -.023, p=0.001). However, the relationship between VR intercept/slope and both depressive symptoms and anxiety was much stronger and more significant in participants who reported a history of depression (see Table 40-41; Fig, 24a-d; 25a-d).

		Depressive symptoms		**Anxiety symptoms**		**DS**		**PAL**		**SWM**		**VR**	
		Intercept	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*
	Age	**-.019*****	.0031	**-.017*****	-.00073	**-.023*****	**-.00099**	**-.024*****	-.000007	**-.057*****	**-.0054*****	**-.33*****	**-.025*****
	Gender	**-.14****	.014	**.13*****	-.0023	**-.22*****	.023	**.032***	**-.024****	**.40***	-.0027	.33	**-.45*****
Depressive symptoms	**Intercept**												
	Slope	***.033***											
Anxiety symptoms	**Intercept**	***1.22*****	-.007										
	Slope	***.34*****	***.083*****	***-.26*****									
DS	**Intercept**	***-.13*****	-.016	***-.085*****	-.018								
	Slope	***-.02****	.0019	*-.0028*	-.00014	**-0.030*****							
PAL	**Intercept**	***-0.064*****	.0080	***-.058*****	-.0024	***0.31*****	***-.010****						
	Slope	-.0084	-.0047	*-.0069*	.00043	*.0016*	***.0053****	***-.011****					
SWM	**Intercept**	***-.14****	.026	***-.17*****	.014	***.54*****	*.0093*	***.45*****	*.0031*				
	Slope	***-.039****	-.0054	*.010*	***-.023****	*-.0031*	***.0094****	***-.026****	***.016*****	-.033			
VR	**Intercept**	-.27	.0084	***-.28****	-.12	***3.79*****	*-.073*	**1.81*****	**-.098****	**4.33*****	-.096		
	Slope	***-.19****	.0027	-.042	-.030	***0.14*****	***.065*****	**.084*****	**.056*****	**.42*****	**.13*****	**1.18*****	-

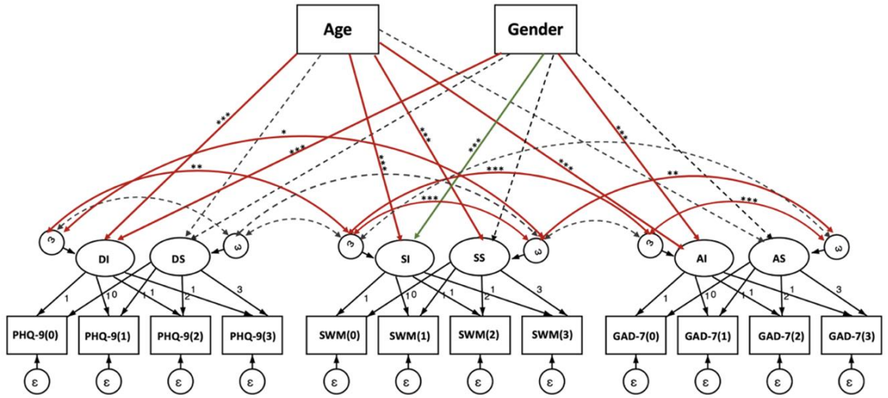
Table 43. Unstandardized regression coefficients and correlations between depressive symptoms, anxiety symptoms and four cognitive measures in participants without a history of depression. Model fit: $\chi^2(199)= 432.37$; $p<0.001$; RMSEA = 0.011; CFI = 0.997

		Depressive symptoms		**Anxiety symptoms**		**DS**		**PAL**		**SWM**		**VR**	
		Intercept	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*	*Intercept*	*Slope*
	Age	**-.075*****	.00046	**-.053*****	-.0022	**-.018*****	-.0010	**-.018*****	-.0013	**-.043*****	-.0030	**-.25*****	**-.017****
	Gender	**.34***	-.047	**.18*****	-.057	**.19*****	-.028	-.011	-.0063	**.35*****	.014	-.031	**-.35****
Depressive symptoms	Intercept												
	Slope	.066											
Anxiety symptoms	Intercept	**7.77*****	-.011										
	Slope	**1.08*****	**.40*****	**-.54***									
DS	Intercept	**-.50*****	-.014	**-.31*****	-.020								
	Slope	-.036	-.0074	-.015	-.0033	**-.024***							
PAL	Intercept	**-.23*****	.028	**-.21*****	-.0055	**.31*****	**-.014****						
	Slope	-.034	-.014	-.024	-.0027	-.011	**.013*****	-.010					
SWM	Intercept	**-1.15*****	.12	**-1.05*****	-.040	**.65*****	-.013	**.49*****	-.0036				
	Slope	-.033	-.028	.050	-.012	-.00045	.009	-.021	**.013***	-.057			
VR	Intercept	**-3.24*****	-.16	**-3.42*****	.041	**4.20*****	**-.12***	**1.98*****	-.089	**5.61*****	-.22		
	Slope	**-1.14*****	-.11	**-.60*****	.035	**.25*****	**.095*****	**.089****	**.068*****	.49	.13	**2.55*****	-

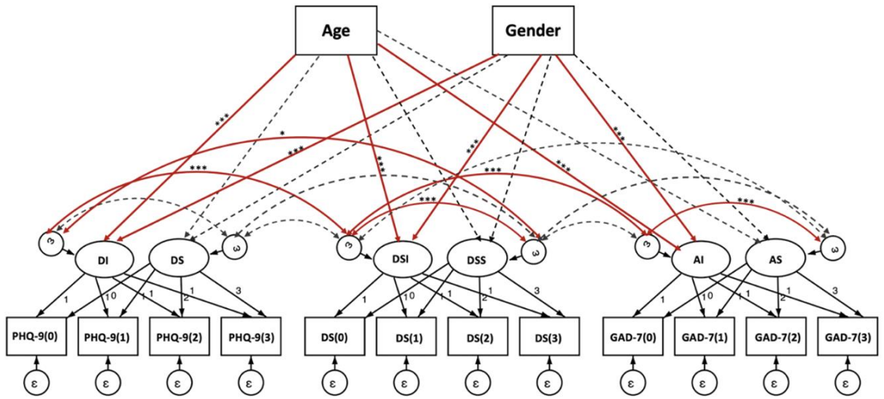
Table 44. Unstandardized regression coefficients and correlations between depressive symptoms, anxiety symptoms and four cognitive measures in participants with a history of depression. Model fit: $\chi^2(199)= 354.51$; $p<0.001$; RMSEA = 0.012; CFI = 0.996



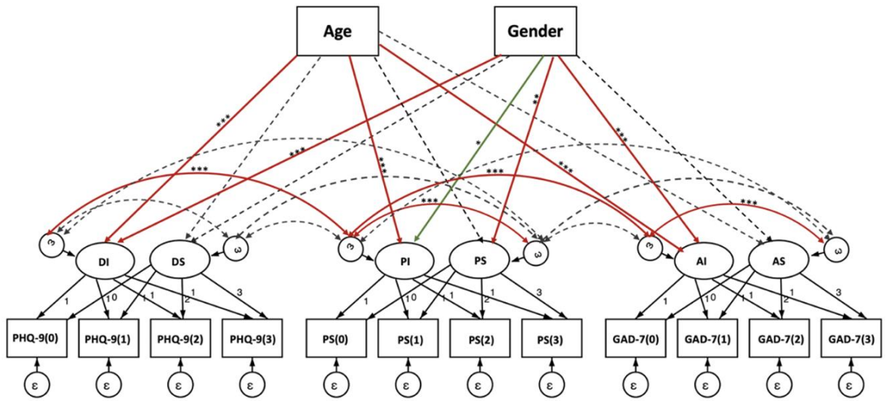
a)



c)



b)



d)

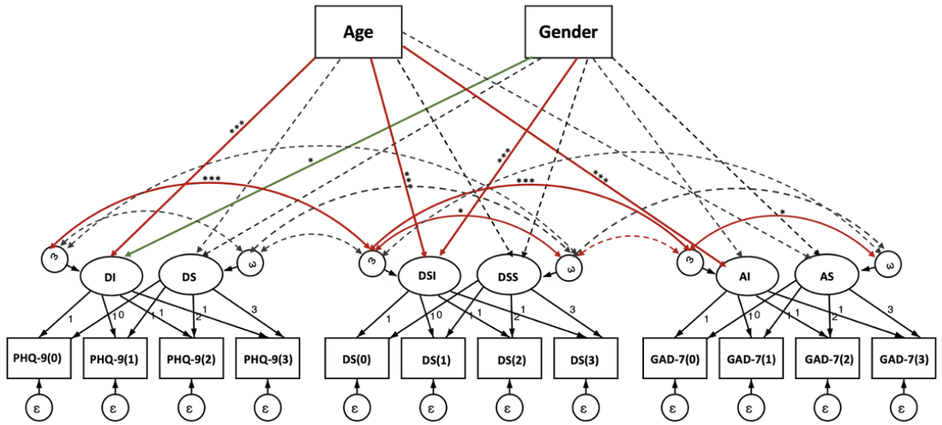
Fig.46a-d Latent growth curve model of anxiety, depressive symptoms and (a) VR (b) DS (c) SWM (d) PAL performance with time-invariant predictors (Age and Gender) for participants without history of depression. For clarity, the growth curve for only one cognitive measure is shown in each graph. DI/DS = depression intercept/ slope; AI/AS = anxiety intercept/anxiety slope; DSI/DSS = Digit Span intercept/slope; PI/PS = Paired Associates Learning intercept/slope; SI/SS = Spatial Working Memory Intercept/Slope; VI/VS = Verbal Reasoning intercept/slope.

significant negative associations or negative covariances.

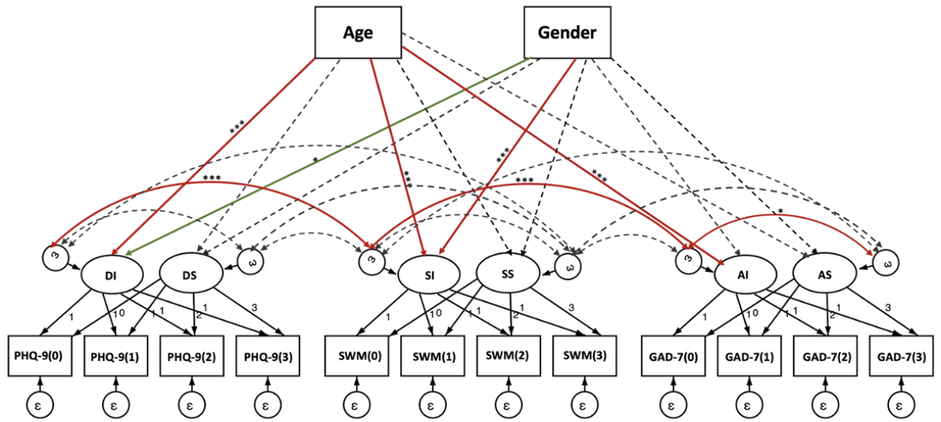
significant negative associations or negative covariances.

non-significant associations or covariances

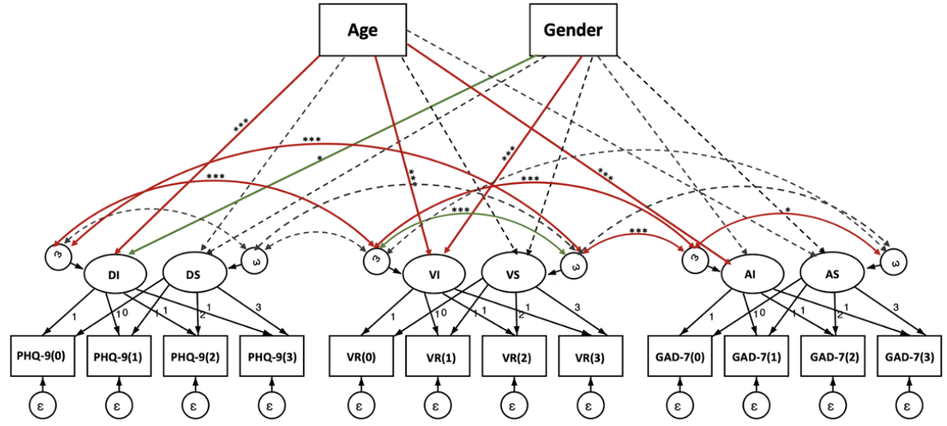
*** p<0.001| ** p< 0.01| *p<0.05



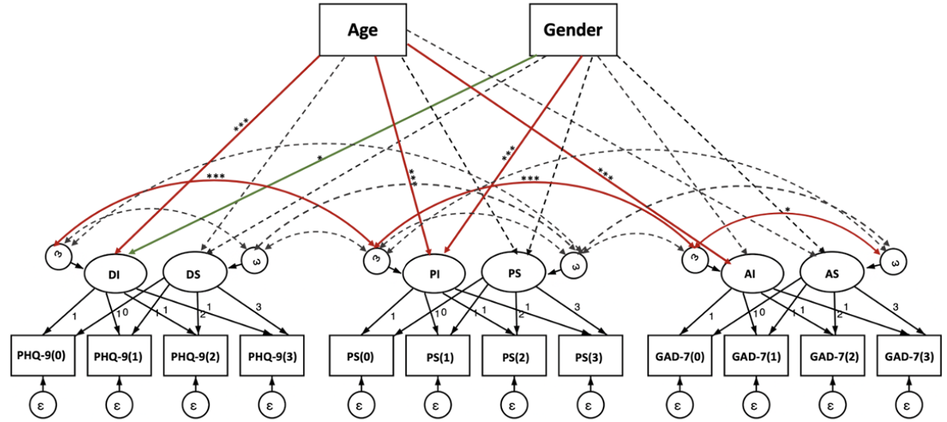
a)



b)



c)



d)

Fig.47a-d Latent growth curve model of anxiety, depressive symptoms and (a) DS (b) SWM (c) VR (d) PAL performance with time-invariant predictors (Age and Gender) for participants with a history of depression. For clarity, the growth curve for only one cognitive measure is shown in each graph. DI/DS = depression intercept/ slope; AI/AS = anxiety intercept/anxiety slope; DSI/DSS = Digit Span intercept/slope; PI/PS = Paired Associates Learning intercept/slope; SI/SS = Spatial Working Memory Intercept/Slope; VI/VS = Verbal Reasoning intercept/slope.

significant negative associations or negative covariances.

significant negative associations or negative covariances.

non-significant associations or covariances

*** p<0.001| ** p< 0.01| *p<0.05

6.4 Discussion

The present study investigated the relationship between depressive symptoms, anxiety symptoms and the performance on four cognitive domains in the general population of adults aged 50 or above, using several models. We observed significant associations between affective symptoms and cognitive performance, as well differences in patterns of these associations as between categories of participants with and without history of depression.

One of the most consistent findings was the one regarding the association between depressive symptoms and performance on Digit Span (DS) test, a measure of attention and verbal working memory. Cross-sectionally, both the severity of depressive symptoms on PHQ-9 scale and the presence of clinically significant depressive symptoms were associated with worse performance on DS. The same was observed in three-year cross-lagged models, which showed that both the severity of baseline depressive symptoms and the presence of clinically significant depressive symptoms predicted worse performance on DS at year 3. However, when all four waves were analysed using cross-lagged panel models, it could be observed that the majority of effects were driven by the associations between baseline and the first year of follow-up. A possible explanation in that albeit significant, the effects are very subtle, and therefore the power to identify them may be lost at later waves due to attrition.

Another important observation is that the negative associations between depressive symptoms and DS performance between baseline and Year 3 were reciprocal. This suggests that in the short term, poorer performance on working memory may also predict higher depressive symptoms. This observation is supported by the findings from LGCM analysis, which indicated that there exists both a negative correlation between the initial levels of depressive symptoms and the rate of "growth" in DS performance, and a negative correlation between the initial levels of DS performance and the rate of increase in depressive symptoms. In other words, higher depressive symptoms tended to be associated with steeper decline in working memory scores, and higher working memory scores predicted lower growth in depressive symptoms. However, three-year cross-lagged associations only showed a negative effect of depressive symptoms on verbal working memory scores; the same was observed for clinically significant depressive symptoms.

Anxiety proved to have an independent effect on the longitudinal performance on Digit Span, Verbal Reasoning and Spatial Working Memory tests. While DS is mostly seen as a

measure of the verbal working memory/attention domain of executive function, SWM assesses the visuospatial aspect of working memory. Our analysis showed that SWM performance at baseline was significantly associated with anxiety, not depressive symptoms, both when measured continuously and categorically. Similar findings were observed in three-year cross-lagged models, although only for measures of clinically significant anxiety and depression symptoms. Finally, LGCM analysis, we observed a significant negative correlation only between the slopes of anxiety symptoms and SWM performance, suggesting that the increase in anxiety symptoms over time may be associated with a decrease in SWM performance. This corresponds to findings previously reported by several studies. One showed that threat-evoked anxiety was specifically associated with disruptions in spatial working memory, and not verbal working memory (Lavric et al., 2003). Two more recent longitudinal studies showed that anxiety symptoms in older adults negatively affected longitudinal performance on Symbol Digit Modalities/Letter-Digit Substitution test (Gulpers et al., 2019; Burhanullah et al., 2020). While these are tests of processing speed, they also rely on visuospatial skills and working memory and therefore overlap with self-ordered search tasks used in our study to assess spatial working memory. Another recent study also showed that anxiety was independently associated with decline on attention, language and visuospatial skills z-scores (but not memory; Krell-Roesch et al., 2021).

The observed associations between depressive symptoms and DS, and anxiety symptoms and SWM, were only significant in the group of participants who did not report having a history of depression, suggesting that they may represent associations specific of late-onset affective symptoms. However, this needs further investigation.

The relationship between depressive symptoms, anxiety and performance on Paired Associates Learning test, a measure of episodic memory, was less consistent across several models, and generally weaker. We did observe a negative effect of depressive symptoms at baseline on PAL performance at Year 3, and also the negative correlation between the initial levels and the slope of depressive symptoms and the slope of PAL – however, none of these remained significant after stratification by history of depression, possibly due to loss of power, since the observed overall effect was very small. Therefore, in our sample, we only observed very weak effects of depressive symptoms on longitudinal episodic memory function. Emerging deficits in episodic memory have been shown to be early predictors of dementia, in particular Alzheimer's disease, therefore the mild association observed may be explained by the subset of depressive symptoms prodromal to dementia – however, in general, our findings indicate that there is a stronger link between affective symptoms and executive function rather

than episodic memory. Previous studies have shown conflicting results in this respect. Lohman et al. showed that patients with elevated depressive symptoms at baseline performed worse on HVLT and AVLT recall tests at baseline and had steeper decline in delayed recalled functioning longitudinally (2014). A more recent population cohort study also showed that higher depressive symptoms at baseline predicted self-reported memory problems at 10 years (Hill et al., 2019). However, a different study showed among five cognitive domains including episodic memory, language, working memory, executive function, and processing speed, the latter was the most important domain impaired in LLD, followed by executive function (Sheline et al., 2006). Deficits in processing speed were shown to fully mediate the effect of depression on other cognitive domains. Similar findings were presented in a study by Sexton et al., who showed that processing speed and executive function were the core cognitive domains impaired in LLD, explaining differences in episodic memory and language skills (2012). Generally, it is possible that longitudinal impairment in episodic memory in patients with late-life depression could be a feature of incipient dementia. Our cohort, however, was internet-based, so it is likely that participants with incipient dementia characterised by episodic memory decline would drop out, leaving those with better PAL performance in the sample.

Finally, depressive symptoms predicted worse performance on Verbal Reasoning test, which assesses general intelligence and reasoning skills. With regards to this domain, however, the effects were more pronounced in participants who reported having a history of depression. This can be observed in the stratified three-year cross-lagged model, as well as in the stratified LGCMs.

The study has a number of limitations. First, the measures of affective symptoms rely largely on self-report and therefore may lack accuracy. One attempt to overcome this consisted in applying rather stringent criteria to classifying participants based history of depression, where only those who reported both subjectively experiencing and having been diagnosed with depression were treated as having been previously depressed, and only those who reported neither were treated as never depressed. This, however, resulted in a reduction of sample size to just below 15,000 due to the exclusion of participants who couldn't be classified with certainty.

The cohort was not designed to target depressed elderly participants specifically, therefore the overall levels of both depression and anxiety symptoms in the sample is rather low. Given the large sample size, this is possibly an accurate reflection of the prevalence and severity of depressive symptoms in the population aged 50 and above in the UK: 7.4% of the initial sample presented with depressive symptoms above the threshold of clinical significance,

which corresponds with the estimates of the prevalence of late-life depression in the population (which, however, vary markedly between studies). Finally, a large dropout rate may have contributed to the loss of participants with worse cognitive functioning to follow-up, since the comparison of baseline characteristics in Table 1 suggests that participants with higher scores on each domain at baseline tended to remain in the study. It is reasonable to assume that the associations between affective symptoms and cognitive functioning may have been stronger in case participants with worse functioning had remained in the study.

6.5 Conclusions

Our study demonstrated significant three-year associations between depressive symptoms, anxiety and executive functioning in a population cohort of people aged above 50. Both depressive symptoms and anxiety symptoms were shown to independently affect cognitive functioning longitudinally. In particular, depressive symptoms predicted worse functioning on verbal working memory tasks, while anxiety symptoms were independently associated with worse functioning on visuospatial working memory tasks. These effects were specific to patients without a history of depression. Both depressive and anxiety symptoms were associated with worse functioning on tasks measuring general intelligence, which, in contrast, was more robust in participants with a history of depression. The association between depressive symptoms and episodic memory was weaker and lost significance after stratification by history of depression.

Whether observed associations can be attributed to prodromal dementia cases or are a proxy of depressive symptoms, cannot be inferred from the present study, since no outcome data concerning the progression to dementia is available for this cohort. However, the future steps will include analysing Alzheimer's disease polygenic risk scores in relation to the observed associations in order to establish whether some of them may be driven by the underlying Alzheimer's pathology.

Chapter 7, Part A. The comparison of plasma inflammatory markers between elderly depressed inpatients and non-depressed controls: a cross-sectional study

Abstract

Introduction

The role of inflammation in major depression has been the focus of many researchers over the past years. However, less is known with respect to late-life depression. The present cross-sectional study aimed to compare plasma concentrations of 12 cytokines and chemokines between elderly depressed subjects and healthy controls.

Methods

One hundred thirty-six elderly patients diagnosed with major depression were recruited in several inpatient psychiatric units in Norway; 103 non-depressed cognitively stable elderly individuals were recruited from routine surgery waiting lists as controls. Plasma levels of the following inflammatory factors were compared between the two groups: IL-1β, IL-1ra, IL-6, IL-10, IL-17a, IL-18, IL-33, TNFα, CD40L, IFN-γ, CCL-2 and CCL-4. First, multiple linear regression analysis was performed to compare levels of cytokines between the two groups; next, binary logistic regression was performed using depression status (depressed vs controls) as outcome, and each inflammatory factor dichotomised at the median as predictor, with Bonferroni-corrected p-value threshold set at $p<0.004$. Differences in plasma levels of inflammatory factors between patients with early-onset, late-onset depression and healthy controls were investigated using ANCOVA analysis, using multiple-comparison post-hoc correction.

Results

Fully adjusted multiple linear regression analyses revealed significant increases in the levels of IL-1ra, IFN-γ, CCL-2, CCL-4 and IL-17a in depressed patients compared to controls. Higher vs lower levels of IL-1ra and IFN-γ significantly and independently predicted depression status in logistic regression analysis. No clinically significant differences were observed between EOD and LOD with regards to plasma inflammatory markers concentration.

Conclusion The study demonstrated significant increases in several plasma inflammatory markers in patients with moderate-to-severe late-life depression compared to healthy controls. While the present study highlighted the involvement of inflammatory factors in the pathogenesis of late-life depression, further longitudinal studies with repeated measures of biomarkers are needed to evaluate the temporal relationship between late-life depression and systemic inflammation.

7.1 Introduction

Late-life depression is a serious medical condition which affects about 2% of older adults and is associated with substantial healthcare burden (Kok and Reynolds, 2017). Moreover, having a depressive episode after the age of 60-65 has been consistently associated with increased likelihood of developing dementia later in life (Diniz et al., 2013; Cherbuin et al., 2015; Lee et al., 2020), as well as with accelerated cognitive decline (John et al., 2018).

There is a burgeoning literature implicating the role of inflammation in the pathogenesis of major depression. The main immunomodulating agents researched in this respect are cytokines – small proteins that act as signalling molecules and regulate the immune response. Elevated levels of systemic and neuro-inflammation in depression have been shown to decrease neurogenesis, leading to neurodegeneration and reduced hippocampal volumes, stimulate the activation of the hypothalamic-pituitary-adrenal (HPA) axis, downregulate the expression of brain-derived neurotrophic factor (BDNF), and induce indoleamine 2,3-dioxygenase 1 (IDO1) which degrades tryptophan increasing kyneurine and quinolinic acid, leading to hyposerotonergia and hyperglutamatergia (Borsini et al., 2016; Bo et al., 2018).

Quite a few studies and meta-analyses have shown elevated levels of a number of pro- and antiinflammatory cytokines in depressed patients, including IL-6, CRP, TNF-α, IL-1ra, IFN-y, IL-10, IL-18 and a few other (Howren et al., 2009; Haapakoski et al., 2015, Koehler et al., 2017; Smith et al., 2018). However, much less is known about inflammation specifically in late-life depression. A meta-analysis by Ng et al. focused on peripheral levels of Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF- α) and C-Reactive Protein (CRP) and demonstrated elevated levels of IL-1β and IL-6 in late-life depression compared to controls, but not of TNF- α or CRP (Ng et al., 2018). Data on other inflammatory markers in late-life depression has been scarce.

Elucidating the role of inflammation in late-life depression appears especially important in light of the fact that elevated inflammatory markers have also been observed in neurocognitive disorders (Swardfager et al., 2010, Chen et al., 2018, Lai et al., 2017, Su et al., 2019). In fact, some studes have shown the peripheral inflammatory factors might mediate the relationship between late-life depression and dementia (Gallagher et al., 2016; Royall et al., 2017).

One of the challenges in studying the pathological or immunological markers of late-life depression lies in the fact that depression in the elderly is a recognizably heterogenous condition. An important source of heterogeneity is the fact that late-onset geriatric depression

(LOD) may represent a pathologically distinct condition compared to early-onset recurrent depression (EOD) with an episode in late life (Naismith et al., 2012). However, few of the studies addressing inflammation in late-life depression distinguish between the phenotypes. A study by Rozing et al. showed that levels of C-reactive protein are elevated in LOD compared to EOD; this was also confirmed by Vogelzangs et al., although only in men (Rozing et al., 2019; Vogelzangs et al., 2012). The latter study also showed elevated TNF-α in men with a later onset of depression. Two studies compared the levels of IL-1β between LOD and EOD patients, but only one demonstrated a significant elevation in EOD compared to both LOD and healthy controls(Thomas et al., 2005; Diniz et al., 2010). Other commonly described inflammatory markers of late-life depression have not been addressed from this angle.

The present study compares levels of 12 plasma cytokines and chemokines, representing different aspects of immune responses, between 136 elderly patients referred to psychiatric services for late-life depression and 103 non-depressed elderly participants. This is the first study to address such a wide spectrum of inflammatory markers in a sample of geriatric patients diagnosed with major depression in clinical settings.

7.2 Objectives

The primary objective of the study was to compare levels of plasma inflammatory markers between depressed elderly patients and mentally healthy control subjects.

The secondary objective was to investigate differences in inflammatory cytokines between patients with early- and midlife-onset, late-onset depression and never-depressed controls.

7.3 Methods

Design and Sample

The study had a cross-sectional design.

Depressed elderly participants were recruited to the PRODE (Prognosis of depression in the elderly) cohort between December 1st, 2009 and January 1st, 2013. The original cohort included 169 patients suffering from a late-life depressive episode diagnosed according to ICD-10 criteria. Seventeen subjects were also diagnosed with dementia at baseline and therefore

were not included in the present analysis; cytokine data was available for 136 patients. A detailed description of the cohort has been previously published (Borza et al., 2015).

Non-depressed participants were recruited to the COGNORM study from 2012 to 2013 at Oslo University Hospital and Diakonhjemmet Hospital, Oslo. A total of 172 patients, aged 64 years or older in the year of inclusion, undergoing elective gynecological, orthopedic, or urological surgery in spinal anaesthesia, were assessed with a multi-domain battery of cognitive tests prior to surgery. Patients were excluded if they had dementia, previous stroke with sequela, Parkinson's disease or other acknowledged or suspected brain diseases likely to influence cognition. Patients were also excluded if they had a current depression score above 8 on MADRS. Cytokine data was available for 103 control participants.

Patient characteristics

Registered demographic characteristics of participants included age, gender, education level (in years), and marital status. In addition, smoking status was assessed since cigarette smoke has been previously linked to increased levels of inflammation (Strzelak et al., 2015). Smoking was initially assessed as three categories: "Never smoked", "Quit smoking in the past" and "Current smoker", however, exploratory analyses showed no difference in inflammation between participants who had never smoked and those who quit, therefore smoking was recoded as a binary variable.

Clinical measures

The assessment of mental state was performed by trained clinical specialists. Major depression was diagnosed by psychiatrists or clinical psychologists using ICD-10 criteria. History of mental disorders, including the presence, number and duration of past depressive episodes, was recorded during clinical interviews.

Depressed patients were categorised as "Early- or midlife-onset" (EOD) if they reported having a history of depression with age of onset below 60, and as "Late-onset" (LOD) if they reported a history of depression with age of onset at age 60 or above, or had their first episode of depression on admission to the study.

The severity of current depressive symptoms was assessed with the Montgomery and Åsberg Depression Rating Scale (MADRS). The scale consists of 10 items assessing depressive symptoms that are rated on a scale from 0 to 6 (total score 0–60); higher scores indicate more severe symptoms.

Cognitive performance was evaluated using the Mini Mental State Examination (MMSE) scale, with a score range of 0–30, where lower score indicates worse performance.

Physical comorbidity

Data on comorbid ICD-10 diagnoses was available for all participants. Present medical comorbidity was coded as binary variables using the following categories: "heart disease" (including diagnoses related to coronary heart disease, heart failure and arrythmia), hypertension, diabetes, cancer, cerebrovascular disorders, head injuries, and autoimmune disorders.

Cytokine analysis

Blood samples were drawn by venipuncture and collected for assessment in sterile serum tubes on admission to psychiatric or surgical unit for PRODE and COGNORM patients, respectively. Frozen specimen were further shipped to the Oslo University Biobank and stored at -70^{o}C. A total of 12 inflammatory markers were selected based on their previously reported association with depression, and specifically late-life depression. These included IL-1β, interleukin-1 receptor antagonist (IL-1ra), IL-6, IL-10, IL-17a, IL-18, IL-33, TNFα, cluster of differentiation 40 ligand (CD40L), interferon (IFN)-γ, and chemokine ligands (CCL)-2 and CCL4.

The markers were analyzed according to the manufacturer's protocol using a bead-based multiplex immunoassay panel (Bio-Techne, Minneapolis, MN) based on xMAP Technology (Luminex, Austin, TX). Inflammatory marker concentrations were calculated using a

5-parameter standard curve based on standards that were supplied by the manufacturer. All analyses were run at the same time, with the exception of 1 of the 10 plates which had to be reanalysed due to a technical error (reanalysis data was used for CD40L and IL-10. Values below the lower limit of quantification (LLOQ) were set to 25% of LLOQ, and standard curves with a high LLOQ were selected to obtain a similar sensitivity for all samples analyzed. Frequencies of values below LLOQ for each of the cytokines are presented in Table 11 in Chapter 2 .All values were reported in picogram/millilitre.

Statistical analysis

The normality of the distribution of outcome variables (plasma cyto- and chemokine levels) was examined using histograms and Q-Q plots. Cytokine values were winsorised (outliers replaced with mean score +/− 2.5 SD).

Baseline differences in clinical and demographic characteristics were analysed using t-tests and chi-square tests and their nonparametric/exact analogues as appropriate.

Differences in the levels of inflammatory biomarkers between depressed and non-depressed subjects were assessed using multiple linear regression, adjusted for covariates in a stepwise manner. Model 1 presented the results of univariate associations, Model 2 was adjusted for age and gender; Model 3 was further adjusted for smoking status; and Model 4 was further adjusted for physical comorbidities. Only covariates known/hypothesised to influence both inflammatory status and depression were added (i.e. while years of education or marital status have a strong association with depression, they're not known to have a direct effect on inflammation and therefore were not included as covariates).

Assumption of independence of observations was checked using the Durbin-Watson statistic and multicollinearity was excluded by inspecting correlation coefficients and Tolerance/VIF values. Influential observations were identified for each model by examining DFBeta coefficients and Cook's distances; where observations had both high DFBetas (>2/sqrt(N)) and Cook's distance (>4/N), analyses were rerun excluding those. Heteroscedasticity was assessed graphically using scatterplots of predicted residuals, as well as using the Breush-Pagan test. When there was evidence of potential heteroscedasticity in the data, heteroscedasticity consistent standard errors were calculated.

To investigate the association between high levels of inflammation and depression status, values of each inflammatory marker were dichotomised at the median. While arbitrary, this is in line with the previous research (Penninx et al.,) Binary logistic regression was performed with depression status as outcome variable. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for univariate analysis (Model 1), and analysis adjusted in a stepwise manner for demographics (Model 2), demographics and smoking status (Model 3), and further for physical comorbidity (Model 4). For results from logistic models, a more conservative Bonferroni-corrected p value of < 0.004 was used in order to adjust for the high likelihood of spurious statistical results deriving from simultaneously investigating 12 inflammatory markers for each definition of depression.

Differences in plasma levels of cytokines between LOD, EOD and controls were investigated using ANCOVA analysis adjusted for the same covariates as above, using multiple-comparison post-hoc correction for significant models.

Sensitivity analysis was performed by excluding controls with a history of depression (n=8). Besides, where 50% or more of cytokine values in either of the cohorts were below LLOQ, a sensitivity analysis was run using binary measures of each cytokine (detectable/non-detectable).

All analyses were performed using Stata/MP version 16.1.

7.4 Results

7.4.1 Demographic and clinical characteristics

Mean age of participants was 75.0 years (SD 6.91); the majority were female (63.18%). The participants had on average 12 years of education (IQR 9-15). Most were married (50.63%) or widowed (34.73%).

Median MADRS score was 1 (IQR 0-3) in the control group and 26 (IQR 21-32) in the MDD group. Depressed patients were older than non-depressed ones, and had a higher proportion of females ($p<0.01$). At the same time, non-depressed patients had a higher level of education ($p<0.001$). Only 8 people (7.21%) in the control group reported having a history of depression, compared to 104 (68.9%) in the MDD group ($p<0.001$). Full comparison of demographic and clinical characteristics between depressed and non-depressed participants is presented in Table 42.

7.4.2 Plasma inflammation in depressed patients vs controls: linear regression models

Simple linear regression analysis revealed significant differences between depressed patients and controls in levels of CCL-2, CCL-4, IFN-γ, IL-10, IL-6, IL-17a, IL-1ra, IL-33 and TNF-α (See Table 43).

After the first step of adjustment (for age and gender), TNF-α and IL-6 levels were no longer significantly associated with depression. After full adjustment, differences remained

significant for *CCL-2*, *CCL-4*, *IFN-γ*, *IL-17a*, and *IL-1ra*. *Fig.1* illustrates the differences in inflammatory markers which remained significant after full adjustment.

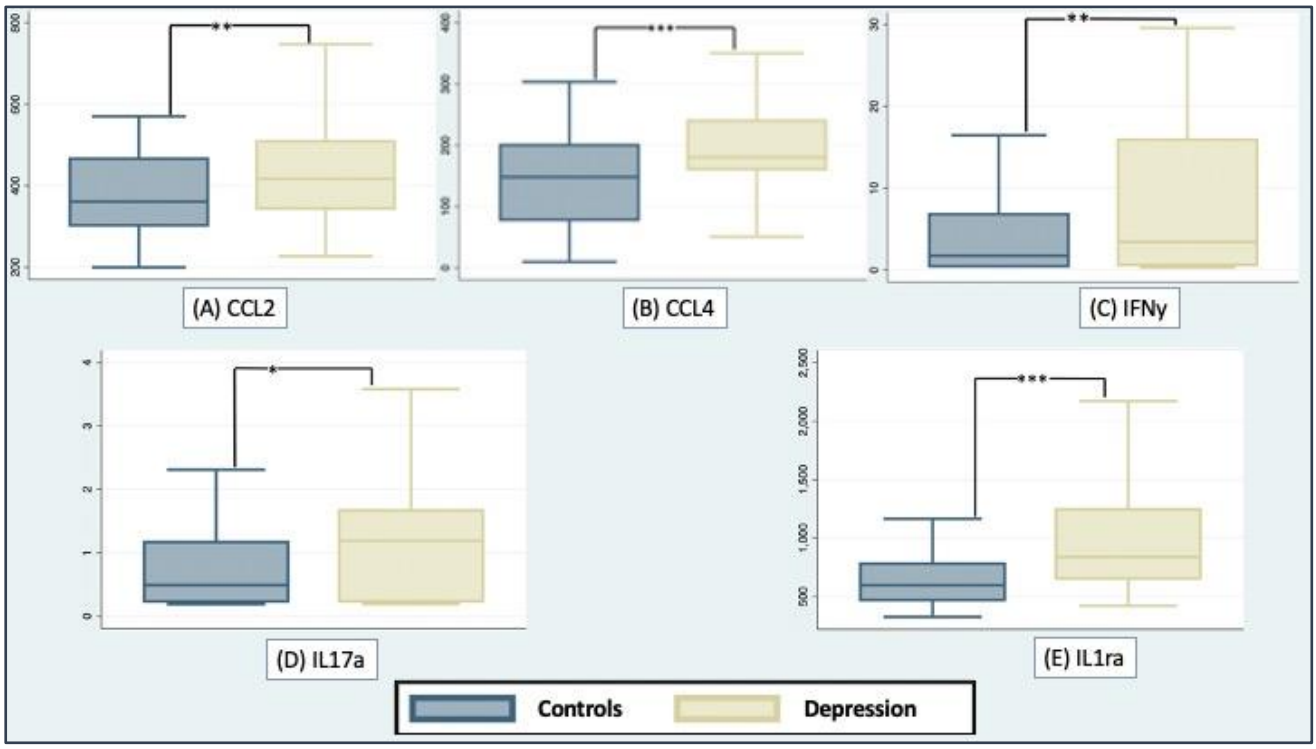


Fig.48 Differences in median plasma concentrations of cyto- and chemokines between patients with late-life depression and healthy controls. All presented values are in pg/mL. (A) CCL-2; (B) CCL-4; (C) IFN-γ**;** (D) IL-17a; (E) IL-1ra; ; *** p<0.001; ** p<0.01; *p<0.05

7.4.3 Low- vs high-level inflammation in depressed patients vs controls: results from binary logistic regression

In univariate binary logistic regression, depression was significantly associated with higher levels of CCL-4, IL-1ra, IFNγ, and IL-33; the associations with IL-10, CCL-2 and TNF-α were significant below the Bonferroni-corrected threshold (See *Table 44*).

In a fully adjusted model, depression was significantly associated with higher levels of IFN-γ and IL-1ra. When mutually adjusted, IFN-γ and IL-1ra showed independent significant effects **(**See Table 2**).** TNF-α, IL-33, CCL-4 and CCL-2 were all significant below the general p-value threshold, but did not survive Bonferroni-correction.

7.4.4 Age of depression onset and levels of plasma cytokines

Three-way ANCOVA models were significant for CCL2 (p=0.02), IFN-γ (p=0.002), CCL4 (p<0.001), Il1ra (p<0.001), and TNF- α (p=0.04). Post-hoc analysis showed that CCL2 (432.37 vs 377.91, p = 0.037; 443.42 vs 377.91, p=0.005), CCL4 (183.78 vs 144.61, p=0.014; 194.22 vs 144.61, p <0.001), Il-1ra (1018.69 vs 646.62, p<0.001; 1042.82 vs 646.62, p<0.001) and IFN-γ (9.14 vs 4.71, p = 0.015; 8.53 vs 4.71, p = 0.006) levels were significantly elevated in depressed patients irrespective of age of onset. After adjustment, CCL-2 and CCL-4 only remained significantly elevated in LOD vs controls. However, none of the inflammatory markers differed between EOD and LOD participants.

7.4.5 Sensitivity analysis

When participants with a history of depression were excluded from the control group, differences in inflammatory markers mostly remained significant in fully adjusted models, however not for IL-33 (p = 0.053). When participants with a history of depression were excluded from the control group, differences in inflammatory markers remained unchanged in fully adjusted models.

Sensitivity analysis based on detectability levels was performed for IL-1β and IL-10 using binary measures (below or above LLOQ). No differences in results of previously reported analyses were observed for Il-10; however, logistic regression with depression status as outcome (see section 3.3) and IL-1β dichotomised as detectable vs non-detectable showed that IL-1β is a significant predictor of depression in a univariate model (OR 2.48, 95%CI 1.48 – 4.15, p<0.001), and also significant, although above the Bonferroni-corrected p-value, in a fully adjusted model (OR 2.26, 95% 1.26 – 4.05, p=0.006). When further adjusted for other cytokines, IL-1β dichotomised by detectability was not an independent predictor of depression, unlike IFN-γ and IL-1ra.

	Depression (N=136)	**Controls (N=103)**	**Test statistic**	**p-value**
Numerical characteristics				
Age (Mean(SD))	76.10(6.88)	73.55(6.73)	t = -2.87, df(237)	0.002
Years of education (Median, IQR)	9 (8-12)	14 (12-17)	W = 8.52	<0.001
MADRS (median, IQR)	26(21-31)	1(0-3)	W = 6.71	<0.001
MMSE (median, IQR)	27(24-29)	29 (29-30)	W = -13.20	<0.001
Categorical characteristics				
	N(%)	N(%)	**χ2**	**p-value**
Gender (female)	98 (72.06)	53(51.46)	10.69	0.001
Marital status				
Married	55 (40.44)	66 (64.08)	16.36	0.001
Widowed	57 (41.90)	26 (25.24)		
Single	10 (7.35)	1 (0.97)		
Divorced/separated	14 (10.29)	10 (9.71)		
Physical/mental health history				
Smoking status (yes)	11(10.68)	27(20.61)	4.18	0.041
Cancer	30 (22.06)	35 (33.98)	4.21	0.040
Diabetes	13 (9.56)	8 (7.77)	0.24	0.63
Hypertension	67 (49.26)	38 (36.89)	3.64	0.056
Cerebrovascular	21 (15.44)	14 (13.59)	0.16	0.69
Head injury	35 (26.52)	10 (9.71)	10.55	0.001
Autoimmune dis.	11 (8.09)	6 (5.83)	0.45	0.50
Heart disease	47 (34.56)	20 (19.42)	6.66	0.01
History of depression	91 (67.41)	8 (7.77)	85.54	<0.001

Table 45. The comparison of demographic and clinical characteristics between patients with late-life depression and controls. Test statistic for relevant tests (Student's t-test, Wilcoxon rank sum test or Pearson's chi-square test) and p-values are presented for differences between patients and controls.

	Model 1 (β, 95%CI)	p-value	Model 2 (β, 95%CI)	p-value	Model 3 (β, 95%CI)	p-value	Model 4 (β, 95%CI)	p-value	R2(fully adjusted model)
CCL2	**42.15 (11.50 - 72.80)**	**0.007**	**41.13 (8.73-73.54)**	**0.013**	**51.74(18.17-85.31)**	**0.003**	**53.50 (17.34 – 89.65)**	**0.004**	0.13
CD40L	301.50 (-109.80 - 712.80)	0.15	196.53(-209.60 – 602.67)	0.32	86.98(-300.24 - 474.20)	0.66	215.61 (-195.27 - 626.50)	0.30	0.13
IL-1β	0.11 (-0.04 – 0.25)	0.14	0.10(-0.06 - 0.27)	0.22	0.13(-0.04 - 0.29)	0.14	0.10 (-0.07 – 0.28)	0.25	0.04
IL18	4.07(-13.99 – 22.13)	0.66	10.33 (-7.88 – 28.55)	0.27	7.08(-12.35 - 25.01)	0.51	10.78 (-8.33 - 29.88)	0.27	0.14
IL6	**0.62 (0.12 – 1.11)**	**0.015**	0.33(-0.13 - 0.78)	0.16	0.21(-0.25 - 0.67)	0.37	0.30(-0.23 - 0.82)	0.27	0.09
CCL4	**58.15 (37.83 – 78.47)**	**<0.001**	**43.11 (22.27 – 63.96)**	**<0.001**	**35.48(13.81 - 57.15)**	**0.001**	**36.19 (14.91 - 57.47)**	**0.001**	0.19
IFNγ	**4.58 (2.88 – 6.73)**	**<0.001**	**4.04(2.25-5.83)**	**<0.001**	**3.57(1.59 - 5.54)**	**<0.001**	**4.18(2.15 - 6.20)**	**<0.001**	0.15
IL12p40	0.59 (-1.12 – 2.29)	0.52	0.28 (-1.50 – 2.06)	0.76	**0.31 (-1.55 – 2.17)**	**0.74**	0.22 (-1.75 – 2.19)	0.83	0.02
IL10	**2.59 (0.53 – 4.65)**	**0.014**	**2.06 (-0.23 – 4.34)**	0.08	1.69(-0.81 - 4.17)	0.18	2.47 (-0.02 - 4.96)	0.05	0.10
IL17a	**0.26 (0.05 – 0.47)**	**0.014**	**0.38(0.17-0.58)**	**<0.001**	**0.33(0.09 - 0.56)**	**0.006**	**0.30 (0.03 - 0.56)**	**0.03**	0.07
IL1ra	**243.47 (151.90 - 335.04)**	**<0.001**	**219.53(126.61-312.44)**	**<0.001**	**217.16(122.22 - 312.11)**	**<0.001**	**235.59(123.63 - 347.56)**	**<0.001**	0.11
IL33	**0.46 (0.13 – 0.79)**	**0.007**	**0.46(0.13-0.80)**	**0.007**	**0.40(0.03 - 0.77)**	**0.033**	0.17 (-0.25 - 0.59)	0.43	0.04
TNF-α	**0.27(-0.21 – 0.74)**	**0.026**	0.25(-0.24 – 0.74)	0.31	0.46 (-0.06 - 0.96)	0.081	0.29(-0.23 - 0.82)	0.28	0.02

Table 46. The results of linear regression models comparing the differences in plasma cytokine levels between patients with late-life depression and control subjects

	CCL2	CD40L	IL-1β	IL-18	IL-6	CCL4	IFNγ	IL-10	IL12p40b	IL-17a	IL-1ra	IL-33	TNF-α
Model 1 (OR [95%CI])	1.82[1.11-2.99]†	1.27[0.78-2.07]	1.62[0.99 – 2.65]	1.19[0.73-1.95]	1.45[0.89-2.37]	**2.70[1.63-4.47]*** **	**3.44[2.05-5.77]*** **	1.72[1.04-2.86]†	1.29 [0.77 – 2.15]	1.52[0.93 - 2.49]	**3.48 [2.09-5.82]*** **	**2.12[1.29-3.49]** **	2.07[1.26-3.4]*
Model 2 (OR [95%CI])	1.65[0.99-2.76]	1.19[0.71 - 2.00]	1.74[1.03-2.93]†	1.53[0.90-2.61]	1.26[0.75 - 2.13]	**2.26[1.34 - 3.83]** **	**3.92[2.25 - 6.82]*** **	1.70[1.004-2.88]†	1.17[0.69 – 2.00]	1.68[1.00-2.85]†	**3.29[1.93-5.59]*** **	2.14[1.26 - 3.61]*	1.85[1.10-3.11]†
Model 3 (OR [95%CI])	1.84[1.08 - 3.13]†	1.04[0.61 - 1.79]	1.67[0.98-2.87]	1.47[0.85-2.53]	1.13[0.66-1.96]	2.15[1.26 - 3.69]*	**3.48[1.98 - 6.12]*** **	1.77[1.03 - 3.05]†	1.26[.73 - 2.19]	1.55 [0.90 - 2.65]	**3.03[1.76 - 5.22]*** **	1.95[1.14 - 3.34]*	1.95[1.14-3.32]†
Model 4 (OR [95%CI])	2.14[1.21 - 3.81]†	1.21[0.68-2.15]	1.60[0.90-2.81]	1.70[0.94-3.04]	1.17[0.66 - 2.11]	2.14[1.21 - 3.80]*	**3.77[2.04 - 6.95]*** **	1.63[0.91 - 2.91]	1.15[0.64 – 2.07]	1.500[0.84 - 2.68]	**3.09[1.74 - 5.51]*** **	1.80[1.01 - 3.2]†	1.97[1.12 - 3.47]†

Table 47. The associations between low- and high-level inflammation and depression status
***** p<0.001; ** p<0.04 *p< 0.01 †p<0.05**
Bonferroni-corrected significance threshold is set at p<0.004

7.5 Discussion

We demonstrated substantial differences in the concentrations of plasma inflammatory markers between older depressed patients and non-depressed cognitively normal older adults. The levels of pro-inflammatory cytokines IL-17a, IFN-γ, pro-inflammatory chemokines CCL-2 and CCL-4 and anti-inflammatory cytokine IL-1ra were significantly higher in older depressed patients compared to controls. We also demonstrated that above-median concentrations of IL-1ra and IFN-γ significantly discriminated depressed patients from controls.

Previous studies have provided inconsistent results with regards to IFN-γ concentrations in the plasma of depressed patients, with some pointing to decreased levels, other reporting higher IFN-γ levels (Köhler et al, 2017; Dahl et al., 2014). IFN-γ is a cytokine critical for innate and adaptive immunity. In the CNS, its functions are associated with inducing indoleamine 2,3-dioxygenase 1 (IDO1), which degrades tryptophan and leads to increases in the concentration of kyneurine and quinolinic acid, which in turn results in decreases in serotonin levels (Inserra et al., 2019). One possible explanation of studies reporting higher levels of IFN-γ, including our study, is that this elevation may represent a functional characteristic: IFN-γ was shown to downregulate IL-10, IL-1β and to inhibit Treg cell accumulation by IL-33 – elevation of some of these factors (IL-10, IL-33) was observed in our study, although not after full adjustment. Therefore, IFN-γ elevation in our sample may reflect a reactive state associated with intense general levels of inflammation in the depressed group.

Interleukin-1 receptor antagonist (IL-1ra): unlike other factors, it's an anti-inflammatory cytokine, and acts like an inhibitor of IL-1 family cytokines. Our finding that IL-1ra is elevated in LLD is in line with a large bulk of previous research: at least two meta-analyses have shown increased levels of IL-1ra in MDD patients compared to controls (Howren et al., 2009; Osimo et al., 2020). One study previously investigated plasma IL-1ra in LLD, and showed that levels of this cytokine were significantly higher in depressed patients, and also, higher IL-1ra predicted depression incidence over 6 years of follow-up (Milaneschi et al., 2009).

Pro-inflammatory cytokine IL-33, belonging to the IL-1 family, and pro-inflammatory cytokine IL-17a, which was shown to work in concert with IL-1 family, were also higher in depressed participants in our sample (although IL-33 lost significance after full adjustment,

therefore these results should be treated with caution). These findings are rather novel, since very few studies have addressed the role of these two factors in depression, and especially in LLD. There has been some indication of elevated IL-33 levels in cross-species studies (Kudinova et al., 2016), and IL-17a was associated with depressive symptoms in rodent models (Kim et al., 2012), however, Saraykar et al. found no significant difference in IL-17a between patients with LLD and controls (2018).

In our study, both CCL-2 and CCL-4 were shown to be elevated in elderly depressed patients. CCL-2 and CCL-4 are known as "chemokines", or small chemotactic cytokines. They have been shown to induce chemotaxis, leukocyte and macrophage migration, and propagate inflammatory response. With respect to the CNS function, chemokines have been implicated in the modulation of neurotransmitter release (Milencovic et al., 2019). However, while CCL-2 and CCL-4 are both known to exert pro-inflammatory effects, previously published meta-analyses showed different directions of change in the two factors in MDD patients: elevation of CCL-2 and decrease in CCL-4 (Eyre et al., 2016; Leighton et al., 2017). One meta-analysis also showed that antidepressant treatment may decrease CCL-2 levels in depressed patients (Köhler et al., 2017). This finding was not consistent with respect to other medical conditions: e.g.in a diabetes study, patients were shown to have higher CCL-2 levels than their healthy siblings, but there was a trend for lower CCL-4 levels (Thorsen et al., 2014); while in cancer patients, both markers were elevated compared to controls (Lopez et al., 2018).

Strengths and limitations

There are several limitations to this study. First, while it points to significant correlations between plasma inflammation and major depression, it does not allow us to evaluate the temporal associations between depressive symptoms and inflammatory factors and draw conclusions regarding causal relationships. Currently, there is little consensus on whether inflammation represents a state or trait feature of depression, and whether cross-sectional associations persist over time. A systematic review which included only longitudinal studies of the association between plasma inflammatory markers, concluded that higher levels of IL-6, IL-8 and TNF-a could predict the development of depression during follow-up (Martínez-Cengotitabengoa et al., 2016). A more recent longitudinal study demonstrated that, in depressed patients, higher circulating IL-6 levels were associated with a significantly slower decline in depressive symptoms over 2 years of follow-up (Rozing et al., 2019). However, another study (though not in late-life depression) found that while IL-1Ra, IL-6, IL-7, IL-8, IL-

10, G-CSF, and IFN-γ were higher in major depression during an acute episode, their levels reversed to normal post-treatment (Dahl et al., 2014).

Another potential limitation is that only plasma cytokine measures were available for both depressed patients and control participants. Whether peripheral inflammation reflects CNS inflammation enough to be used as its measure, is debatable. On the one hand, several studies demonstrated that cytokines efficiently permeate the blood-brain barrier (BBB), suggesting that plasma cytokine concentrations can serve as markers of CNS inflammation (Yarlagadda et al., 2009). On the other hand, studies of cytokine correlations between CSF and plasma in psychiatric patients have showed mixed results. In a study by Miller et al., CSF concentrations of interleukin-1β, interleukin-23 and interleukin-33 were associated with perinatal depression, but plasma concentrations were not; correlation between CSF and plasma measures was at least moderate (2019). Wijeyekoon et al. found no correlations between plasma and CSF cytokines and their soluble receptors in Parkinson's patients. In another study, however, CRP levels in plasma and CSF were strongly correlated, and clusters of CSF inflammatory markers were associated with high plasma CRP (>3mg/L) and correlated with depressive symptom severity (Felger at al., 2020). The majority of studies assessing inflammatory markers in major depression have measured plasma concentrations of cyto- or chemokines. Only one meta-analysis focused on CSF biomarkers: it indicated significantly higher IL-6 and IL-8 levels in depressed patients (of all ages) compared to controls, but failed to confirm differences in TNF-α and IL-1β (Wang et al., 2018). Whether plasma measures of inflammation indeed are a valid indicator of neuroinflammation and whether plasma cytokine analysis is a useful tool for exploring the neurobiology of LLD, remains to be determined.

The vast majority of studies assessing inflammatory markers in major depression have measured plasma concentrations of cyto- or chemokines. There was only one meta-analysis that focused on CSF biomarkers: it indicated significantly higher IL-6 and IL-8 levels in depressed patients (of all ages) compared to controls, but failed to confirm differences in TNF-α and IL-1β (Wang et al., 2018). Whether plasma measures of inflammation indeed present a valid indicator of neuroinflammation and whether plasma cytokine analysis is a useful tool for exploring the neurobiology of late-life depression, remains to be determined.

In addition, two of the cytokines – IL-10 and Il-1β had over 50% of values below lower limit of quantification. When dichotomised by detectability, results for IL10 remained unchanged, however, patients with detectable levels of Il-1β were more likely to have

depression compared to those with undetectable levels. Therefore, negative results with respect to Il-1β should be treated with caution.

The strength of the study lies in the fact that it included a thoroughly phenotyped clinical sample of elderly depressed inpatients, and analysed a wide array of cytokines. This was the first study to demonstrate elevated IL-33 and IL-17a levels in late-life depression, and also the first one to show higher CCL-2 and CCL-4 concentrations specifically in late-onset depression. However, data on some factors consistently implicated in the pathophysiology of major depression, e.g. interleukin 8 (IL-8) and C-reactive protein (CRP), was not available for this sample. Besides, IL-6 - the cytokine most frequently associated with major depression, including late-life depression, - lost significance in our analysis after adjustment, and some factors did not survive adjustment for multiple comparisons. This may be due to the insufficient power of the sample to detect significant differences, since the sample size is relatively small.

Chapter 7, Part B. Peripheral inflammatory markers as predictors of conversion from late-life depression to dementia: Results from the PRODE cohort

Abstract

Introduction Higher levels of plasma and CSF inflammatory markers have been observed in many studies and meta-analyses in both major depression and dementia. However, few have addressed inflammatory markers as a possible link between depression in later life and cognitive decline using a longitudinal design. Two previous studies have shown that plasma inflammatory markers may mediate the relationship between clinically significant depressive symptoms and cognitive decline (Gallagher et al., 2016; Royall et al., 2017), although a recent study in patients with type 2 diabetes failed to replicate these findings (Carr et al., 2021). To our knowledge, this is the first study to investigate an array of inflammatory markers as potential predictors of progression from late-life depression to dementia in a naturalistic clinical cohort of patients admitted to psychiatric units for late-life depression, with no dementia at baseline.

Objectives The objective of the study has been to investigate whether the levels of plasma inflammatory markers at baseline could predict progression from no dementia to dementia in a clinical cohort of patients with late-life depression (aged ≥ 60).

Methods The study was performed in the PRODE (Prognosis of Depression in the Elderly) cohort (Borza et al., 2015). The sample included 152 patients diagnosed with late-life depression; 96% were receiving inpatient treatment in a psychiatric unit. About half of the patients (53.1%) were diagnosed with recurrent early- and midlife-onset depression (age at onset <60), while the rest had a late onset (at age ≥ 60). A neuropsychological test battery was administered on admission and before discharge. Baseline biomarker data was available for 136 patients, for the following range of cytokines and chemokines: IL-1β, IL-1ra, IL-6, IL-10, IL-17a, IL-18, IL-33, TNFα, CD40L, IFN-γ, IL12p40, CCL-2 and CCL-4. After discharge, patients were followed up at 1 year and 3 years. Outcome data for the incidence of dementia on at least one follow-up was available for 138 patients. Predictors of conversion to dementia were analysed using Cox proportional hazards regression. Sensitivity analysis was performed by excluding patients with MMSE score below 25 post-treatment.

Results Thirty-six patients (26.1%) were diagnosed with dementia during follow-up. None of the baseline inflammatory markers predicted conversion to dementia either in univariate or adjusted analyses; inflammatory markers also did not significantly affect performance on neurocognitive tests either at baseline or at follow-up. History of depression, age of onset and

number of previous depressive episodes also did not differ between converters and non-converters. Sensitivity analysis did not change these findings.

Conclusion In a cohort of 152 elderly participants admitted to inpatient units for late-life depression, plasma inflammatory markers did not predict progression to dementia or worse performance on neurocognitive tests. Clinical factors (age of onset, recurrence, number of previous episodes) also did not affect the risk of progression to dementia.

7.7 Introduction

Dementia is a clinical syndrome which represents a group of conditions characterised by varying manifestations and pathways but sharing a common feature of causing progressive cognitive decline and eventually leading to loss of functioning in elderly people. The prevalence of dementia in the world is growing at alarming rates: the estimated increase in the worldwide elderly population in the decades ahead (from about 600 million now to 1.5 billion in 2050) is expected to lead to a tripling of dementia cases by 2050 unless new interventions prevent or slow the trajectory of cognitive decline. This stresses the demand for further breakthroughs in our understanding of the origins of dementia and pathways involved in its progression.

A recognised factor affecting the risk of developing dementia is depression in late life. According to the latest Lancet commission report, late-life depression leads to two-fold increased risk of dementia, higher than diabetes, smoking or social isolation (Livingston et al., 2020).

One of the potential mechanisms linking late-life depression and dementia is neuroinflammation. The role of inflammation in both depression and cognitive decline has been studied extensively over the past decade. A number of studies have reported an association between late-life depression and elevated levels of pro-inflammatory cytokines (Biggelaar et al., 2007; Baune et al., 2012, Forti et al., 2010, Bremmer et al, 2018). Inflammation has been implicated as a potential factor in the development of dementias, specifically Alzheimer's disease (Ng et al., 2018, Swardfager et al., 2010, Chen et al., 2018, Lai et al., 2017, Su et al., 2019). However, very few studies have addressed the interplay between inflammation, depression in the elderly and risk of dementia or cognitive decline. This is important, as it provides a potential opportunity for dementia prevention. Gallagher et al. demonstrated that elevated CRP levels mediated the longitudinal relationship between depression in the elderly and cognitive decline (Gallagher et al., 2015). Another study showed that elevated levels of IL-6 were negatively associated with cognition in late-life depression (Charlton et al., 2018).

Our study examined the role of an array of serum cytokines and chemokines in cognitive decline in patients diagnosed with late-life depression.

The **primary objective** was to investigate whether plasma inflammatory factors predicted progression from late-life depression to dementia in a cohort of non-demented elderly patients with late-life depression.

The **secondary objective** was to investigate the relationship between clinical characteristics of late-life depression (course, age of onset) and inflammation or risk of progression to dementia.

In addition, we assessed cross-sectional associations between severity of depression, inflammation, and cognitive performance assessed by a neuropsychological test battery, and explored whether impairment on particular cognitive domains in depression was predictive of subsequent dementia.

7.8 Methods

7.8.1 Sample

The study was performed using the data from the PRODE (Prognosis of depression in the elderly) cohort. PRODE is a prospective study of 152 geriatric depressed patients across several clinical centers in Norway between December 1st, 2009 and January 1st, 2013. Patients were included if they were diagnosed with major depression according to ICD-10, and did not have a diagnosis of dementia. The majority of patients (n=146; 96%) were admitted to psychiatric units for major depression. All patients received treatment for depression in accordance with standard treatment protocols. Patients were assessed in four waves: on admission, at discharge/post-treatment (on average 1.7 months after inclusion), one year after discharge/end of treatment (14 months on average), and again 3 years (38 months on average) after discharge/end of treatment. Clinical and neuropsychological data were collected by clinicians and trained researchers using a wide range of standardized clinical, psychiatric, and neuropsychological assessment tools.

7.8.2 Procedures and assessment

A detailed description of the cohort has been published previously (Borza et al., 2015), and is presented in Chapter 2 (Methods).

Mental health

The diagnosis of major depression was made by a psychiatrist or clinical psychologist in accordance with ICD-10 criteria.

The severity of current depressive symptoms was assessed with the Montgomery and Aasberg Depression Rating Scale (MADRS). The scale consists of 10 items assessing depressive symptoms that are rated on a scale from 0 to 6 (total score 0–60); higher scores indicate more severe symptoms.

Cognitive assessment

Diagnosis of dementia

The diagnosis of dementia was made by clinical consensus at 1 year and 3 years in accordance with ICD-10 criteria, based on clinical assessment and cognitive testing (see below).

General cognition

General cognitive performance was assessed using the the Mini Mental State Examination (MMSE) scale, with a score range of 0–30, where lower score indicates worse performance. MMSE at baseline, on discharge and at 1 year was administered face-to-face by clinicians, while at year 3, cognition was assessed using telephone-based MMSE. For the purpose of the present analysis, the final telephone-based MMSE scores were converted to match the face-to-face MMSE scores using the conversion table presented in Newkirk et al., 2003. Scores on specific MMSE subscales (memory, orientation, attention, language, and construction) were derived additionally for the analysis of the association between cognitive performance in depression and risk of progression to dementia.

Neuropsychological test battery

The neuropsychological test battery consisted of the following tests:

Trail Making Test:

Part A of the Trail making Test requires patients to quickly connect numbered circles ranging from 1 to 25 scattered on a page in sequence, whereas Part B assesses attention, visuomotor processing speed, and mental flexibility by requiring patients to connect circles in alternating numerical (1–13) and alphabetical (A–L) sequences (Reitan & Wolfson, 1985). Results on the TMT were scored according to existing age-adjusted norms derived from Ivnik et al. (1996). Test-retest reliability is proven to be acceptable for TMT-A and good for TMT-B (0.75 and 0.85, respectively) (Giovagnoli et al., 1996).

COWAT word and category fluency:

Word fluency was measured by two subtests of the Controlled Oral Word Association Test (COWAT). Letter fluency is measured as the total number of words the patient is able to produce starting with the letters F, A and S within a time limit of 1 min for each letter. Similarly, category fluency is measured as the total number of items named for the two categories "animal" and "clothing" (Benton, 1967). Acceptable test-retest reliability (0.74) has been proven for letter fluency (Ruff et al., 1996).

Immediate recall, delayed recall and recognition were measured using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) tests. CERAD immediate recall is measured as the number of words the subject is able to recall across the three trials, with a total possible score of 30.

CERAD delayed recall is measured as the number of words the subject is able to reproduce after a delay of 10 min. Subjects are then given a list of ten novel words mixed with the ten words from the original list.

CERAD recognition is measured as the total number of correct positive and negative responses of whether each word was part of the original list or not, with a total possible score of 20.

Test-retest reliability scores for the three subtasks are shown to range between 0.5-0.8 (Welsh-Bohmer and Mohs, 1997).

Assessment of improvement after treatment

Improvement of depressive symptoms after treatment was measured using several variables, blind to cytokine measurement: (a) as the absolute difference in MADRS score at baseline and post-treatment, where lower scores indicated poorer response to treatment; (b) as "response" defined as at least a 50% improvement in MADRS score, and (c) as "remission" defined as MADRS score below 9 post-treatment. In addition, the CGI (clinical global impression) scale was used as measure of improvement after treatment. The scale has five categories, from "much better" to "worse", and for convenience was dichotomized into patients who improved (n=121) and patients who did not improve or got worse (n=47).

Covariates

Data on age, gender, years of education, marital status, height and weight was collected from all participants. BMI was calculated using height and weight values. Data on comorbid ICD-10 diagnoses was also available for all participants. Present medical comorbidity was coded as binary variables using the following categories: coronary heart disease, heart failure, arrythmia, hypertension, diabetes, cancer, cerebrovascular disorders, head injuries, and autoimmune disorders. In addition, the score on the General Medical Health Rating (GHMR), a rapid global rating scale of medical comorbidity in dementia patients, was used as a covariate in some of the analyses. GMHR has been found to be a highly reliable "bedsite" rating scale (Lyketsos et al., 1999)

7.8.3 Cytokine analysis

Blood samples were drawn by venipuncture and collected for assessment in sterile serum tubes within 2 weeks of first contact with the patient. Frozen specimen were further shipped to the Oslo University Biobank and stored at -70^{o}C. A total of 13 inflammatory markers were selected based on their previously reported association with depression or cognitive decline/dementia. These included IL-1β, interleukin-1 receptor antagonist (IL-1ra), IL-6, IL-10, IL-17a, IL-18, IL-33, IL12p40, TNFα, cluster of differentiation 40 ligand (CD40L), interferon (IFN)-γ, and chemokine ligands (CCL)-2 and CCL4.

The markers were analyzed according to the manufacturer's protocol using a bead-based multiplex immunoassay panel (Bio-Techne, Minneapolis, MN) based on xMAP Technology (Luminex, Austin, TX). Inflammatory marker concentrations were calculated using a 5-parameter standard curve based on standards that were supplied by the manufacturer. All analyses were run at the same time, with the exception of 1 of the 10 plates which had to be reanalysed due to a technical error (reanalysis data was used for CD40L and IL-10. Values below the lower limit of quantification (LLOQ) were set to 25% of LLOQ, and standard curves with a high LLOQ were selected to obtain a similar sensitivity for all samples analyzed. All values were reported in picogram/millilitre.

7.8.4 Missing data and attrition

Complete data on all clinical variables and cognitive measures at baseline was available for 63% of the participants. Baseline MMSE scores were missing in 5% of the patients, and missingness did not depend on age, depression severity, general clinical condition or outcome, and therefore missing values were considered missing completely at random (MCAR). Missingness of other cognitive variables was predicted my severity of depression.

Complete data on clinical variables and cognitive measures at discharge was available for 64% of participants, mostly due to missingness on cognitive tests other than MMSE. Missing cognitive test data was predicted by CGI alone.

Multiple imputation was performed as sensitivity analysis for variables with missing values at baseline and at discharge. Results of analyses using multiple imputation did not differ substantially from complete case analyses adjusted for variables predicting missingness. Complete case analysis results are presented.

Outcome data (dementia status) was available for 138 of the initial 152 patients at year 1; and for 129 at year 3. Attrition at year 1 was due to death (n=6), withdrawal from study(n=6); 2 patients were lost to follow-up. Further dropout by year 3 was mostly due to death (n=10). Patients who had available data on all four assessments had higher baseline MMSE (OR 1.35, $p<0.001$) and significantly better improvement (CGI-based) post-treatment (OR 3.6, $p=0.007$).

7.8.5 Statistical analysis

The distributions of values of plasma inflammatory biomarkers were carefully analysed for extreme values and compared with previously published studies to identify unexpectedly low or high levels.

The normality of the distribution of main predictor variables (plasma cyto- and chemokine levels) was examined using histograms and Q-Q plots. For each of the cytokines, extreme values were examined, unexpectedly high or low values (those exceeding 4 SD from the mean) were dropped (maximum 5.8% of values). Remaining values were winsorised (outliers replaced with mean score +/− 2.5 SD).

Differences in proportions and means/medians of baseline characteristics between patients with and without dementia at follow-up were assessed using χ^2 and t-test statictics or Wilcoxon rank sum test for nonparametric data.

Cross-sectional associations between measures of cognition, depression and inflammatory markers was analysed using multiple linear regression, as were associations between inflammation, cognition and improvement in depressive symptoms post-treatment. Assumption of independence of observations was checked using the Durbin-Watson statistic and multicollinearity was excluded by inspecting correlation coefficients and Tolerance/VIF values. Unusual or influential residuals were assessed using Cook's distances; the normality of the distribution of residuals was assessed using standardized normal probability plots and estimated by Shapiro-Wilk tests. Heteroscedasticity was assessed by examining scatterplots of

predicted residuals. Where there appeared indications of the violation of the homoscedasticity assumption, robust linear regression was used.

Each linear regression was performed in a stepwise manner: unadjusted (Model 1), adjusted for demographics (Model 2; demographic variables included age, gender and education for associations between depression and cognition and age and gender for associations between inflammation and either depression or cognition) and further adjusted for ApoE genotype and physical illness (Model 3).

Predictors of conversion to dementia were analysed using Cox proportional hazards regression. Lowest time to diagnosis of dementia was used as time function. In accordance with the "rule of thumb" for including predictors in Cox regressions, there need to be at least 10 events per variable (EPV), although some authors have argued that the rule is too arbitrary and may be relaxed (Vittinghoff et al., 2007). Nevertheless, in order to avoid strong violations of the EPV rule and overfitting, we only adjusted for covariates which proved to be significant predictors of progression to dementia in univariate models: age, baseline MMSE, APOE genotype and GMHR score for inflammatory markers and course of depression; and age, APOE genotype, GMHR score and change in MADRS for performance on cognitive tests. Hazard ratios with 95% confidence intervals were calculated.

All analyses including inflammatory markers as predictors were adjusted for multiple comparisons using the Bonferroni correction method. The corrected significance threshold was set at 0.05/13 = 0.0038. Similarly, a Bonferroni-corrected threshold was applied to analyses of cognitive tests as predictors of conversion to dementia: the new threshold was set at 0.05/12 = 0.0042.

7.8.6 Sensitivity analysis

Sensitivity analysis was performed by excluding those who had an MMSE score below 25 after treatment, in order to ensure that they were without dementia at baseline.

7.9 Results

7.9.1 Descriptive statistics

Baseline characteristics

At baseline, patients were on average 76.3 years old (SD 6.8), and predominantly female (73.7%). Mean MADRS score pre-treatment was 26.5(SD 8.41); most patients were moderately depressed (61.1%). Detailed summary of patient characteristics is presented in Table 45a-b.

Median MMSE score at baseline was 27 (IQR 24-29); and 38 (26.4% of patients with available MMSE data) had a baseline MMSE score below 25.

The majority of patients reported having a previous episode of depression (68.9%). Of those who had a history of depression, 69.4% had an onset of the first depressive episode before the age of 60; and the majority (39.4%) reported having 3-5 previous episodes of depression, followed by 5 or more episodes (26%).

More than half of the patients reached remission after treatment (56.8%), and the majority (72.8%) responded to therapy. However, about a quarter of patients were non-responders. There was not a significant change in average MMSE score after treatment. However, the proportion of patients with MMSE score < 25 was significantly lower at baseline ($p<0.001$).

Cognitive outcomes at follow-up

Of 138 patients who had outcome data on at least one follow-up date, 36 converted to dementia; among those, 12 were diagnosed after 1 year, and 24 after 3 years of follow-up. The comparison of clinical and demographic variables between converters and non-converters is presented in Table 2. Those who converted were older on average (78.86±7.2 vs 75.31±6.42, $p<0.01$), and had lower MMSE scores on admission (25(22-27) vs 28(26-29), $p<0.001$), as well as post-treatment. Converters did not differ from non-converters in baseline depression severity, however they had worse improvement post-treatment (33.3% vs 15.7% , $p<0.001$).

Mild cognitive impairment (MCI) diagnosis was not available at baseline, however, at year 1, 34 patients were diagnosed as having MCI. Of those, 19 converted to dementia by year 3.

7.9.2 Cross-sectional associations between depression, inflammation and cognition: Baseline and post-treatment

Severity of depression and baseline inflammation

No correlation between any of the inflammatory markers and severity of depression measured by MADRS score was observed at baseline. Patients with severe depression had lower IL-18 scores compared to moderately depressed patients, however this was not significant at Bonferroni-corrected threshold after full adjustment for all covariates($\beta = -46.1$, $p = 0.024$).

There was no correlation between any of the inflammatory markers and the absolute change in MADRS score after treatment.

Cognitive performance and baseline inflammation

No significant correlations were also observed between MMSE score at baseline and any of the inflammatory markers. For performance on other cognitive tests, only a mild negative correlation was observed between COWAT verbal fluency and TNFa ($r = -.28$, $p=0.002$), however in a fully adjusted model, this association was only significant below the general, not Bonferroni-adjusted threshold ($\beta = -1.02$, $p = 0.032$).

Cognitive performance and depression severity

There was also no association between depression severity and the performance on any of the cognitive tests with the exception of CERAD delayed recall. Surprisingly, performance on this test was very mildly positively associated with depression severity univariately ($\beta = .07$, $p=0.007$), but this was not significant after full adjustment.

Worse improvement on MADRS score had a significant negative association with CERAD immediate recall score post-treatment ($\beta = -.16$, $p=0.001$). This association remained highly significant after adjustment for demographics ($\beta = -.15$, $p<0.001$), however was below the Bonferroni-adjusted threshold for significance after full adjustment ($\beta = -.12$, $p=0.02$).

7.9.3 Predictors of conversion to dementia: inflammation and clinical course

In Cox proportional hazards regression, none of the inflammatory markers predicted conversion to dementia either univariately or after adjustment.

The factor significantly associated with conversion to dementia after full adjustment was improvement on MADRS post-treatment (HR = 0.93, 95% CI 0.89-0.97, p=0.001), indicating that an improvement of 1 point on MADRS scale post-treatment was associated with a 7% decreased risk of progression to dementia. Neither response nor remission were significantly predictive of conversion in univariate models, but they appeared as significant predictors after adjustment (HR 2.32, 95%CI 1.07 - 5.06, p = 0.034; HR 2.35, 95%CI 1.05 - 5.24, p = 0.037, respectively).

7.9.4 Cognitive Predictors of conversion to dementia

Baseline

In univariate Cox regression models, only MMSE orientation subscale and COWAT category fluency score were significantly predictive of conversion to dementia (HR 0.59, 95%CI 0.44-0.78, p<0.001; HR 0.92; 95%CI 0.87-0.97, p=0.002). COWAT verbal fluency, TMT-B and MMSE delayed recall were only significant before adjustment for multiple comparisons.

In models fully adjusted for confounders, none of the tests were significant below the Bonferroni-corrected threshold; MMSE orientation was marginally significant(p=0.006). MMSE attention and calculation subscale and COWAT verbal and category fluency were both significant at p<0.05.

Post-treatment

In unadjusted models, only MMSE attention and calculation subscale was significant below the corrected threshold (HR 0.72, 95%CI 0.59 – 0.87, p=0.001), while poorer performance on MMSE orientation subscale, TMT-A, CERAD immediate and delayed recall and both COWAT tests were only significant before adjustment for multiple comparisons.

After adjustment for confounders, performance on the MMSE calculation subscale was the strongest predictor of conversion and the only one significant below the adjusted threshold (HR 0.64, 95%CI 0.50 – 0.81, p<0.001). Worse performance on CERAD immediate recall, TMT-A, and both COWAT tests were significant predictors before adjustment for multiple comparisons.

7.9.5 The role of age of onset of depression

There was no difference in the risk of conversion to dementia between patients with first-onset depression, recurrent late-onset depression and early-onset depression. The number of past episodes also wasn't a significant predictor.

Patients with early-onset depression performed significantly worse on COWAT verbal fluency test ($\beta = -3.78$; $p=0.011$). No difference was observed on any of the other tests.

We did observe significantly higher baseline IL18 levels between recurrent late-onset depression and first-episode depression ($\beta = 59.33$; $p=0.002$ after full adjustment), and between early-onset depression and first-episode depression ($\beta = 42.96$; $p=0.001$ after full adjustment).

7.9.6 Sensitivity analysis

There were 106 patients with MMSE score within the normal range (25 or above) post-treatment; 10 of them had lower MMSE on admission (18-24). Twenty-one patient in this group (21.43%) converted to dementia during follow-up. Response to treatment remained significantly predictive of conversion (HR 2.54, 95%CI 1.03-6.24, $p=0.043$), while no inflammatory marker was.

None of the cognitive tests post-treatment were significant below the Bonferroni-adjusted threshold; COWAT verbal fluency and CERAD delayed recall remained significant below the general threshold in unadjusted models ($p=0.013$, $p = 0.042$, respectively). COWAT verbal fluency remained significant below the general threshold ($p=0.016$) after full adjustment.

		Total sample	Dementia	No Dementia		
		N (%)	**N(%)**	**N(%)**	**χ^2**	**p-value**
Gender	Female	112 (73.7)	25(69.4)	79(76.7)	1.26	0.39
Marital status	Married	67(39.6)	18(36.7)	47(45.2)	5.63	0.074
	Widowed	71(42.01)	24(49)	36(34.6)		
	Single	13(7.7)	1(2.04)	11(10.6)		
	Divorced/Separated	18(10.7)	6(12.24)	10(9.6)		
Past history of depression	1 vs 0	104(68.9)	25(69.4)	69(67.7)	0.039	0.84
Late-onset depression	LOD vs LOD	77 (53.1)	18 (54.6)	53(53.0)	0.0238	0.88
ApoE genotype ε4 allele	ε4 carriership	51(37.5)	17(53.1)	29(31.9)	4.57	**0.033**
GMHR (Poor health)	Poor vs good	74(48.7)	22(61.1)	42(40.8)	4.44	**0.035**
CGI	No improvement vs improvement	37(24.5)	12(33.3)	16(15.7)	5.12	**0.024**

Table 48a. The comparison of demographic characteristics between converters and non-converters (categorical measures)

	Total sample	Dementia (n=36)	No Dementia (n=103)	Test statistic	p-value
Age (mean, SD)	76.1(6.79)	77.8(7.15)	75.3(6.42)	t=-2.189 (151)	**0.03**
Years of education (median, range)	9(3-20)	9(6-18)	9(3-20)	z=0.886	0.378
BMI (median, range)	23.62(15.5-40.3)	23.72(16.6-37.9)	23.4(15.5-40.3)	z=-.402	0.689
Age of first onset of depression (median, range)	62.5(15-88)	62.5(18-88)	60(15-87)	z=-.850	0.397
MMSE (median, range)	27(15-30)	24(15-30)	28(18-30)	z=4.913	**<0.001**
COWAT(median, range)	28(8-62)	24(11-45)	30(8-62)	z=2.671	**<0.01**
Trail Making Test A (median, range)	77(35-240)	86.5(39-240)	75(35-240)	z=-1.83	0.068
Trail Making Test B(median, range)	186(50-855)	240(50-780)	180(69-855)	z=-2.85	**<0.01**
MADRS (mean, SD)	25.8(8.67)	23.89(9.89)	26.97(8.2)	t=2.01	**0.046**
MADRS change post-treatment	-15.14(10.13)	-11.35(9.9)	-17.92(9.45)	t=-3.79	**<0.001**

Table 48b. The comparison of demographic characteristics between converters and non-converters (continuous measures)

	(a)Unadjusted model		(b)Adjusted model*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
IL-1β	0.96(0.56-1.63)	0.87	0.94(0.54 – 1.62)	0.81
IL-18	1.001 (0.99-1.01)	0.62	1.00 (0.99 - 1.01)	0.29
IL-6	0.99 (0.80 – 1.24)	0.99	0.94 (0.73 – 1.20)	0.65
IL12p40	0.97(0.83 – 1.15)	0.76	0.92 (0.77 – 1.11)	0.38
CCL-2	1.0(0.99-1.00)	0.44	1.00(0.99 – 1.00)	0.21
CCL-4	1.0(0.99 – 1.01)	0.87	1.00 (0.99 – 1.00)	0.15
CD40L	1.0(0.99-1.00)	0.78	1.0(0.99-1.00)	0.52
IFNg	0.97(0.93 – 1.01)	0.15	0.97(0.94 – 1.01)	0.13
IL10	0.99 (0.97 – 1.03)	0.83	0.97(.94 - 1.00)	0.09
IL-17a	1.06 (0.75 – 1.49)	0.75	1.12(0.76 – 1.65)	0.57
IL-1ra	1.00 (0.99-1.00)	0.93	1.00 (0.99-1.00)	0.53
IL-33	0.85 (0.66 = 1.10)	0.23	0.80 (0.55 – 1.15)	0.22
TNF-a	0.97 (0.83 – 1.13)	0.68	0.96 (0.81-1.13)	0.60

Table 49. Cox proportional hazard regression models assessing the role of inflammatory markers in progression to dementia; (a) Unadjusted model (b) Adjusted for age, baseline MMSE, APOE carriership and GMHR

7.10 Discussion

The main purpose of the study was to explore whether peripheral inflammation can predict conversion to dementia in patients with late-life depression. This hypothesis hasn't been investigated thoroughly until recently, although a multitude of studies point to the role of inflammation in both depression and dementia or cognitive decline. To our knowledge, only three longitudinal studies with a similar design have been performed to date.

Gallagher et al. studied an association between depressive symptoms and cognitive decline in the ELSA (English Longitudinal study of Ageing) cohort. Significant depressive symptoms were defined as 4 or more points on the Centre for Epidemiological Studies Depression scale (CES-D) scale, cognitive performance was measured using delayed recall and verbal fluency tests. The study demonstrated that the relationship between depressive symptoms and cognitive performance after 4 years was fully mediated by C-reactive protein (CRP) concentrations and physical activity (Gallagher et al., 2016).

Another study explored an array of proteomic factors and showed that a number of them mediated the 1-year relationship between significant depressive symptoms (Geriatric Depression Scale (GDS)-30 ≥ 10) and a latent variable created for a dimensional measurement of "disabling (i.e., "dementing") cognitive performance". Resistin was the strongest mediator; other significant mediators included Macrophage Inflammatory Protein type 1 alpha (MIP- α, or chemokine CCL-3), Tissue Inhibitor of Metalloproteinase type 1 (TIMP-1) and Vascular Cell Adhesion Molecule type 1 (VCAM-1).

However, the most recent study performed in a sample of patients with Type 2 Diabetes failed to replicate these findings. They showed that although C-reactive protein, IL-6, TNF-α and fibrinogen levels were higher in patients with depression (Hospital Anxiety and Depression Scale (HADS) score ≥8) compared to non-depressed ones, and depression was associated with a 2.5-fold increase in risk of dementia, none of the inflammatory markers mediated this relationship.

To our knowledge, our study is the first to examine the potential mediating role between depression diagnosed in clinical inpatient settings and progression to dementia after 3 years of follow-up. Despite focusing on a wider array of inflammatory factors than the study by Carr et al., our study did not demonstrate a significant effect of any of the inflammatory factors on the risk of progression to dementia.

An obvious limitation of the present study is the absence of control subjects. A longitudinal comparison of factors predicting conversion to dementia between depressed patients and controls was not possible using the COGNORM cohort which was used for the previously reported cross-sectional study, since there were no dementia cases by three-year follow-up among control subjects.

Notably, despite the significant differences in inflammation between depressed patients and controls observed in the previous study, in the depressed sample alone, the severity of depression was not correlated with the concentration of any of the inflammatory markers. A plausible explanation is that since the absolute majority of patients were hospitalized for depression, the overall severity at baseline was quite homogenous, with prevailing moderate-to-severe cases. The severity of baseline depression wasn't a significant predictor of progression to dementia either.

Despite the substantial proportion of patients who converted to dementia (26.1%), in absolute numbers, there were only 36 converters, this restricted the number of covariates which could be included in the analysis without violating the assumptions of Cox proportional hazards regression,

and generally limited the power of the study. The studies discussed above which provided positive findings were both performed in samples of several thousand participants. Future research should aim to include larger samples, without compromising the clinical precision of case definition.

Apart from inflammatory markers, we investigated other potential predictors of progression to dementia. Among the cognitive predictors, in patients with an acute depressive episode, worse performance on MMSE orientation subscale proved to be a marginally significant predictor of conversion to dementia (however not in the subset of patients with MMSE >24 post-treatment). On discharge, MMSE calculation performance emerged as a significant predictor. Among the tests with a trend for significance (i.e., significance before Bonferroni adjustment for multiple comparisons), COWAT verbal fluency was consistently associated with higher conversion rate. COWAT verbal fluency maps onto the domains of executive function and language use, supporting the findings of the systematic review presented in Chapter 4 that while more prevalent in late-life depression than episodic memory impairments, executive function deficits should not be discarded as proxy of depression itself and may serve as early signs of dementia alongside episodic memory deficits.

Similarly, to the results reported in Chapter 5, we found absolutely no differences in the risk of conversion between patients with early-onset and late-onset depression. An important observation was that worse improvement during treatment was associated with worse cognitive prognosis: a 1-point improvement in MADRS reduced the risk of conversion by 7%, and no response/no remission was associated with a 2.3-fold increase in risk of conversion. This points to the importance of providing effective and timely treatment for late-life depression, and of continuing research into the biological markers of conversion from late-life depression to dementia in order to develop new drugs targeting biological mechanisms specific to this association.

8.1 Overview of thesis

The objectives of the present thesis were to examine the complex area of the relationship between late-life depression and dementia/cognitive decline from several angles.

Three different cohorts were utilised to answer research questions posed by this thesis. The cohorts represent different types of population. The CRIS study is a retrospective clinical cohort, based on clinical records of almost 4000 patients seen in South London and Maudsley settings who received a diagnosis of depression. While all key variables in this dataset are ascertained via medical diagnoses, a limited number of details are available on patients. Nevertheless, this is a sample drawn from the UK NHS services, and therefore is likely representative of actual clinical population of outpatient services in a large capital city.

The PRODE study, on the other hand, is a classical naturalistic prospective cohort study, with the advantages of accuracy of clinical information, thorough phenotyping of the sample, and close follow-up by clinicians. Moreover, the absolute majority of patients in this sample were admitted for depression, therefore the sample is reflective of a population of patients suffering from more severe depression than the outpatients seen in SLaM services (e.g. 11.2% of the CRIS cohort had severe depression according to ICD-10, compared to as much as 76.9% in the PRODE cohort).

Finally, the third study, PROTECT, is a non-clinical internet-based prospective cohort, and covers a large community sample of people aged over 50 living in the UK. While this cohort did not provide data on dementia incidence, it allowed me to investigate the more subtle aspects of the relationship between depressive symptoms and cognition: the longitudinal associations between the trajectories of depressive symptoms, anxiety symptoms and performance on four different cognitive domains across 3 years of follow-up.

8.2 Summary of findings

The systematic review of biomarkers predicting progression from late-life depression to dementia, found that reduction in hippocampal volumes – a commonly discussed neuroimaging correlate of both depression and dementia – may indeed serve as a potential predictor of conversion, however, more research is needed to identify the laterality of hippocampal changes (some studies implicate the right hippocampus, other the left hippocampus). Besides, a common pitfall of longitudinal studies performed to date is lack of sufficient subtyping of both depression (e.g., into early-onset and late-onset) and dementia (e.g., Alzheimer's disease vs vascular dementia). Another finding of the review that I found interesting to explore further was the role of inflammation as a mediator between depression in late-life and dementia and cognitive decline. At the time of the completion of the initial review, only two studies of relevant design existed, both showing significant mediation. However, as discussed further, my analysis failed to find a significant mediating effect of plasma inflammation, at least in a clinical inpatient sample.

The second results chapter summarised cognitive predictors of progression from late-life depression to dementia. Cognition is a broad field, and while deficits in episodic memory performance are an essential diagnostic feature of Alzheimer's disease, it was not clear whether within the structure of a major depressive episode in late life, they can serve as predictors of conversion to dementia, and what the role of other domains is. The review of 7 studies showed that while 4 of them highlighted episodic memory impairments as predictive of conversion from late-life depression to dementia, three other studies indicated that executive function deficits, namely worse performance on immediate recall and working memory tasks, should not be discounted and may also predict conversion to dementia.

The third results chapter focused on clinical predictors of conversion from late-life depression to dementia. It showed no difference in conversion rates between recurrent and first-episode late life depression. The symptoms of late-life depression predictive of progression to dementia were irritability

and hallucination(s), while such characteristics of depression as "feeling hopeless" and suicidal ideation were associated with lower risk of conversion to dementia.

The fourth results chapter investigated the longitudinal associations between trajectories of depressive symptoms, anxiety symptoms and performance across four cognitive domains: verbal working memory, visuospatial working memory, episodic memory and general intelligence. It showed that both depressive and anxiety symptoms independently affected cognitive performance at follow-up. The study also assessed whether the relationship between depressive symptoms, anxiety symptoms and cognitive performance might have a reciprocal character. Latent growth curve analysis showed that in the overall sample (not stratified into participants with and without a history of depression), the rate of change over time between depressive symptoms and episodic memory scores, and between anxiety symptoms and spatial working memory were negatively correlated – suggesting a possible reciprocal effect. However, only initial levels of depressive symptoms and anxiety symptoms independently predicted worse scores (or lower "growth" in the scores) on verbal working memory and general intelligence tasks. Some differences in the pattern of longitudinal associations between depressive symptoms, anxiety symptoms and cognitive performance were observed for patients with a history of depression and without (see discussed below).

The fifth results chapter included two separate studies performed in the same main cohort. Part A reported the results of a cross-sectional study of the differences in plasma cyto- and chemokine levels between inpatients with late-life depression and non-depressed cognitively intact elderly controls. We found substantial differences between the two groups, particularly in the concentrations of interleukin-1 receptor agonist (IL-1ra) and interferon-gamma (IFN-γ), as well as interleukin 17a and chemokines CCL-2 and CCL-4. Whether plasma inflammatory factors could serve as predictors of progression to dementia, was only analysed in the depressed cohort (PRODE), since there were no dementia cases during follow-up among control participants. None of the baseline plasma inflammatory factors predicted conversion to dementia among depressed patients.

8.3 Discussion

8.3.1 The rate of conversion to dementia in patients with late-life depression

The first notable finding in this thesis is that in both clinical cohorts, despite the differences in clinical settings, study design, and prevailing severity of depression, the rates of conversion from late-life depression to dementia were almost identical: 26.5% in the CRIS cohort, and 26.1% in the PRODE cohort. When only participants without any cognitive impairment were retained in both samples, conversion rates remained comparable: 23.9% vs 21.4% (variation may be explained by differences in the severity of depression, as well as, possibly, slightly higher accuracy of MMSE compared to HoNOS65+ in identifying individuals with significant cognitive impairment). Even the lowest of these estimates (i.e., 21.4% of converters in patients with MMSE≥25 post-treatment in the PRODE cohort) markedly exceeds the estimated incidence of dementia in the general population (7.1% in the UK). This, once again, confirms the increased risk of developing dementia for patients with late-life depression, and warrants further investigation of the links between the two conditions.

8.3.2 Early-onset vs late-onset depression

One of the questions this thesis addressed in every chapter was the difference between early- or midlife- onset depression (EOD; onset before the age of 60) with an episode in late life and late-onset (LOD; onset at age ≥ 60) depression. Contrary to the common assumption that late-onset depression represents a dementia prodrome and is therefore predictive of progression to dementia, we found no significant difference in dementia incidence between EOD and LOD inpatients (Chapter 7A). In the CRIS study (Chapter 5), in univariate models, recurrent depression showed a lower rate of conversion to dementia, however, the significance was lost post-adjustment. This points to the fact that while mechanisms may vary, both EOD and LOD present a substantially increased risk of progression to dementia. Our analyses showed that there exist differences between LOD and EOD, but they may be subtle. In particular, in the PROTECT cohort, the patterns of longitudinal relationship between depressive symptoms, anxiety symptoms and performance on four cognitive domains differed substantially between participants who reported having a history of depression and those who did not (although it does not exactly reflect the EOD/LOD dichotomy). For example, depressive symptoms only predicted worse functioning (lower "growth") on verbal working memory (Digit Span test) in participants without a history of depression, while the effect of depression on the decline on general intelligence (Verbal Reasoning) scores was much stronger in the subgroup of previously depressed participants. The associations with episodic memory scores (Paired Associates Learning) were very weak in the overall sample, and not significant in subgroup analysis.

The fact that the effects of depressive symptoms on verbal memory performance were only apparent in the never-depressed group – and therefore could be attributed to late-onset depressive symptoms – highlights the significance of impairment in executive function/working memory for late-life depression, and is consistent with findings from both the review in Chapter 4, and the analysis in Chapter 7A indicating that poorer performance on executive function and verbal fluency tests may be predictive of progression to dementia and should not be discarded as merely a proxy of depression.

8.3.3 Mechanisms linking late-life depression and dementia

As mentioned in the introduction, there is ongoing debate on the exact mechanism linking late-life depression with dementia. One hypothesis is that depression represents a risk factor, increasing neurobiological susceptibility to cognitive impairment. Another one states that late-life depression represents a prodrome of dementia. In addition, there is a "reactive depressive symptoms" hypothesis stating that depressive symptoms may occur as a reaction to emerging and subjectively acknowledged cognitive decline.

The findings of this thesis demonstrate that all three hypotheses are viable and all three mechanisms may operate. The fact that the rate of conversion to dementia did not differ significantly between early-onset and late-onset depression,and did not depend on the previous number of episodes (Chapter 7B) suggests that while depression indeed may be a prodromal state, if the onset is in late life, the risk factor mechanism is no less important to address in order to establish ways of predicting and preventing the onset of dementia. Besides, the longitudinal trajectory analysis in the PROTECT cohort showed that the rates of change in depressive symptoms and episodic memory performance, and of change in anxiety symptoms and spatial working memory performance were correlated, suggesting a reciprocal relationship between depression and cognition. In addition, these findings highlighted the independent effect of anxiety on cognitive performance, suggesting that it should be included in future research alongside depressive symptoms.

8.3.4 Clinical phenotypes and symptoms predictive of conversion to dementia

Apart from focusing on depression based on age of onset, the present thesis investigated the role of specific symptoms and symptom dimensions in predicting progression to dementia (Chapter 5). One hypothesis that I investigated was that symptoms consistent with the "melancholic" depression subtype (first of all, somatic symptoms such as appetite loss and insomnia) would be predictive of conversion to dementia. This assumption was based on the fact that the glucocorticoid cascade hypothesis is one of the leading biological hypotheses linking depression and dementia (discussed in Introduction chapter), and only melancholic depression was linked to HPA-axis abnormalities in our previously published systematic review. However, we did not find any effect of symptoms related to melancholic depression subtype on predicting conversion to dementia, in contrast to a previous study that pointed to melancholic depression bearing a higher risk of progression to dementia. The consistent predictors, among clinical symptoms, were irritability and hallucination(s). While these are features of the proposed "Mild behavioural impairment" syndrome, which is strongly associated with prodromal dementia, the novelty of the findings of the present thesis lies in confirming that when occurring within the framework of a depressive episode, these symptoms may still be predictive of the future incidence of dementia. Interestingly, hallucinations, especially visually hallucinations, have been described as a prodromal feature of not only Alzheimer's disease or vascular dementia, but also – and in fact more frequently than in the prodrome of AD – of dementia with Lewy bodies (DLB; McKeith et al., 2020). The role of major depression as a prodrome of DLB has been studied much less than that of VaD or AD and represents an important focus for future research.

8.3.5 The role of inflammatory biomarkers in late-life depression and dementia

Our study demonstrated substantial differences in the levels of plasma cytokines and chemokines between patients with late-life depression. Some of these findings were in line with previous research (e.g., elevated levels of IL-1ra), for some, previous studies showed conflicting results (e.g., we observed higher levels of IFN-γ or CCL-4 in depressed patients, with previous meta-analyses showing non-significant or decreased levels). Inflammation is a dynamic process, with continuous interaction between pro-inflammatory and anti-inflammatory agents, therefore directions of change may possibly vary due to the stage of inflammatory process. Nevertheless, significant differences in the concentration of a number of inflammatory markers suggests that late-life depression is, at least partially, an inflammation-related condition. An interesting and novel finding was that elevated levels of chemokines were only observed in late-onset depression compared to controls. This may represent a mechanism specific to late-onset depression, possibly to prodromal state of dementia – however, future research into the role of chemokines in specifically in late-onset depression is needed.

With regards to negative findings related to the predictive value of plasma inflammation, although they confirm recently published findings from a cohort of patients with Type 2 diabetes (Carr et al., 2020), to date, there have been too few studies of the longitudinal relationship between depression, dementia and inflammation to strictly rule out the role of inflammation as a link between depression and dementia. Despite being based on a naturalistic prospective cohort, our study did have a number of limitations. First, although cytokines are known to easily pass the blood-brain barrier, and systemic inflammation may be reflective of ongoing neuroinflammation, some studies suggest that plasma levels of inflammation may not be entirely consistent with CSF measures. While CSF measurements are more difficult to obtain, the discrepancies in the findings of four studies assessing the longitudinal association between depression, inflammation and dementia warrant a future study relying on CSF measurements of neuroinflammation. In addition, the role of C-reactive protein (CRP), implicated in one of the previous positive studies, was not investigated in our cohort. Finally, despite a substantial percent of converters, the sample size was relatively small, especially for performing Cox regression analysis without strongly violating the rule of thumb for number of events per covariate. In future studies, it would be useful to investigate the role of inflammatory predictors in a larger cohort of depressed patients, and perhaps comparing longitudinal cognitive outcomes with those in a control sample (which was not feasible in our study due to the absence of dementia cases at 3-year follow-up among controls).

8.4 Clinical implications and implications for further research

8.4.1 General clinical implications

The present thesis confirmed an important role of late-life depression in the risk of subsequent dementia. As shown by two separate studies, the rate of conversion from late-life depression to dementia amounts to around 26%, which highlights the importance of further research into the predictors of progression from LLD to dementia to identify those at risk at an early stage.

Chapter 6 also confirmed that the severity of depressive symptoms, as well as anxiety symptoms, in the general population is associated with worse cognitive functioning at follow-up. In fact, depressive symptoms and anxiety symptoms were shown to affect slightly different subdomains of executive functioning (Digit Span and Spatial Working Memory, respectively), and this points to the importance of taking account of anxiety symptoms when dealing with patients with late-life depression. More research is needed to elucidate the role of anxiety disorders in progression from LLD to dementia. Interestingly, the results of Chapter 6 confirmed the possibility of depressive symptoms being a psychological reaction to worsening cognitive function: the three-year relationship between depressive symptoms and performance on Digit Span test was reciprocal, with comparable effect size. However, to make more solid inferences, these results may need to be replicated in clinical populations; besides, when "clinically significant depressive symptoms" were taken into account, they predicted worse Digit Span performance only, not vice versa.

The meta-analysis showed that there are neurocognitive differences between patients with LLD who later developed dementia and those who didn't; besides, it showed that AD and all-cause dementia may differ with regards to the neurocognitive deficits observed in LLD. The meta-analysis had a number of limitations which prevent us from drawing clinical conclusions: namely, there have only been 6 studies so far exploring the relevant topic, and this didn't allow to distinguish "non-Alzheimer's dementia", or better yet, several specific dementia subtypes as outcome. However, it shows that with more robust research, it may be possible to establish a neurocognitive profile of LLD associated with higher risk of progression to dementia.

8.4.2 EOD vs LOD: does it make a difference at all?

Several chapters of the present thesis have focused on distinguishing between late-onset and early-onset depression. Neither of the two studies performed in clinical population identified age of onset as a significant predictor of conversion (however, the CRIS study relied on recurrence rather than age of onset for this distinction). Therefore, we failed to confirm that LOD is associated with higher risk of dementia – or rather showed that any episode of late-life depressive could bear increased risk of dementia. This brings into question whether age of onset, or distinguishing between EOD and LOD, makes sense at all. The answer, in my opinion, may depend on what specific question we're looking to address. Based on the results of the present thesis alone, age of onset does not seem to be a valid predictor of progression from LLD to dementia – however, other studies have shown different results (e.g. Singh-Manoux et al., 2017; conflicting evidence well summarised in Da Silva et al., 2013). In any case, future research into predictors of progression from LLD to dementia should utilise novel methods of data analysis, such as prediction modelling: unlike exploratory research that traditional statistics represent, prediction modelling is only interested in the ability of a set of variables to predict outcome with adequate accuracy, without explaining causal relationships. It would be interesting to see if age of onset stands out as a significant predictor in this model; this research may shed light on whether age of onset is an important factor to consider when trying to identify LLD patients at risk for dementia.

However, there is a substantial amount of literature (as summarised in Chapter 1, e.g. Naismith et al., 2012) pointing to potential differences in the underlying pathology between EOD and LOD. Our own study (Chapter 5) also showed subtle differences in neurocognitive performance between patients with and without a history of depression. While ultimately it may prove unimportant in terms of predicting progression to dementia, distinguishing EOD and LOD may be vital for the understanding of causal pathological mechanisms linking depression and dementia.

The best study design to address the question (while minimising bias) of the exact mechanisms linking late-life depression and dementia would definitely be a prospective cohort study allowing for many years, maybe decades, of follow-up (to include and prospectively follow up early-onset as well as late-onset cases), and measuring a wide range of biomarkers. However, this is hardly feasible within a researcher's lifetime. Therefore, the second best research design would be a combination of retrospective analysis of clinical data (to ascertain history of depression) and prospective follow-up of patients recruited at the stage of a late-life episode.

Retrospective ascertainment always comes with a risk of bias, especially in older patients with depressive symptoms. Therefore efforts should be made to minimise potential bias. One approach is, wherever possible, to request clinical records of prior psychiatric assessments. Where this is not possible, it may be useful to involve more than one source of information, e.g. to rely not only on self-recall, but also on reports from family members/spouse. Finally, it may be useful to ask several questions about past history of depression to reach higher specificity: for example, in Chapter 6, in an attempt to minimise recollection bias, I only classified participants as having a history of depression if they gave a positive answer to both questions "Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row" and "Have you ever been diagnosed with depression?", and classified participants as having no history of depression if they answered "no" to both. However, while increasing specificity (which may be desirable with an internet-based sample), this, may lead to a decrease in sample size and therefore power.

Whether the cut-off for late-life depression should be set at 60 or 65, also is currently unclear, and studies tend to use both thresholds freely. There has been little research which would allow to justify the use of either threshold. However, since late-onset Alzheimer's is diagnosed at 65 or above, it may be more reasonable to consider late-life depressive episodes as starting at 60 or above, to allow for the 5-year gap as a potential prodromal period.

8.4.2 Potential novel treatment targets

A key focus of the present thesis has been on peripheral inflammatory markers in late-life depression and progression to dementia. In general, at the moment there doesn't deem to be sufficient evidence to suggest targeting inflammation in late-life depression. One of the findings of our study was that higher inflammatory markers were not associated with poorer treatment response (which in turn was a predictor of progression to dementia); this is consistent with findings of another study: van Dyk et al. showed that inflammatory factors did not predict treatment response, whether patients were treated with escitalopram+memantine, or escitalopram alone (2020). Therefore, there is not enough evidence yet to claim that inflammation is the mechanism through which conventional treatments work.

Using anti-inflammatory agents for late-life depression hasn't gained sufficient evidence either: a recent study performed in the ASPREE cohort showed that treating late-life depression with aspirin was associated with both worse affective and cognitive outcomes compared to placebo (Berk et al., 2021).

A promising treatment target may lie in the area of neurogenesis factors. A study by Anacker et al. observed signs of more active neurogenesis in the subgranular zone of the hippocampal dentate gyrus in patients treated with antidepressants, and these changes were also associated with better cognition (2011). A specific antidepressant often discussed in terms of positive effects on neurogenesis is vortioxetine. Vortioxetine has been shown to modulate hippocampal plasticity and in particular neurogenesis in rodents as well as increase adult hippocampal neurogenesis-dependant cognition (e.g., pattern separation; Betry et al., 2015). Besides, a study using fMRI demonstrated reduced activation in the in dorsolateral prefrontal cortex and left hippocampus, and across a network of temporal-parietal areas, after only 14 days of treatment with vortioxetine compared with placebo (Smith et al., 2018).

Studies of HPA-axis activity with regards to late-life depression specifically have been rather scarce, therefore it is hard to make conclusions as to whether HPA-axis is involved in treatment response or could be targeted to achieve better cognitive outcomes. However, there has been some evidence that in anxiety in later life, salivary cortisol changes were associated with changes in immediate and delayed memory (Lenze et al., 2011). These results possibly warrant further research, aothough it may be complicated as HPA-axis function has been shown to follow a non-linear pattern in late-life depression (Penninx et al., 2007).

Functional connectivity has been implicated as a potential mechanism of action not only of psychopharmacological treatments, but also of psychological treatment. For example, neuroplasticity-based computerized cognitive remediation (nCCR) has been shown to reverse age-related declines in information encoding and processing and induce change in the underlying neural functions in patients with late-life depression (Morimoto et al., 2014). Another recent study showed that higher rsFC in the subgenual cingulate ACC could be a marker of response to behavioural psychotherapies. The development of psychological therapies to augment medication in LLD therefore deserves further emphasis.

8.5 Conclusions and plans for future research

The present thesis investigated the relationship between depression (or depressive symptoms) in late life and dementia and cognitive decline using three longitudinal cohorts (plus one control sample for a cross-sectional analysis).

Systematic review 1 (Chapter 3) found that potential biomarkers predicting progression from late-life depression to dementia include lower hippocampal volumes and decreased functional connectivity in the hippocampal area, as well as elevated levels of plasma inflammatory factors. This was further investigated in chapter 7.

Systematic review 2 (Chapter 4) found that deficits in executive functioning and working memory observed during an episode of late-life depression may be predictive of future progression to dementia to a similar degree than deficits in episodic memory

Original study 1 (Chapter 5) found no difference in progression to dementia between recurrent depression and first-episode depression, and demonstrated that irritability and hallucination(s) were the two symptoms of late-life depression strongly and consistently associated with progression to dementia

Original study 2 (Chapter 6) demonstrated significant longitudinal relationships between depressive symptoms, anxiety symptoms, and four cognitive domains; and showed differences in these relationships between patients with and without a history of depression

Original studies 3 and 4 (Chapter 7 A&B) showed that late-life depression was associated with higher levels of plasma inflammatory markers compared to non-depressed cognitively intact control subjects; however, baseline plasma inflammation did not predict progression to dementia in depressed patients. Besides, the study showed no effect of age of onset of depression on the rate of progression to dementia.

Both late-life depression and dementia are severe disabling disorders, with aetiology and pathological underpinnings of both still not well understood, and treatments lacking efficacy. However, the importance of continuing research into these two conditions is highlighted by the fact that the two are tightly linked. The present thesis demonstrated that at least a fifth of patients presenting with late-life depression will develop dementia within a period from 3 months to 10 years from the day depression was diagnosed.

In future, I will continue research into the field of the relationship between late-life affective symptoms and cognitive performance, perhaps paying more attention to anxiety symptoms as well. The nearest step would be further research in the PRODE cohort: planned is a study of the role of adult hippocampal neurogenesis (AHN) in late-life depression and conversion to dementia. Using the novel in vitro AHN assay established by Professor Sandrine Thuret at King's College London (KCL), we will employ the HPC03A/07 hippocampal progenitor cell (HPC) line to investigate the differences in AHN markers between patients with LLD and controls and the differences between converters and non-converters to dementia. Besides, full access to the UKBB data has been obtained; using these data and in cooperation with Lingfeng Xue a PhD student who has recently joined Prof Aarsland's team, we will explore the possibility of developing prediction models for predicting risk of progression from LLD to dementia. Besides, I plan to use polygenic risk scores (PRS) available for the PROTECT cohort to explore whether the associations between depressive symptoms, anxiety symptoms and performance across the four cognitive domains is associated with the PRS for Alzheimer's disease. I will also explore the effect of inflammation indirectly, by analysing the role of PRS for C-reactive protein in the observed associations.

Appendix 1. An description of data cleaning used for the analysis of the PRODE cohort + Table D (R2 values for individual predictors in linear regression models)

Below, I present three approaches to data analysis – I did this to ascertain that the main findings stay consistent across all models.

I started with running all my models in raw values – just how they were sent to me in SPSS files.
For linear regression, I first ran them without checking for influential observations and heteroscedasticity. These results can be seen in the yellow part of the table.
Then, in the green part of the table, I presented the results after I addressed regression assumptions, including influential observations and heteroscedasticity.

How I addressed influential observations:

I used two parameters that indicate the presence of influential observations – Cook's distances and DFBetas. I set the parameters of regression in such a way that only if both DFBetas and Cook's distances indicated a significant influential observation, these would be excluded from analysis.

Heteroscedasticity:

I checked heteroscedasticity with the estat hettest command – and if the test was significant, I used the robust estimates.

Why do we need data cleaning?

If you look at the histograms, you'll see how much variablility there is in the initial data. This warranted exploration and addressing the outliers.

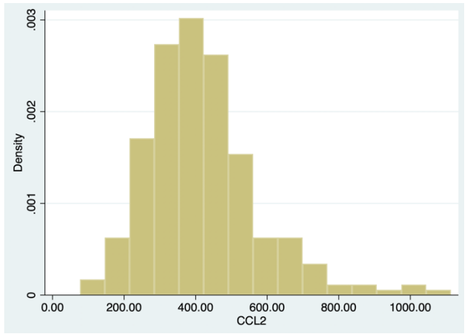
Below are histograms for three versions of data preparation

- **A.** Unchanged
- **B.** Winsorised at 2.5 SD (Stata command winsor2 var, replace cut (5 95)
- **C.** Trimmed the data slightly and then winsorised it. When I say trimmed slightly – I mean **first**, I explored extremes. The rule for IQR specifies that iqr(1.5) corresponds to extreme values. Now, I was very conservative and only trimmed those which were distant from the median above iqr(3). After I dropped these extreme extremes, I winsoriszed the data as in (B). As you can see in the in the histograms, this allowed for some of the distributions to approximate normal – others became at least typical skewed, not single-peak.

Here's what happened during trimming:

replace CD40L =. if CD40L >= 7330 | CD40L <1000 (20 values dropped)
replace IL1b =. if IL1b >3.32 (11 dropped)
replace IL12p40 =. if IL12p40 >112. (12 dropped)
replace IL18 = . if IL18 > 389 | IL18 <79 (22 dropped)
replace IL6 = . if IL6 >11. (12 dropped)
replace CCL4 =. if CCL4 >338 | CCL4 < 11 (23 dropped)
replace IFNg =. if IFNg >27 (11 dropped)
replace IL10 = . if IL10>35 (11)
replace IL17a = . if IL17a > 4.04 (12)
replace IL1ra = . if IL1ra > 2173 (11)
replace IL33 = . if IL33 > 7.32 (11)
replace TNFa = . if TNFa <0.3 | TNFa >9.33(23)

The only trouble was with IL12p40 – the spread was so high that when exploring extremes, and trimming them, I was only left with 6 values, so I decided to not use it for C…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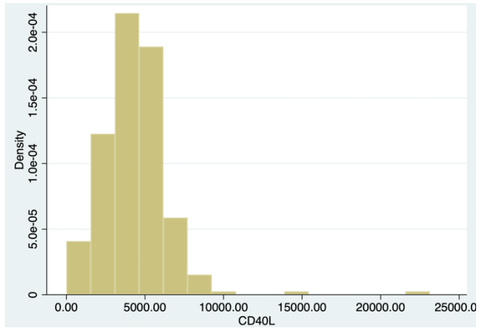
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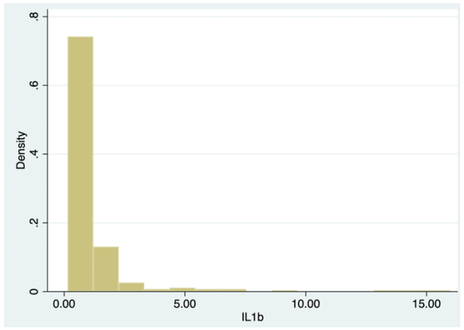
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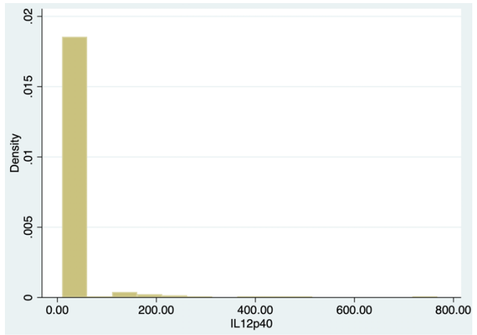
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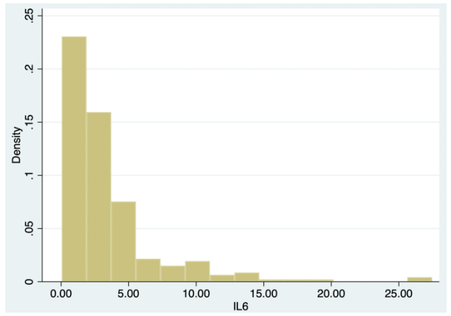
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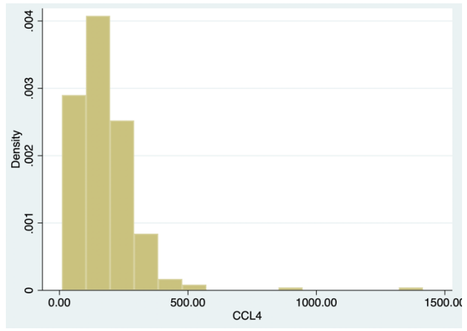
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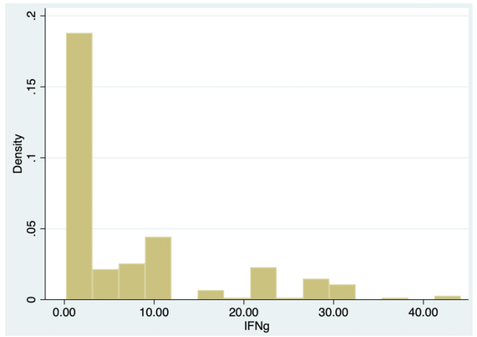
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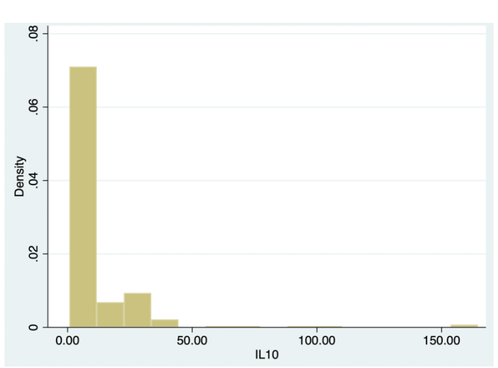
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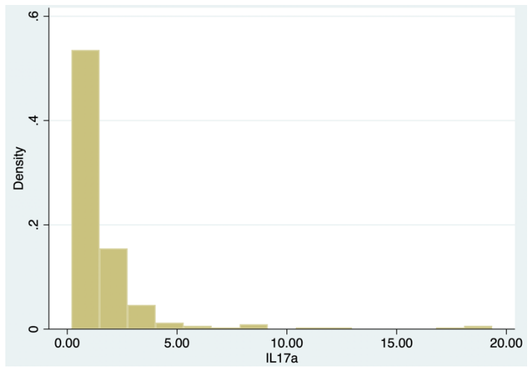
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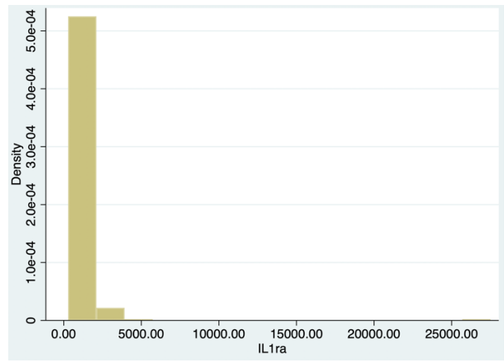
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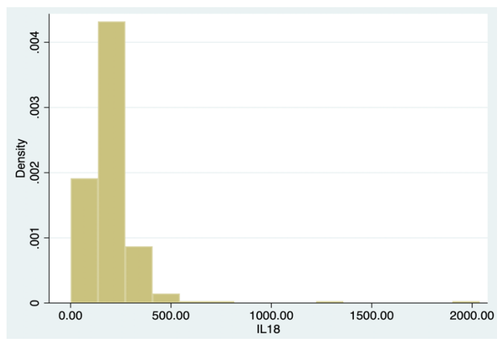
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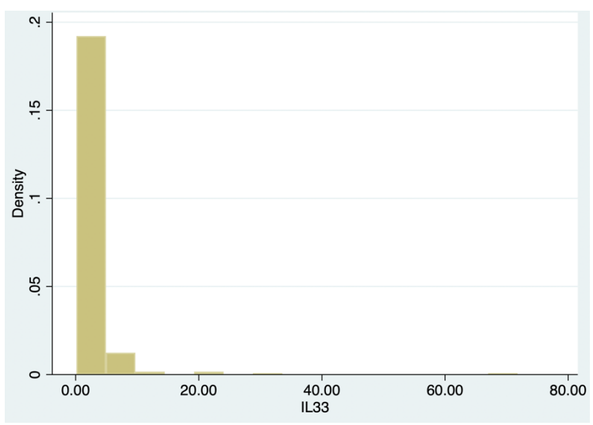
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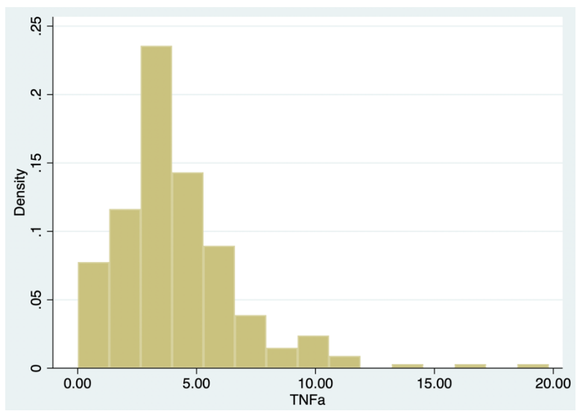
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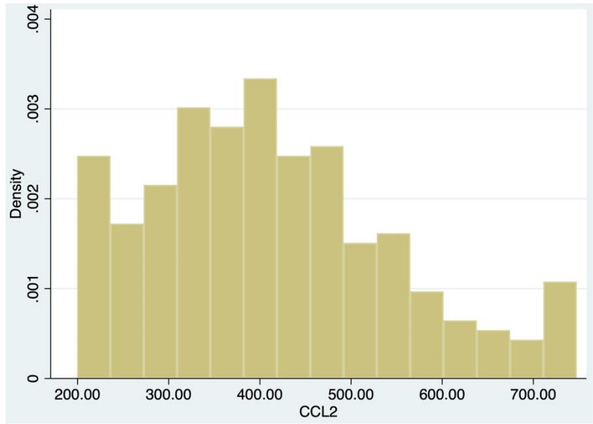
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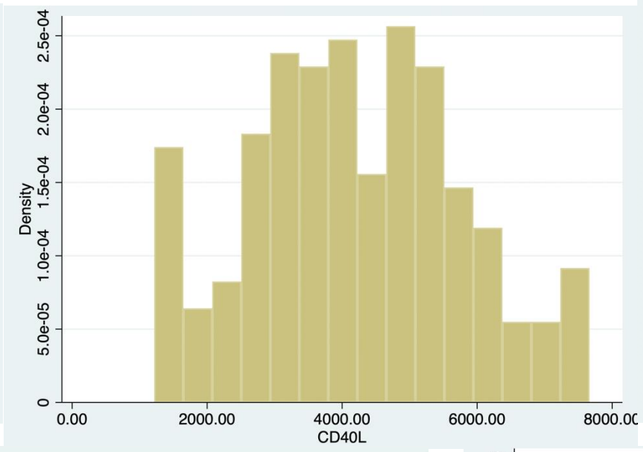
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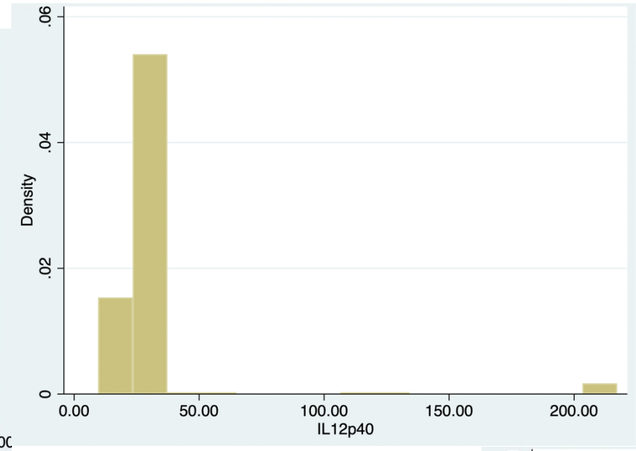
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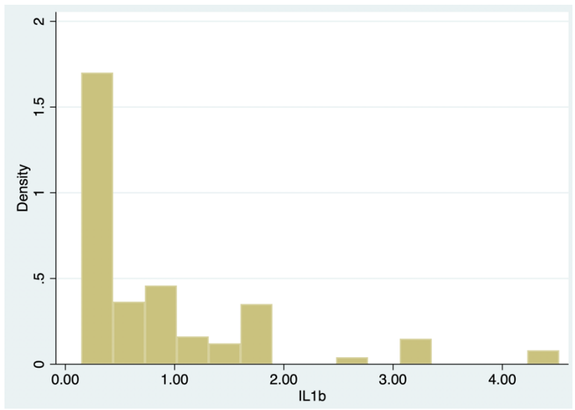
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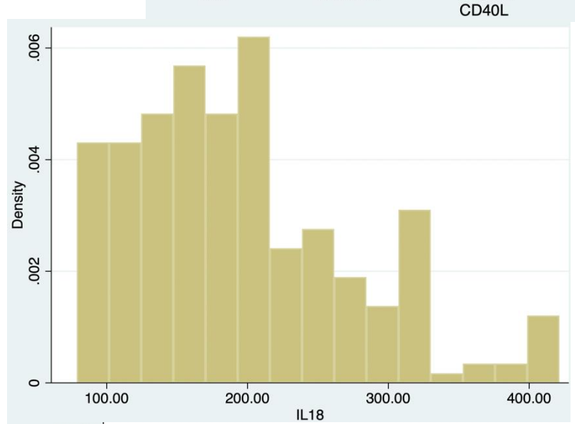
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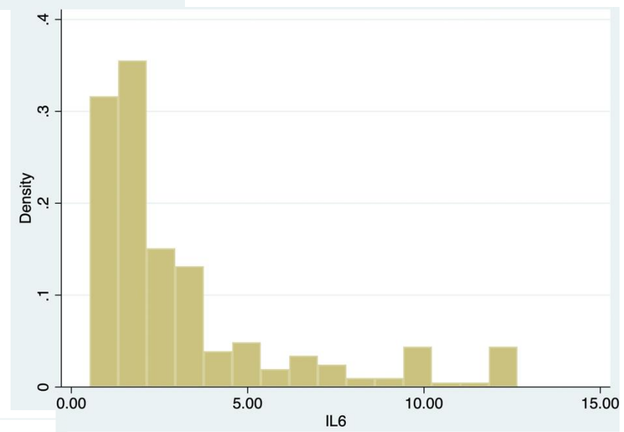
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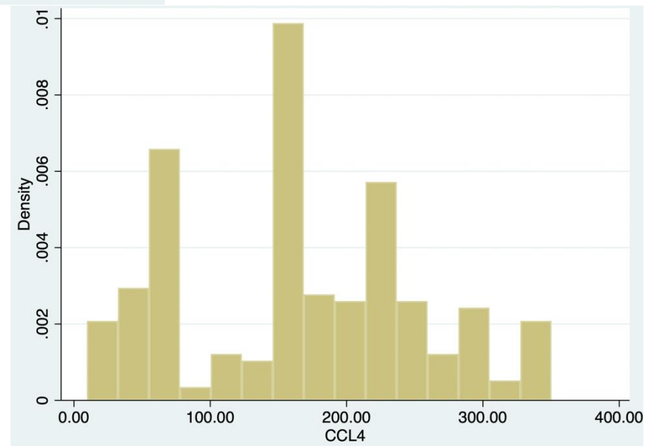
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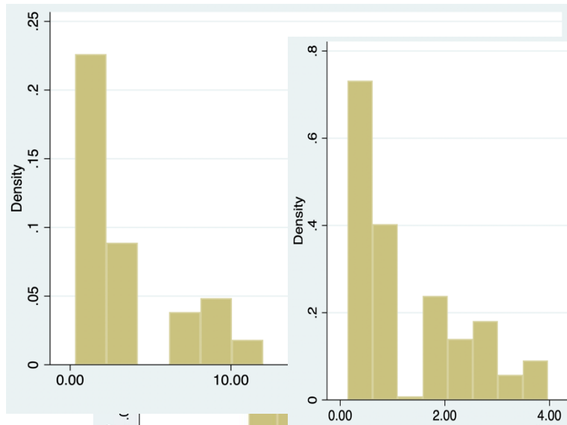
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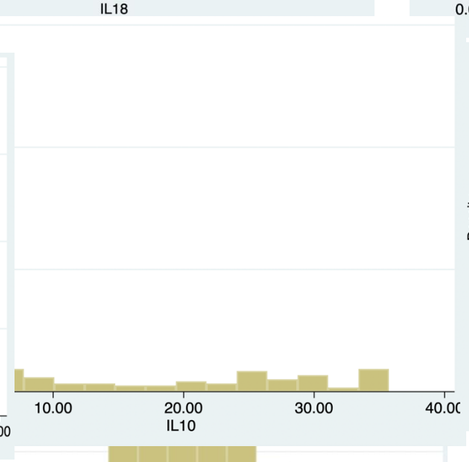
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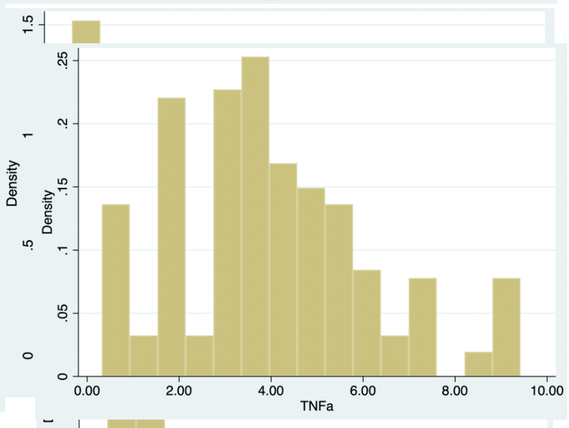
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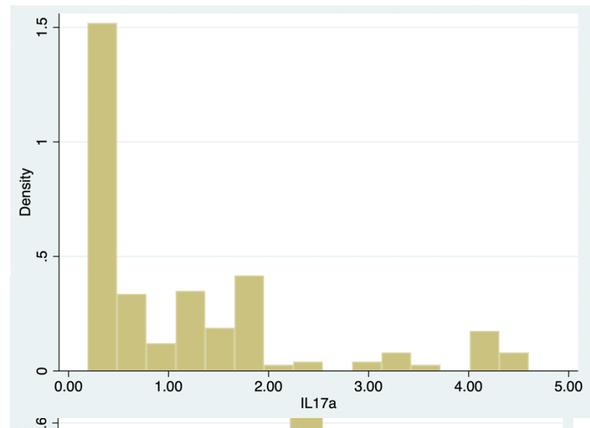
10.00
TNFa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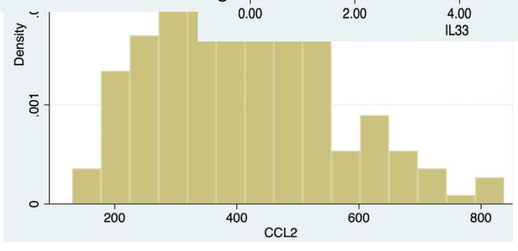
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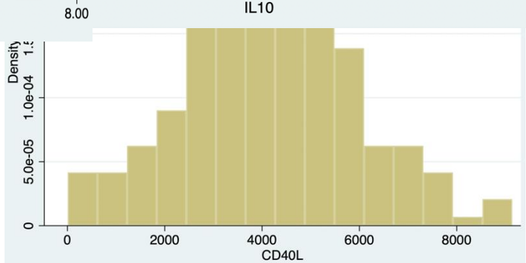
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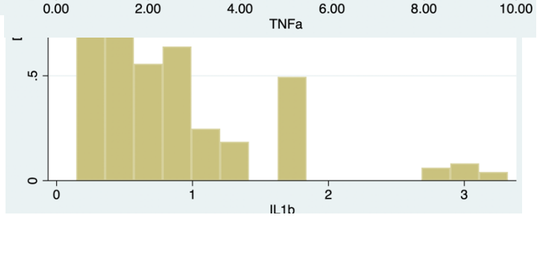
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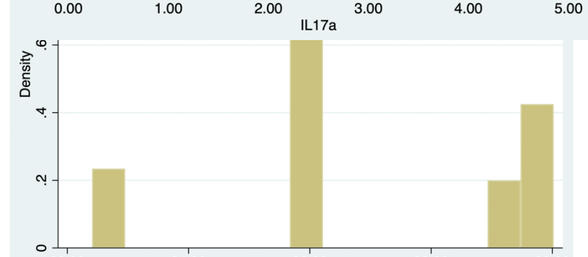
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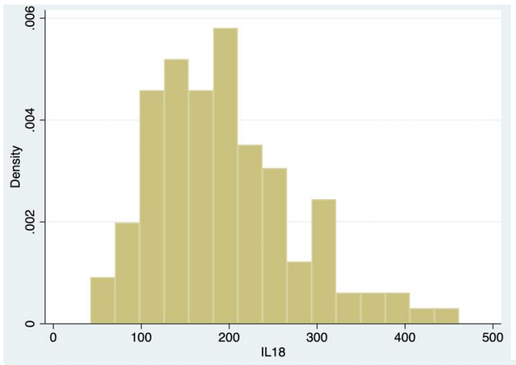
C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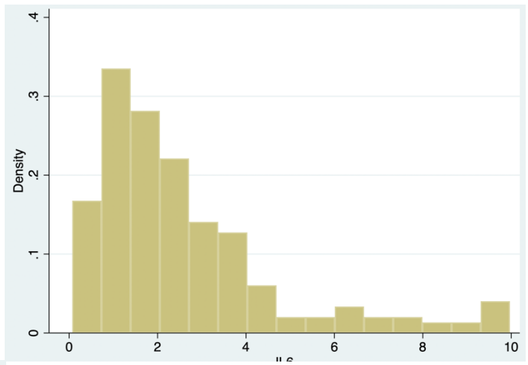
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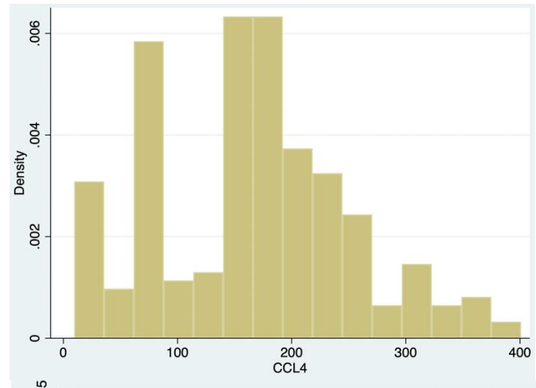
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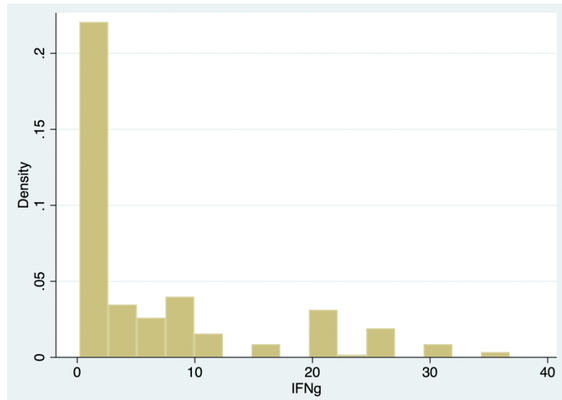
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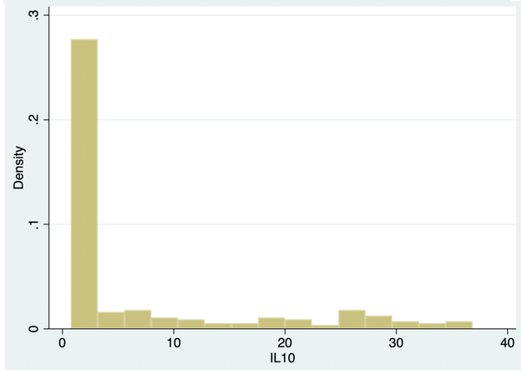
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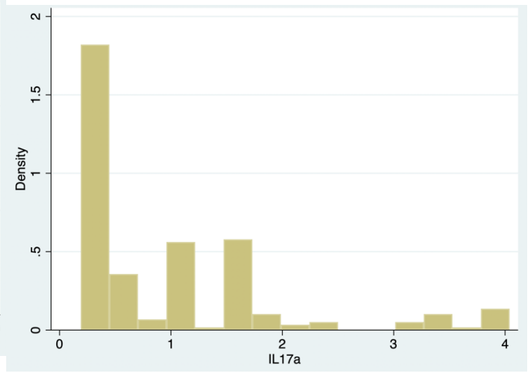
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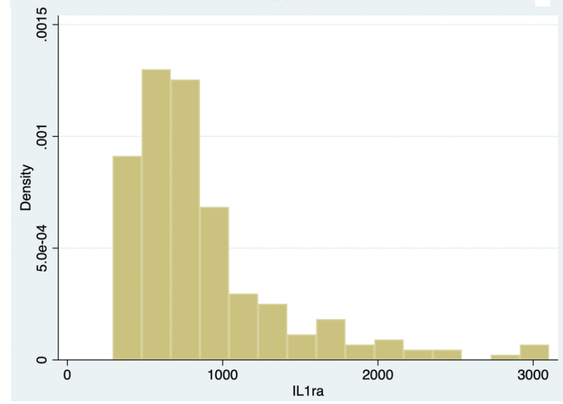
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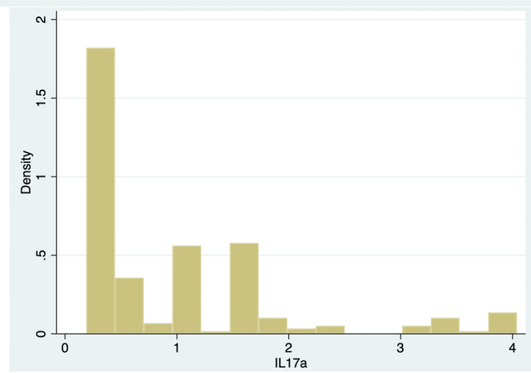
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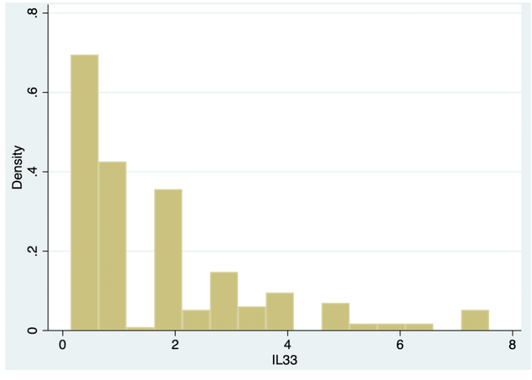
Density
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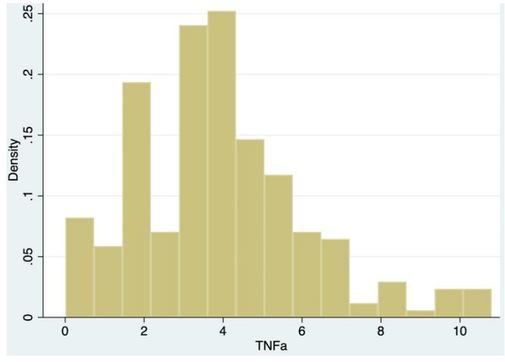
Density
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.25
0
2
4
6
8
10
TNFa

So, what are the results then?

Below are tables presented for options A, B and C.
Each table contains the results for just plain regression (yellow), and regression after checking assumptions and excluding values with influential DFbetas and cook's distances (green) – I didn't do plain regressions for C, but can do if needed

A	**Model 1(unadj, assumptions not checked)**	**p-value**	**Model 4(fully adjusted., assumptions not addressed)**	**p-value**	**R2(fully adjusted model, assumptions not addressed)**	**Model 1 (unadj., Assumptions addressed**	**P-value**	**Model 4 (fully adj, assumptions addressed)**	**p-value**	**R2(fully adjusted model, assumptions addressed)**
CCL2	**57.35 (19.58-84.79)**	**0.004**	**66.29 (23.14 – 109.46)**	**0.003**	0.04	**52.19 (20.46 - 83.92)**	**0.001**	**55.79 (19.43 – 92.14)**	**0.003**	0.15
CD40L	44.20 (-528.99 – 617.39)	0.87	-224.41 (-841.82 - 393.01)	0.48	0.07	296.51 (-129.01 - 722.03)	0.171	251.43 (-221.47 - 724.34)	0.29	0.076
IL-1β	-.26 (-0.71 – 1.19)	0.26	-.37 (-.88 – 0.13)	0.15	-0.0006	0.16 (-.032 – 0.35)	0.102	0.11 (-.12 – 0.33)	0.35	0.023
IL18	-31.66 (-74.62 – 11.29)	0.836	-26.43 (-73.73 – 20.78)	0.27	0.72	-12.87(-34.30 – 8.55)	0.24	6.80 (-15.41 - 29.02)	0.55	0.12
IL6	**0.94 (.0024 – 1.86)**	**0.044**	0.59 (-.35 – 1.52)	0.22	-.021	**0.76 (0.23 – 1.29)**	**0.005**	0.32(-0.21 - 0.84)	0.24	0.09
CCL4	**55.46(22.47 – 88.44)**	**0.001**	**41.62 (5.52 – 77.72)**	**0.024**	0.08	**44.30 (22.62 – 65.98)**	**<0.001**	**35.71 (11.27 - 60.15)**	**0.004**	0.08
IFNγ	**3.96 (1.59 - 6.32)**	**0.001**	**3.73 (1.12 - 6.35)**	**0.005**	0.03	**3.83 (1.95 – 5.71)**	**<0.001**	**4.27(2.25 - 6.29)**	**<0.001**	0.13
IL12p40	-16.88 (-34.08 - .33)	0.054	**-23.39 (-43.16 - -3.64)**	**0.021**	0.0031	.40 (-3.48 – 4.27)	0.84	-3.05 (-9.60 – 3.51)	0.36	0.03
IL10	**4.18 (-0.93 – 9.30)**	0.108	4.58 (-1.28 – 10.44)	0.125	-0.0098	1.54 (-1.18 – 4.26)	0.27	2.33 (-.43 - 5.09)	0.098	0.06
IL17a	-.012(-0.61-0.58)	0.96	-.064 (-.71 – 0.59)	0.85	0.003	**0.32 (.049 – 0.60)**	**0.021**	**0.11 (-0.26 - 0.48)**	**0.554**	0.03
IL1ra	**571.10(105.34-1036.88)**	**0.016**	462.41(-62.29 - 987.12)	0.084	0.03	**344.71 (218.50 - 470.92)**	**<0.001**	**294.56(154.53 - 434.60)**	**<0.001**	0.12
IL33	0.69 (-.72-2.01)	0.34	.020 (-1.59 – 1.64)	0.980	-0.069	**.57 (0.11 – 1.033)**	**.016**	0.45 (-0.058 - 0.91)	0.053	0.03
TNF-α	**0.67(0.046 - 1.30)**	**0.035**	0.45 (-.24 – 1.14)	0.204	0.02	**.54(0.022 – 1.06)**	**.041**	0.48(-0.54 - 1.02)	0.068	0.08

B	Model 1(unadj, assumptions not checked)	p-value	Model 4(fully adjusted., assumptions not addressed)	p-value	R2(fully adjusted model, assumptions not addressed)	Model 1 (unadj., Assumptions addressed	P-value	Model 4 (fully adj, assumptions addressed)	p-value	R2(fully adjusted model, assumptions addressed)
CCL2	**58.93 (25.95-91.91)**	**0.001**	**66.98 (30.021 – 103.95)**	**<0.001**	0.05	**42.15 (11.50 - 72.80)**	**0.007**	**53.50 (17.34 – 89.65)**	**0.004**	0.13
CD40L	301.50 (-109.80 – 712.80)	0.15	189.43 (-253.3 - 632.17)	0.48	0.06	301.50 (-109.80 - 712.80)	0.150	215.61 (-195.27 - 626.50)	0.30	0.13
IL-1β	-.051 (-0.29 – 0.19)	0.68	-.067 (-.34 – 0.21)	0.15	-0.0347	0.11 (-.035 – 0.25)	0.137	0.10 (-.072 – 0.28)	0.25	0.04
IL18	-19.43 (-40.06 – 1.20)	0.065	-8.95 (-31.38 – 13.47)	0.27	0.08	4.07(-13.99 – 22.13)	0.66	10.78 (-8.33 - 29.88)	0.27	0.14
IL6	**0.89 (.15 – 1.63)**	**0.018**	0.59 (-.21 – 1.39)	0.22	0.0086	**0.62 (0.12 – 1.11)**	**0.015**	0.30(-0.23 - 0.82)	0.27	0.09
CCL4	**46.47(25.53 – 67.41)**	**<0.001**	**37.72 (14.76 – 60.69)**	**0.024**	0.10	**58.15 (37.83 – 78.47)**	**<0.001**	**36.19 (14.91 - 57.47)**	**0.001**	0.19
IFNγ	**4.10 (1.91 - 6.28)**	**<0.001**	**4.04 (1.63 - 6.45)**	**0.001**	0.04	**4.58 (2.88 – 6.73)**	**<0.001**	**4.18(2.15 - 6.20)**	**<0.001**	0.15
IL12p40	**-12.45 (-20.50 - -4.40)**	**0.003**	**-14.23 (-23.55 - -4.91)**	**0.003**	0.0094	.59 (-1.12 – 2.29)	0.52	0.22 (-1.75 – 2.19)	0.83	0.024
IL10	2.46 (-0.35 – 5.27)	0.086	2.37 (-0.76 – 5.51)	0.137	0.0084	**2.59 (0.53 – 4.65)**	**0.014**	2.47 (-.021 - 4.96)	0.052	0.10
IL17a	0.17(-0.13-0.48)	0.26	0.15 (-.19 – 0.50)	0.38	-0.0001	**0.26 (.053 – 0.47)**	**0.014**	**0.30 (0.029 - 0.56)**	**0.03**	0.07
IL1ra	**362.12(242.41-481.84)**	**<0.001**	**325.94(196.74 - 455.14)**	**<0.001**	0.10	**243.47 (151.90 - 335.04)**	**<0.001**	**235.59(123.63 - 347.56)**	**<0.001**	0.11
IL33	**0.54 (0.078-1.01)**	**0.022**	.39 (-.13 – 0.91)	0.14	0.04	**.46 (0.13 – 0.79)**	**.007**	0.17 (-0.25 - 0.59)	0.43	0.04
TNF-α	**0.68(0.14 - 1.21)**	**0.014**	0.54 (-.05 – 1.13)	0.073	0.02	.27(-0.21 – 0.74)	.026	0.29(-0.23 - 0.82)	0.27	0.02

C	Model 1	p-value	Model 4	p-value	R2(fully adjusted model)
CCL2	**58.04(27.08-89.0)**	**<0.001**	**53.23(17.02 – 89.44)**	**0.004**	0.124
CD40L	353.043(-34.83–740.91)	0.074	306.34(-102.33 - 715.0)	0.141	0.155
IL-1β	0.08(-0.59 – 0.21)	0.26	0.058 (-0.085 – 0.20)	0.425	0.062
IL18	1.93 (-16.4 – 20.25)	0.836	15.03(-5.17 - 35.24)	0.144	0.130
IL6	**0.37 (.0045 – 0.74)**	**0.047**	0.082(-0.29 - 0.45)	0.660	0.147
CCL4	**51.92(31.37 – 72.46)**	**<0.001**	**36.65 (14.78 - 58.53)**	**0.001**	0.172
IFNγ	**4.58 (2.89 - 6.28)**	**<0.001**	**4.26(2.26 - 6.26)**	**<0.001**	0.134
IL10	**2.65 (0.75 – 4.55)**	**0.006**	1.75 (-.54 - 4.03)	0.133	0.084
IL17a	**0.24 (.07-.41)**	**0.006**	**0.35 (0.12 - 0.59)**	**0.003**	0.104
IL1ra	**280.98 (193.95-368.01)**	**<0.001**	**238.33 (134.40 - 342.26)**	**<0.001**	0.137
IL33	**0.55 (.24-.86)**	**<0.001**	**0.42 (0.049 - 0.78)**	**0.027**	0.087
TNF-α	**0.47(0.0026 - 0.93)**	**0.049**	0.30(-0.23 - 0.84)	0.260	0.067

And how does this translate to the logistic regression results? There is no difference between A and B because winsorising doesn't change the median (and therefore dichotomising at the median remains the same); for some of the variables, trimming also didn't change the median much

Options A and B:

	CCL2	CD40L	IL-1β	IL-18	IL-6	CCL4	IFNγ	IL-10	IL12p40b	IL-17a	IL-1ra	IL-33	TNF-α
Model 1 (OR [95%CI])	1.82[1.11-2.99]†	1.27[0.78-2.07]	1.62[0.99 – 2.65]	1.19[0.73-1.95]	1.45[0.89-2.37]	**2.70[1.63-4.47]*** **	**3.44[2.05-5.77]*** **	1.72[1.04-2.86]†	1.29 [0.77 – 2.15]	1.52[0.93 -2.49]	**3.48 [2.09-5.82]*** **	**2.12[1.29-3.49]** **	2.07[1.26-3.4]*
Model 2 (OR [95%CI])	1.65[0.99-2.76]	1.19[0.71 - 2.00]	1.74[1.03-2.93]†	1.53[0.90-2.61]	1.26[0.75 - 2.13]	**2.26[1.34 - 3.83]** **	**3.92[2.25 - 6.82]*** **	1.70[1.004-2.88]†	1.17[0.69 – 2.00]	1.68[1.00-2.85]†	**3.29[1.93-5.59]*** **	2.14[1.26 - 3.61]*	1.85[1.10-3.11]†
Model 3 (OR [95%CI])	1.84[1.08 - 3.13]†	1.04[0.61 - 1.79]	1.67[0.98-2.87]	1.47[0.85-2.53]	1.13[0.66-1.96]	2.15[1.26 - 3.69]*	**3.48[1.98 - 6.12]*** **	1.77[1.03 - 3.05]†	1.26[.73 - 2.19]	1.55 [0.90 - 2.65]	**3.03[1.76 - 5.22]*** **	1.95[1.14 - 3.34]*	1.95[1.14-3.32]†
Model 4 (OR [95%CI])	2.14[1.21 - 3.81]†	1.21[0.68-2.15]	1.60[0.90-2.81]	1.70[0.94-3.04]	1.17[0.66 - 2.11]	2.14[1.21 - 3.80]*	**3.77[2.04 - 6.95]*** **	1.63[0.91 - 2.91]	1.15[0.64 – 2.07]	1.500[0.84 - 2.68]	**3.09[1.74 - 5.51]*** **	1.80[1.01 - 3.2]†	1.97[1.12 - 3.47]†

Option C:

	CCL2	CD40L	IL-1β	IL-18	IL-6	CCL4	IFNγ	IL-10	IL-17a	IL-1ra	IL-33	TNF-α
Model 1 (OR [95%CI])	2.03[1.24-3.34]*	1.22[0.75-2.00]	1.47[0.89 – 2.42]	1.18[0.72-1.93]	1.60[0.97-2.64]	**2.70[1.63-4.47]*** **	**3.44[2.05-5.77]*** **	1.72[1.04-2.86]†	1.06[0.64 - 1.74]	**3.56 [2.13-5.95]*** **	**2.12[1.29-3.49]** **	2.07[1.26-3.4]*
Model 2 (OR [95%CI])	1.83[1.09-3.08]†	1.13[0.67 - 1.91]	1.59[0.94-2.70]	1.53[0.90-2.61]	1.42[0.83 - 2.42]	**2.26[1.34 - 3.83]** **	**3.92[2.25 - 6.82]*** **	1.70[1.004-2.88]†	1.14[0.68-1.92]	**3.39[1.99-5.77]*** **	2.14[1.26 - 3.61]*	1.85[1.10- 3.11]†
Model 3 (OR [95%CI])	2.02[1.18 - 3.45]†	0.99[0.57 - 1.71]	1.52[0.88-2.61]	1.47[0.85-2.53]	1.36[0.78-2.35]	**2.15[1.26 - 3.69]†**	**3.48[1.98 - 6.12]*** **	1.77[1.03 - 3.05]†	1.06 [0.62 - 1.81]	**3.16[1.83 - 5.45]*** **	1.95[1.14 - 3.34]*	1.95[1.14-3.32]†
Model 4 (OR [95%CI])	2.14[1.21 - 3.81]*	1.17[0.65-2.09]	1.50[0.84-2.66]	1.68[0.94-3.02]	1.42[0.79 - 2.55]	2.14[1.21 - 3.80]*	**3.77[2.04 - 6.95]*** **	1.63[0.91 - 2.91]	0.99[0.55 - 1.76]	**3.20[1.80 - 5.71]*** **	1.80[1.01 - 3.2]†	1.97[1.12 - 3.47]†

Conclusion

As can be seen, the main findings remain almost the same regardless of how the data is cleaned.

If we use models that don't drop observations with extreme Cook's distances and DFBetas, IL12p40 is significantly lower in depressed patients compared to controls. However, given how high the variability is for IL12p40, I don't think making inferences from this model is sensible.

Also, unless we trim and winsorise data (unless we go with option C), IL33 is not significantly different between patients and controls

Finally, in the trimmed-and-winsorised data, the R2 are the highest – but I think that's expected, I'm kind of artificially making the data fit…?

Table D

R^2 for univariate linear regressions with cytokine concentration as outcome. In bold are the R^2 values for predictors that were significant

Infl.marker	Depression	Age	Gender	Smoking status	Cancer	Diabetes	Hypertension	Cerebrovascular events	Head injuries	Autoimmune disorders
CCL2	**0.05**	0.0042	**0.034**	0.0011	0.03	**0.007**	0	0.0004	**0.027**	0.0002
CD40L	0.0087	**0.018**	**0.039**	**0.038**	0.0002	0.0002	0.0003	0.001	**0.019**	**0.007**
IL1b	0.01	0.005	0.002	0.007	0.002	0	0.0002	**0.012**	0.006	0.0008
IL18	0.0009	0.004	**0.085**	0	0.0005	0.004	0	**0.014**	**0.032**	0.0001
Il6	**0.025**	**0.025**	0.004	0.0003	0.003	**0.008**	0.004	0.002	0.008	0.0006
CCL4	**0.12**	0.004	**0.06**	**0.014**	0.0087	0.003	0.004	0.02	0	**0.004**
IL12p40	0.002	0.002	0.004	0.003	0.0004	**0.004**	0.003	0.004	0.002	0.002
IFNg	**0.09**	0.002	0.0014	**0.01**	**0.041**	0.0008	0.0001	**0.028**	**0.026**	**0.003**
Il10	**0.025**	0.003	0.006	**0.03**	**0.046**	0.018	0.0004	**0.024**	**0.03**	0
IL17a	**0.023**	0.005	0.0034	0.0012	**0.038**	0.0006	0.004	**0.009**	**0.017**	**0.007**
IL1ra	**0.10**	0.001	**0.02**	0	**0.014**	0	0.004	0.0002	0.0001	**0.004**
Il33	**0.032**	0.003	0.0015	0.0001	**0.019**	**0.004**	0.0007	0.006	**0.011**	**0.007**
TNFa	0.0054	0.01	**0.016**	0.0032	0.0013	0.0004	0.0001	0.004	0	0

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