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Gerontology

**The Association between Blood Pressure,  
Cerebral Perfusion and Late Life  
Depression**

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**Date of Award of Degree: 2020**

## **Declaration**

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

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**Robert Briggs**

Signed: \_\_\_\_\_

Date: \_\_\_\_\_

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## **Abbreviations**

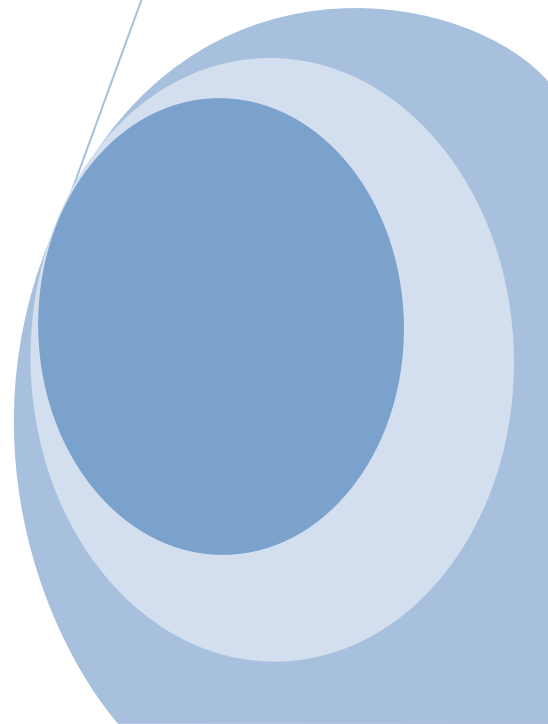
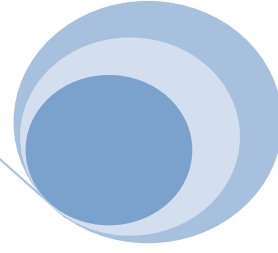
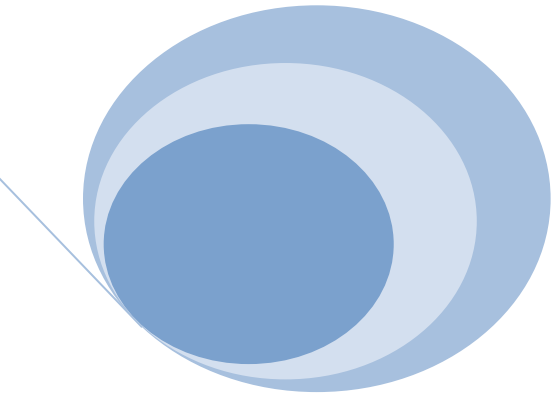
|          |                                                              |
|----------|--------------------------------------------------------------|
| ADL      | Activities of Daily Living                                   |
| AOH-30   | Asymptomatic Orthostatic Hypotension at 30 Seconds           |
| ATC      | Anatomical Therapeutic Classification                        |
| BMI      | Body Mass Index                                              |
| BP       | Blood Pressure                                               |
| CAPI     | Computer Assisted Personal Interview                         |
| CBF      | Cerebral Blood Flow                                          |
| CES-D    | Centre for Epidemiological Studies Depression Scale          |
| CES-D-8  | 8-Item Centre for Epidemiological Studies Depression Scale   |
| CES-D-20 | 20-Item Centre for Epidemiological Studies Depression Scale  |
| CI       | Confidence Interval                                          |
| EOD      | Early Onset Depression                                       |
| FLAIR    | Fluid Attenuated Inversion Recovery                          |
| CAGE     | Cut Down, Angry, Eye Opener, Guilty Questionnaire            |
| GDS      | Geriatric Depression Scale                                   |
| ICPSR    | Interuniversity Consortium for Political and Social Research |
| IOH      | Initial Orthostatic Hypotension                              |
| IRR      | Incident Rate Ratio                                          |
| JAMDA    | Journal of the American Medical Director's Association       |
| LLD      | Late Life Depression                                         |
| MMSE     | Mini Mental State Examination                                |
| MOCA     | Montreal Cognitive Assessment                                |
| MRI      | Magnetic Resonance Imaging                                   |
| NIRS     | Near-Infrared Spectroscopy                                   |
| OH       | Orthostatic Hypotension                                      |
| OH-30    | Orthostatic Hypotension at 30 Seconds                        |

|        |                                                   |
|--------|---------------------------------------------------|
| OR     | Odds Ratio                                        |
| PPH    | Postprandial Hypotension                          |
| SCQ    | Self-Completed Questionnaire                      |
| SIOH   | Symptomatic Initial Orthostatic Hypotension       |
| SOH-30 | Symptomatic Orthostatic Hypotension at 30 Seconds |
| SPECT  | Single-Photon Emission Computed Tomography        |
| SPRINT | Systolic Blood Pressure Intervention Trial        |
| TCD    | Transcranial Doppler                              |
| TILDA  | The Irish Longitudinal Study on Ageing            |
| TSI    | Tissue Saturation Index                           |
| TUG    | Timed Up and Go                                   |
| UCLA   | University of California, Los Angeles             |
| WMH    | White Matter Hyperintensitie                      |





# **CHAPTER 1:** Introduction



### **1.1 Late Life Depression: Introduction**

Depression is a clinical syndrome characterised by persistent symptoms of low mood and/or loss of interest (1). Further symptoms may include sleep and appetite disturbance, fatigue, feelings of worthlessness and guilt, poor concentration and suicidal ideation (2). Diagnosis is clinical, based on a structured diagnostic interview, and generally symptoms need to be present for at least 2 weeks in order to confirm the diagnosis (3).

The World Health Organisation estimates that depression affects over 300 million people worldwide, equating to 4.4% of the world's population (4). Depression has also been identified as the leading worldwide cause of disability, with a global total of over 50 million years lived with disability due to depression in 2015 (4). Depression can have a profound effect on quality of life (5) and functional status (6). In severe cases, depression can lead to suicide (7) and is also strongly associated with non-suicide-related earlier mortality (8).

Late life depression (LLD) is defined as depression presenting after the age of 60 years or depression persisting beyond 60 years (9). While late life is generally characterised by contentment and happiness (10), around 12% of older adults experience significant depressive symptoms (11), with the reported incidence rate of LLD ranging from 0.2-14.1/100 person-years (12).

Depression in later life confers an independently increased risk of falls (13), cardiac events (14), cognitive and functional decline (6, 15) and nursing home admission (16). While the prevalence of depression in later life is actually lower than at earlier ages, increased longevity worldwide coupled with these adverse outcomes places LLD as a major public health concern (17).

Improved understanding of the modifiable biological processes underpinning depression in later life is therefore imperative in order to inform preventative strategies and provide possible treatment targets (18).

### **1.2 Late Life Depression: A Distinct Clinical Entity**

When we consider the changes we undergo physically and psychosocially across the life course, it is no surprise that diseases presenting in earlier life are often quite different entities when they present in later years, even though similar terminology and diagnostic criteria are often applied despite these differences. LLD therefore is very different to depression in earlier life on several levels:

### *Psychosocial Differences*

LLD generally occurs in a different psychosocial context than earlier life depression (ELD). Bereavement, particularly loss of a spouse, is much more common in later life and has been identified as the strongest risk factor for incident LLD (19). Additionally, while loneliness and perceived social isolation can occur at any age, they appear closely related to incident depression in older people (20).

Furthermore, functional decline, which is also more common in later life, appears to be a potent risk factor for incident LLD (21). Disentangling cause and effect in this instance can be challenging however, given the impact depression can have on functional status itself (6).

### *Clinical Differences*

LLD tends to present differently to ELD, with studies demonstrating a higher burden of sleep disturbance, somatic symptoms and weight loss (22) and less endorsement and severity of low mood (23).

LLD also often occurs on a more complex medical background than ELD. Older people with depression have a significantly higher chronic disease burden (24) and are more likely to have polypharmacy and frailty (25). This can sometimes complicate assessment and make treatment more challenging. Identification of LLD can be further complicated by the fact that depressed older patients are also less likely to report symptoms related to depression in the first place (11).

A particularly important clinical feature of LLD is its complex relationship with cognitive decline. While there is some evidence that depression contributes to the development of cognitive deficits (26), it remains unclear whether depression is simply a risk factor for cognitive decline or if it represents a prodromal syndrome prior to the development of dementia (27). Traditionally, it was felt that depression in older people impacted on cognition transiently but that this was reversible once depression had been treated (28), however a prospective study has shown that almost half of a non-demented cohort older of patients with new-onset depressive illness were cognitively impaired at 1 year despite remission of depression (29). Conversely, there is some evidence that non-depressed older people who are diagnosed with dementia have a significantly increased risk of incident depression, raising the possibility of a bidirectional relationship (30).

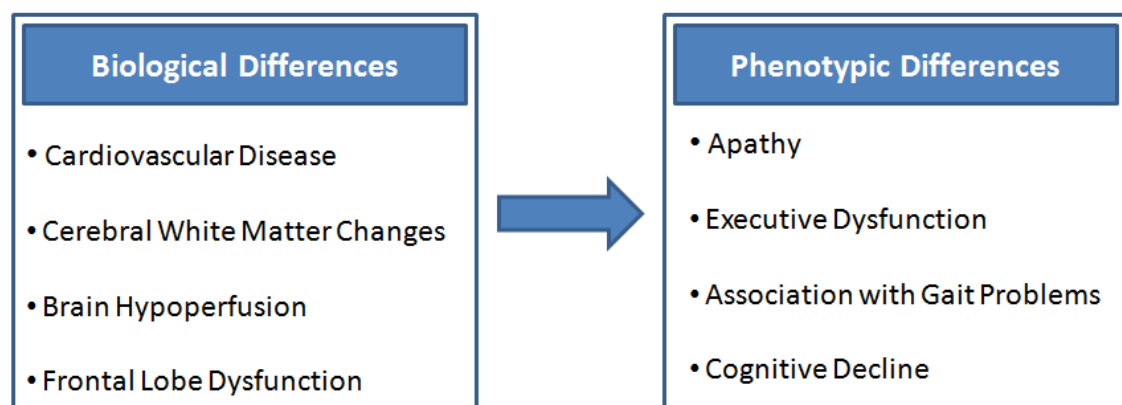
Depression and dementia further overlap in terms of clinical presentation. Apathy can be a prominent feature of LLD and is also commonly seen in dementia (31). In addition, executive dysfunction, also a hallmark of dementia, particularly vascular dementia, is also a common feature of LLD(32).

*Biological Differences: The Vascular Depression Hypothesis*

Given these important phenotypic differences, it is therefore not surprising that LLD is underpinned by different biological factors when compared to depression in earlier life(9).

Figure 1.1 demonstrates how some of these clinical differences are due to underlying biological differences when compared to ELD.

**Figure 1.1: Biological and Phenotypic Changes in Late Life Depression compared to Early Life Depression**



*Notes:*

*Schematic representation of how biological factors underpin phenotypic differences in late life depression, when compared to early life depression.*

Age-related changes in the endocrine and the immune system have been implicated in LLD but the best studied biological factor to date is vascular disease (33).

The concept of the vascular basis for LLD emerged in the 1990's, supported by studies consistently demonstrating an important relationship between LLD and cardiovascular and

cerebrovascular disease (34, 35). Key findings that further supported this hypothesis were the increased burden of cerebral white matter disease seen in older people with depression (36, 37).

Taylor et al have proposed that an important mechanistic pathway involves deficits in systemic hemodynamics and cerebral autoregulation leading to cerebral perfusion deficits, which in turn cause cerebral white matter disease and altered regional brain function, modifying important brain circuits and influencing the development of LLD(33, 36). While this attractive proposal makes sense both clinically and biologically, it is yet to be tested rigorously in large-scale studies.

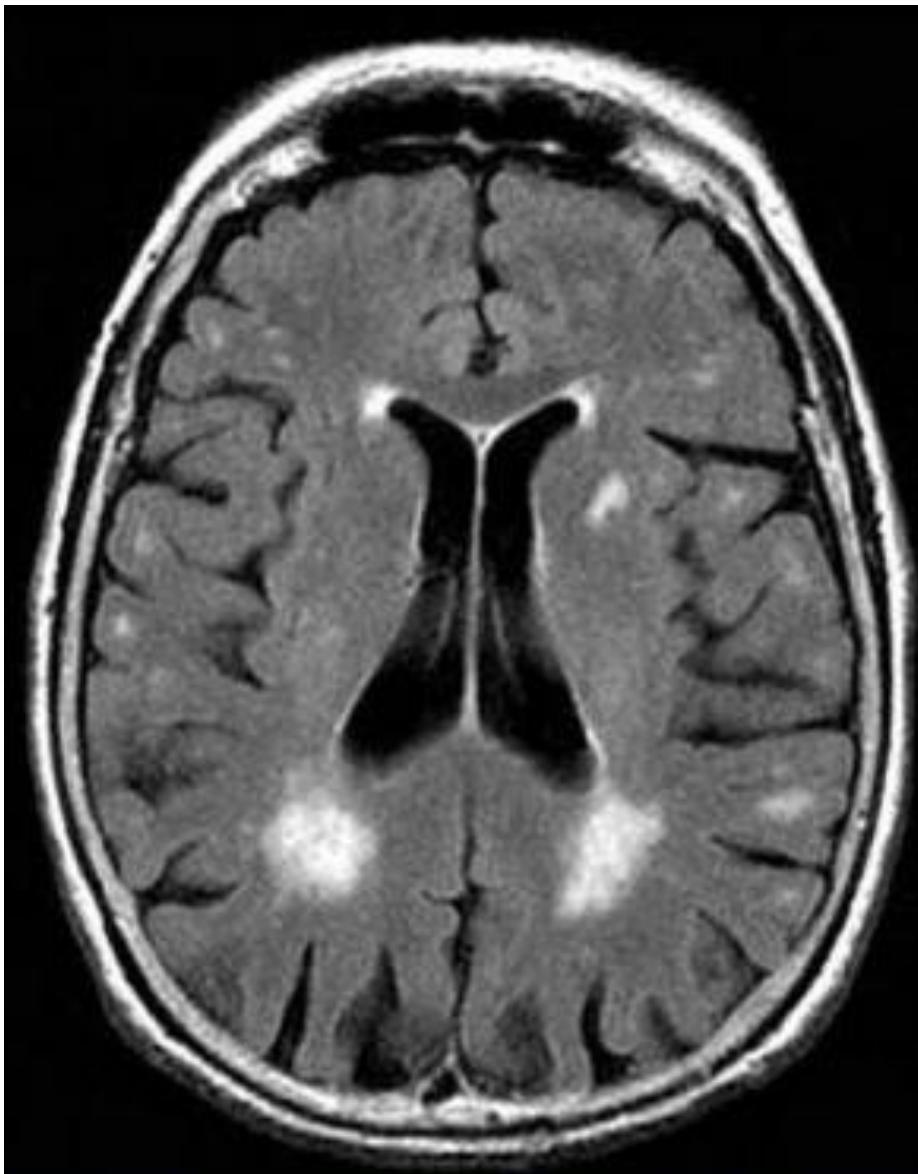
The aim of this study therefore is to closely examine the relationship between cerebral perfusion, white matter disease, blood pressure (BP) and depression, with a particular focus on the frontal lobe. Untangling this relationship is important in order to enhance our understanding of the biological mechanisms that underlie LLD but also because it can inform potential preventative strategies.

We begin by discussing these important factors separately in relation to LLD.

### **1.3Late Life Depression &Cerebral White Matter Disease**

Cerebral white matter disease, or leukoariosis, appears as white lesions called white matter hyperintensities (WMH) on T2/ Fluid Attenuated Inversion Recovery (FLAIR) sequences of brain magnetic resonance imaging (MRI) and is now a radiological hallmark of LLD(38, 39).

**Figure 1.2 Brain Magnetic Resonance Imaging Demonstrating White Matter Hyperintensities**



*Notes:*

*Extensive white matter hyperintensities, predominantly in the periventricular region.*

WMH are associated with a significantly higher risk of incident stroke, dementia and early mortality (40) and WMH burden is now also recognised as a key biological risk factor underpinning LLD (1, 41, 42).

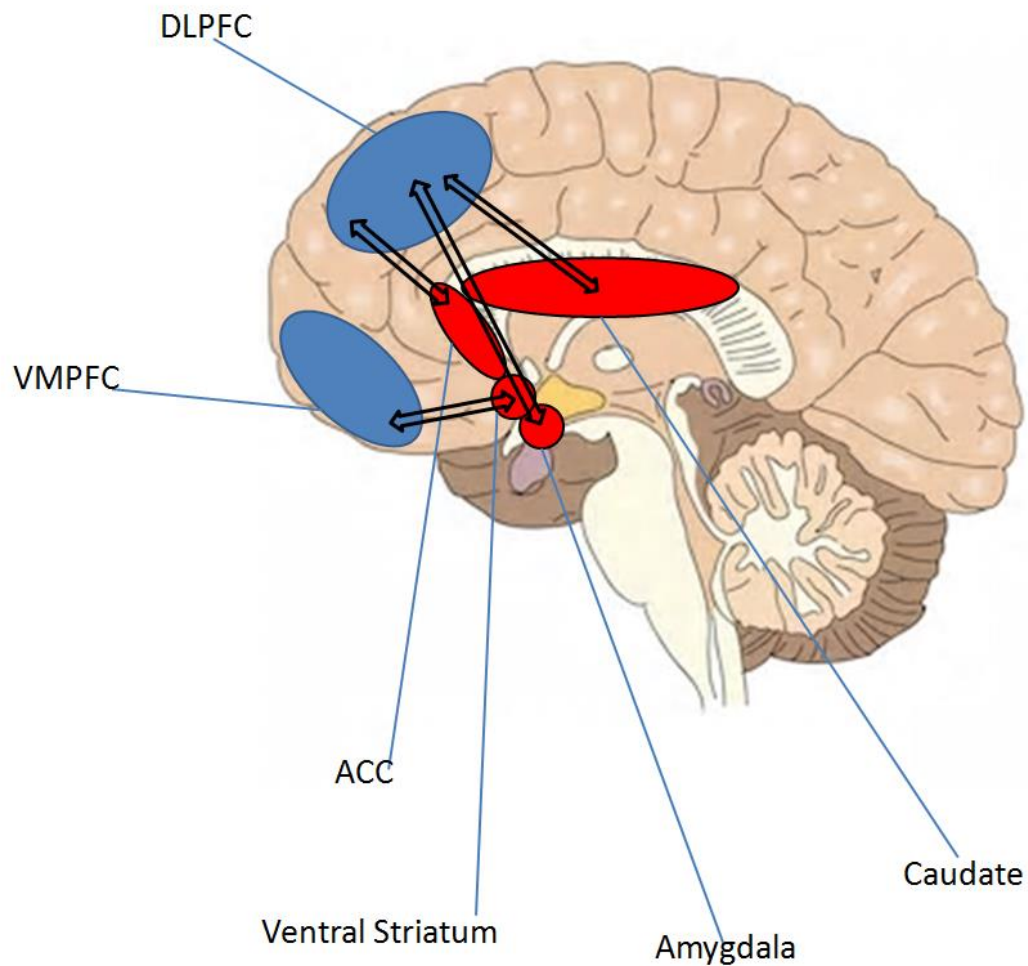
WMH burden independently predicts incident late life depressive symptoms (39). Older people with WMH burden in the upper quintile are 3-5 times more likely to have depressive symptoms compared to those in the lowest quintile (43), while older people with late onset depression have WMH burden scores 0.7-0.8 standard deviations higher than their peers with ELD (44). Additionally, greater progression of WMH is associated with poorer treatment response during both short (12 weeks) and longer term (2 years) interval follow-up (37, 45). It appears that WMH involving the frontal lobe are of particular importance (46) and strategically located WMH may cause depression by interfering with frontal lobe function (47).

Furthermore, studies using functional MRI, MRI with diffusion tensor imaging and electroencephalogram have demonstrated important neural network connections between the frontal lobe and both limbic and subcortical regions which are involved in mood regulation (48-51). Figure 1.3 demonstrates some of these important frontal networks.

Strategically located frontal WMH may therefore disrupt these important connections, causing depression (35). This may also partly explain differences in clinical presentation in LLD. For example, WMH in specific brain regions correlates with apathy, executive dysfunction and reduced processing speed in depressed older people, key clinical features of LLD (52, 53). Furthermore, LLD is particularly associated with other clinical syndromes where frontal connectivity is compromised, including gait problems (54), dementia (55) and other neurodegenerative conditions (56).

Given their close association with incidence and prognosis of LLD, identification of the pathological processes underlying WMH in depression is therefore important in order to inform preventative and therapeutic strategies. Current evidence from post-mortem studies suggests, in keeping with the Vascular Depression hypothesis, that WMH in depression are caused by localized cerebral ischemia (57). While several pathophysiological causes for WMH in depression have been suggested (58), an important cause of localized, strategically located cerebral ischemia is cerebral hypoperfusion (59).

**Figure 1.3 Important Frontal Networks in Depression**



*Notes:*

*Examples of frontal lobe networks identified in depression by magnetic resonance imaging or electroencephalogram studies.*

*Abbreviations: DLPFC = dorsolateral prefrontal cortex; VMPFC = ventromedial prefrontal cortex; ACC = anterior cingulate cortex.*

#### **1.4 Late Life Depression & Cerebral Hypoperfusion**

Cerebral blood flow (CBF) in an adult typically measures 750 millilitres per minute, and is regulated by cerebral autoregulation, which acts to maintain adequate cerebral perfusion despite dynamic BP changes (60, 61). Lassen's initial work in the 1960's posited that CBF was kept relatively constant across a range of mean arterial pressures ranging from approximately 50 to 150 mmHg despite dynamic changes in BP (62), however more recent work has indicated that the ability of autoregulatory mechanisms to buffer extreme BP values may not be as robust as once thought (63).

Figure 1.4 Panel A shows a diagram of Lassen's classical curve, while Panel B reflects more recent work (63). This is important as it highlights the critical relationship between adequate systemic BP and CBF. Cerebral autoregulation may involve myogenic and neural control as well as metabolic adaptations in response to changes in systemic BP (64). When these responses become impaired however, the brain can be exposed to cerebral hypoperfusion and therefore inadequate CBF to meet its demands (65).

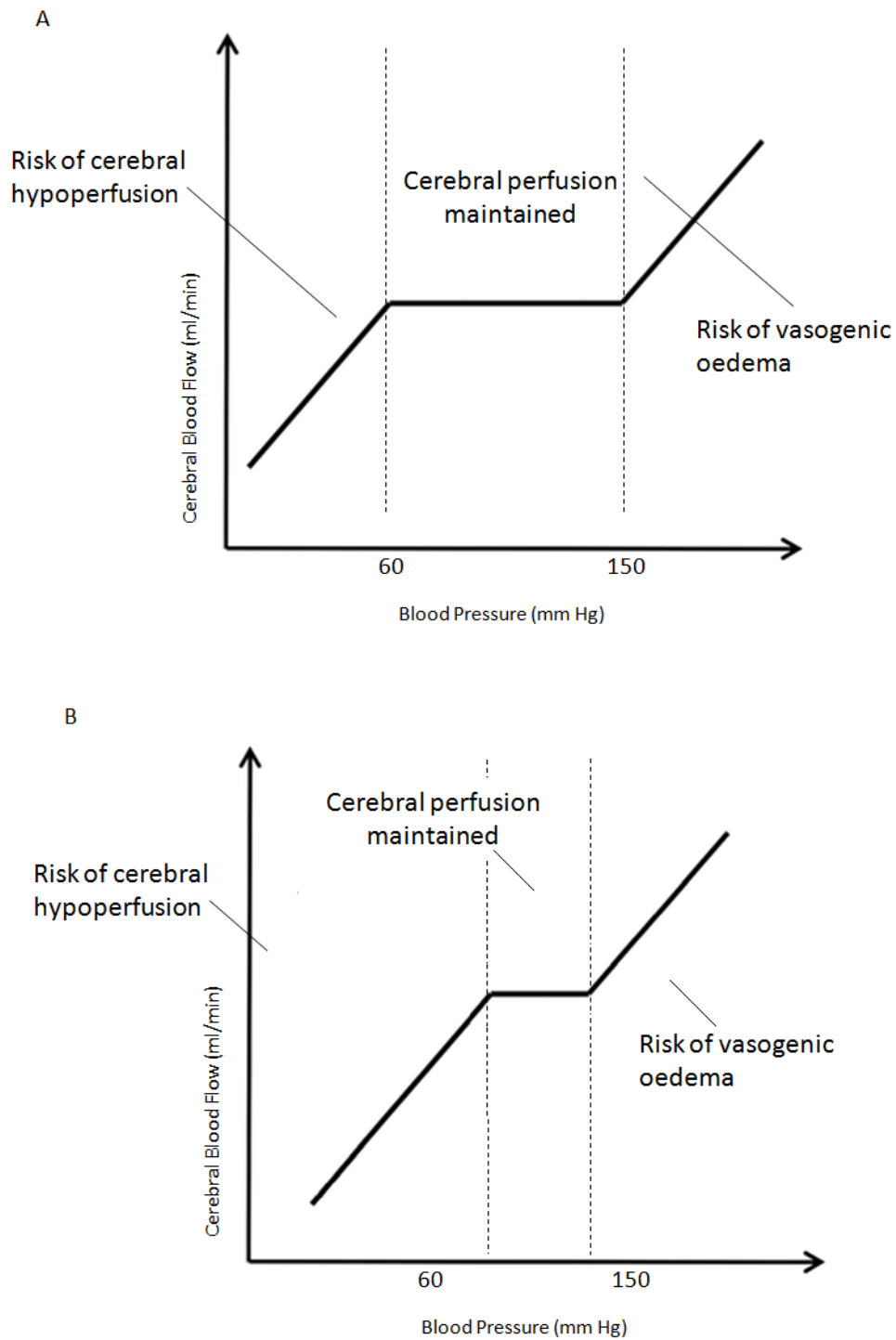
Cerebral perfusion deficits are closely associated with cerebral white matter disease and WMH burden. In a cohort of 85-year-old participants, areas with WMH had a significantly lower CBF measured by contrast-enhanced MRI when compared to normal white matter (66). A further study in a cohort of older participants with heart failure demonstrated that reduced middle cerebral artery blood flow, measured by TCD, was associated with significantly higher WMH burden (67). Additionally, a study of over 200 participants with cardiovascular disease demonstrated that higher total CBF (>675 millilitres per minute) was associated with a 50% reduction in WMH burden after controlling for covariates including age, sex and hypertension (68).

Given these findings, it is not surprising that cerebral hypoperfusion has also been implicated in LLD as neuroradiological studies have consistently demonstrated associations with both global and frontal cerebral perfusion (69, 70). Additionally, decline in CBF is associated with increased depressive symptoms in older people with chronic cardiovascular disease (71, 72) while reduced cerebral perfusion measured by TCD also predicts incident LLD (73).

Furthermore, in a cohort with Parkinson's disease, single-photon emission computed tomography (SPECT) demonstrated cerebral perfusion deficits in fronto-temporal-limbic regions in depressed participants compared to non-depressed controls (74) while LLD is also

independently associated with other conditions related to cerebral perfusion deficits, including syncope and unexplained falls (75, 76).

Importantly, there is also some evidence demonstrating a specific association between cerebral perfusion deficits and WMH specifically in people with depression (77), and while this involves small numbers of participants, it suggests that WMH due to cerebral hypoperfusion may be important mechanistically in LLD.

**Figure 1.4: Schematic of Cerebral Autoregulation Curves**

Notes:

Panel A based on Lassen's work from 1960's; Panel B based on more recent studies (Tan, et al, 2012)

### **1.5 Late Life Depression & Blood Pressure**

It is clear then that BP is an important factor in determining CBF and hypotension is particularly closely linked with reduced cerebral perfusion. Despite the close relationship between depression and vascular disease in later life, there does not appear a direct association with hypertension. There is however an emerging body of evidence demonstrating an association between lower BP, both systemic and orthostatic, and depression in later life, with cerebral hypoperfusion identified as a potential mechanism for this relationship.

#### *Orthostatic Hypotension*

Orthostatic hypotension (OH) is defined as a sustained drop in systolic blood pressure (sBP) by at least 20 mmHg or diastolic BP by at least 10 mmHg within 3 minutes of standing (78). OH is common, affecting one in five people aged 65 years old or older and this prevalence increases with further advancing age(79).

Normally, when we stand from a seated or lying position, blood pools in the legs, causing a drop in venous return, cardiac filling pressure, cardiac output and ultimately systemic BP. This drop in BP reduces firing of baroreceptors located in the carotid sinus and aortic arch, which then act to normalise BP by increasing sympathetic outflow and reducing parasympathetic activity, resulting in peripheral vasoconstriction and tachycardia(80). In later life, this baroreflex response can become less sensitive, leading to prolonged times to stabilise BP and resulting in OH (81).

This prolonged time to BP recovery exposes the brain to reduced cerebral perfusion, particularly in those who develop orthostatic symptoms of dizziness or light-headedness (82). This is corroborated by tilt table studies demonstrating that dynamic systolic BP changes correlate closely with CBF (83). Furthermore, greater drops in orthostatic BP are associated with reduced cerebral perfusion in specific patient groups, such as people with Lewy Body Dementia (84) or a prior history of stroke (85).

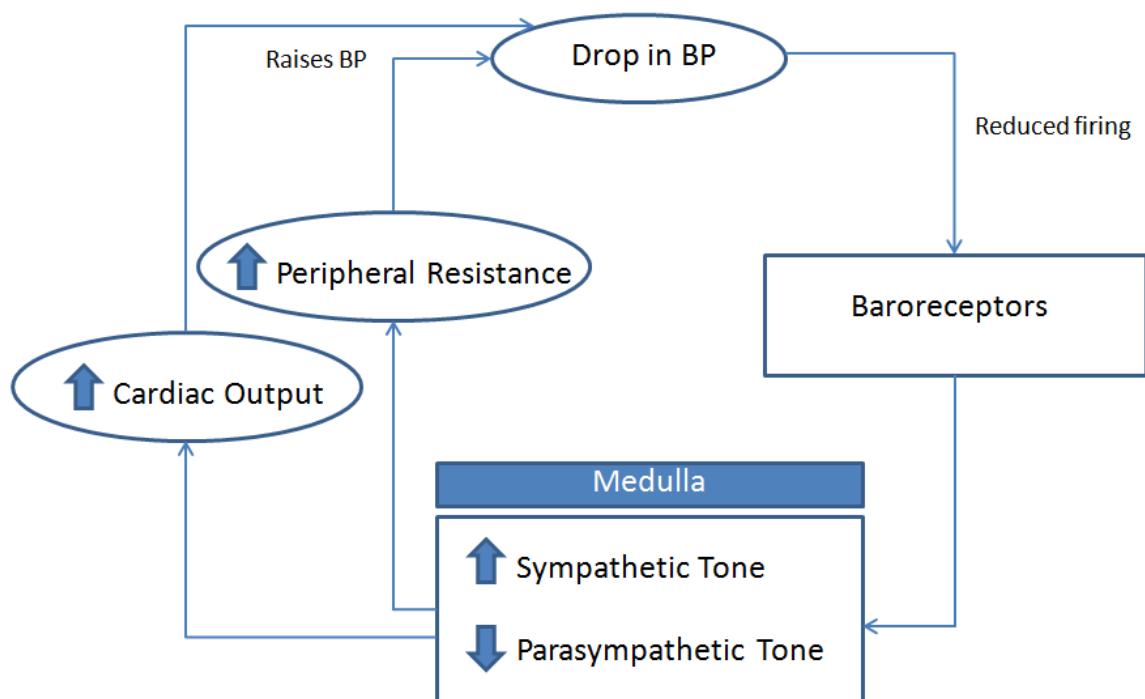
Longitudinal studies further support these findings by demonstrating that OH is an independent risk factor for conditions related to cerebral perfusion deficits, including vascular dementia, falls and stroke(86-88). While there is some cross-sectional evidence linking OH with LLD, as yet this association has not been tested in a longitudinal study(89).

An important limitation of many studies of OH is the method used to measure orthostatic BP. Non-invasive beat to beat BP measurement by active stand using a finometer is a more

sensitive diagnostic test for OH as it allows real-time continuous tracking of BP and captures dynamic BP changes that are often missed with other techniques(90).

Figure 1.6 below demonstrates a typical continuous systolic BP measurement obtained from an active stand using beat-to-beat measurement and compares a normal response with full recovery of BP before 30 seconds post-stand to an abnormal orthostatic response with delayed BP recovery and subsequent 'overshoot' above the baseline BP. Techniques used to measure orthostatic BP are described in detail in Chapter 2.

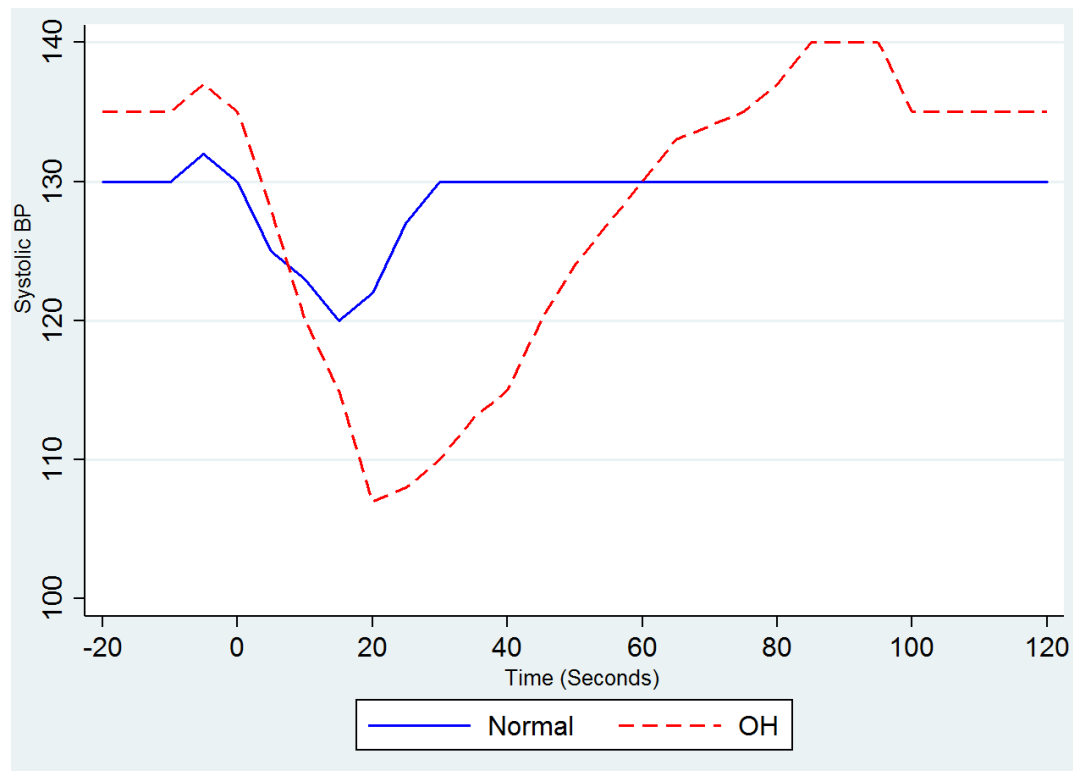
**Figure 1.5: The Baroreflex Response to Hypotension**



*Notes:*

*Schematic representation of baroreflex-mediated response to standing.*

**Figure 1.6: Continuous Systolic Blood Pressure measurements during Active Stand in participants with and without Orthostatic Hypotension**



Notes:

*Finometer data demonstrating measurement of systolic BP during active stand. Participant stands at 0 seconds. Blue line denotes normal response with initial drop followed by full recovery to baseline by 30 seconds. Red line denotes orthostatic hypotension with prolonged blood pressure recovery and subsequent 'overshoot'.*

### *Systemic Hypotension*

There is no widely accepted definition of what value constitutes hypotension in the older person, and rather than a 'one size fits all' approach, BP targets are becoming increasingly individualised, considering both the age and fitness of the patient(91).

International guidelines suggest that in general BP of 130/80 mm Hg is an appropriate treatment target(92) but in an older population there has been an increasing trend towards less strict targets for BP control, and values of 140-150 mm Hg for sBP may be considered optimal in certain circumstances in this setting(93). This has occurred in parallel with an increasing recognition of the adverse effects of persistent hypotension in older people(94, 95).

Even transient hypotension can cause cerebral hypoperfusion(96), which has been cited as the mechanism linking low BP with syncope, falls and cognitive decline (97, 98). Chronically low BP diminishes immediate cognitive performance, particularly in the domains of memory and attention (99), and late life hypotension appears to be a significant risk factor for incident dementia (100, 101).

While cross-sectional studies have also demonstrated a consistent relationship between late life hypotension and depression, longitudinal studies to date are less consistent(102). Studies to date are also limited by not controlling for important covariates, particularly antidepressant use (102).

With the recent Systolic Blood Pressure Intervention Trial (SPRINT) study now suggesting that tighter BP control in older people is beneficial however (103), despite concerns about its generalizability(104), it is important to fully understand the link between low BP, cerebral perfusion, structural brain changes and poorer brain health outcomes, particularly incident depression as it is generally not included as an adverse outcome in BP intervention studies (103, 104).

### **1.6 Late Life Depression, the Frontal Lobe & Gait**

Structural and functional brain changes in the frontal lobe are of particular importance in LLD. As well as higher burden of frontal WMH, older people with late onset depression have higher rates of frontal lobe atrophy (105). Functionally, pathological changes in frontal lobe structure can disrupt neural connections along frontostriatal circuits involved in the regulation of mood and cognition (33, 49). This hypothesis is supported by further studies demonstrating abnormal frontal lobe biochemistry (106), as well as neuropathological studies demonstrating a reduction in frontostriatal neuronal cell volume in depressed older people (105, 107).

Pathological frontal lobe changes have also been implicated in gait disorders in later life (108). Gait disorders are an important, often under-diagnosed, syndrome that affect over one third of community-dwelling people aged over 70 years (109). They are independent predictors of adverse outcomes, such as admission to hospital (110), cognitive decline (111), nursing home admission and death (112).

Gait disorders are generally classified based on the level of sensorimotor deficit involved (113). Lower level gait disorders are due to deficits distal to the central nervous system, e.g. osteoarthritis, while middle level gait disorders are due to focal deficits caused by neurological disease, such as in Parkinson's disease or stroke (113).

In terms of an association with depression however, higher level gait disorders are of particular interest. Higher level gait problems are those which cannot be explained by demonstrable deficits in the pyramidal, extrapyramidal, sensory or cerebellar systems and, like LLD, are strongly associated with cerebral white matter disease, particularly involving the frontal lobe (114), suggesting a potential shared aetiological pathway.

Most work to date examining the link between depression and gait is cross-sectional and longitudinal studies have not yet examined the role of specific gait characteristics (115, 116). Given their high prevalence and the significant impact both conditions have on functional status, as well as the possibility of a common mechanistic pathway involving frontal lobe dysfunction (114), further exploration of this association is important in order to better understanding the link between the conditions, but also in terms of potentially informing preventative strategies.

## **1.7 Hypotheses & Aims**

Based on this appraisal of literature to date our hypotheses are:

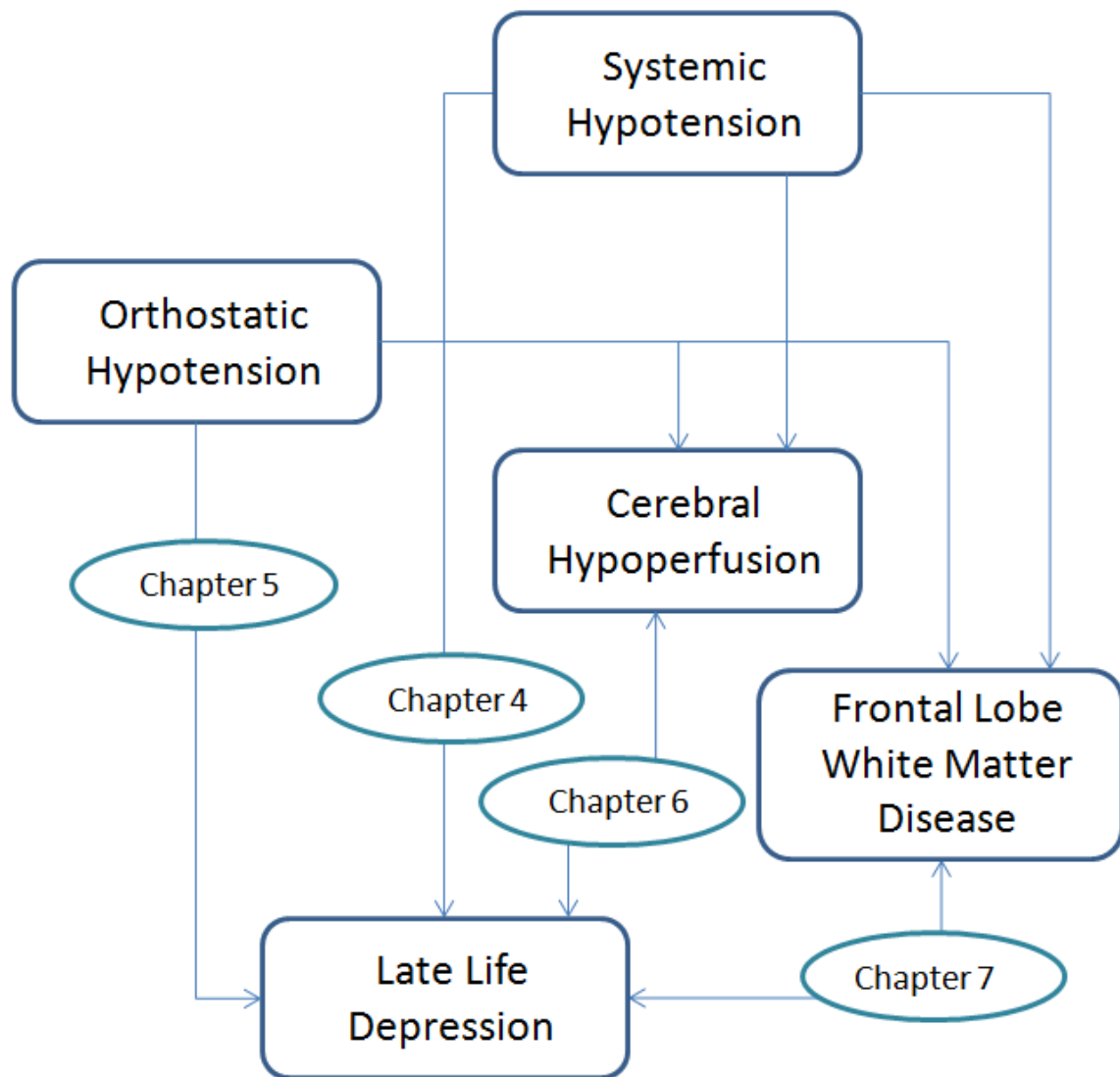
1. Conditions, such as orthostatic and systemic hypotension, which predispose to cerebral hypoperfusion, increase the risk of LLD by causing structural changes in the frontal lobe.
2. Gait disorders, which are related to structural and functional changes in the frontal lobe, are closely associated with depression in later life and could potentially be used to identify those at risk of incident depression.

In order to test this hypotheses we will use the Irish Longitudinal Study on Ageing (TILDA) dataset, involving a sample of adults over 8,000 people aged  $\geq 50$  years at wave 1, with detailed social and biological data which allows us to control for a wide range important covariates and to conduct robust longitudinal analyses. TILDA also incorporates novel objective health measures that will be used in order to test our hypotheses. These will be described in detail in Chapter 2.

### *Hypothesis 1: Blood Pressure, Cerebral Perfusion & Depression*

We will initially undertake a systematic review of available literature assessing the association between hypotension and depression in later life (Chapter 3). We will then conduct longitudinal analyses using data from TILDA examining the relationship between systemic hypotension (Chapter 4) and OH (Chapter 5) and incident depression. Furthermore, we will assess the association between depression and frontal lobe cerebral perfusion, and whether this relationship is modified by systemic and orthostatic BP (Chapter 6). Finally, we will use TILDA brain MRI data to clarify the two-way association between systemic and orthostatic BP and cerebral white matter disease in a cohort of older people (Chapter 7). This plan is illustrated graphically in figure 1.7.

**Figure 1.7: Hypothesised Relationship between Blood Pressure, Cerebral Perfusion and Depression**

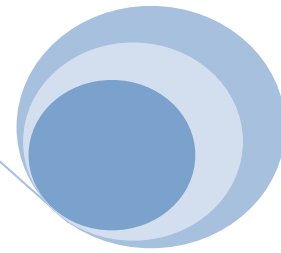
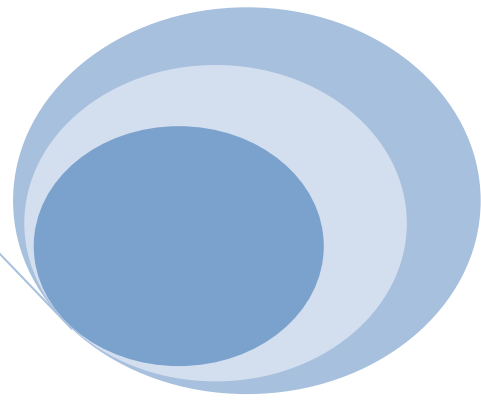


*Hypothesis 2: Late Life Depression & Gait*

Chapters 8 and 9 will focus on the association between gait disturbance and depression within the TILDA cohort.

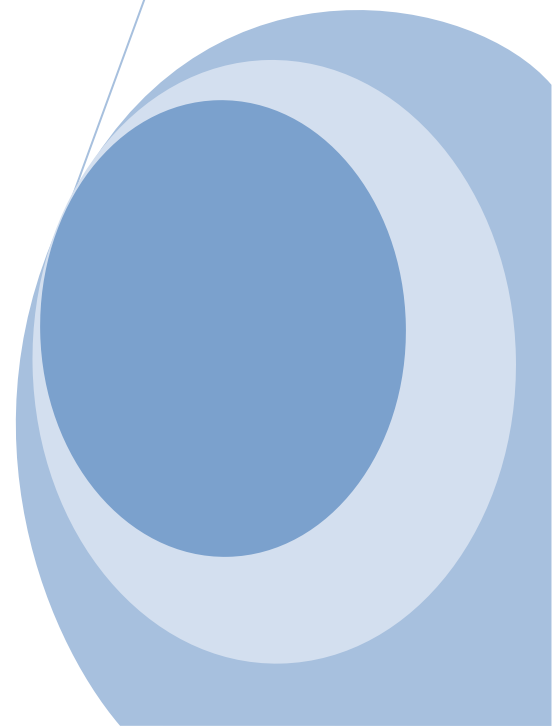
We will examine the longitudinal association between Timed Up and Go (TUG) and LLD, as well as whether spatiotemporal gait parameters such as step length, step width and gait speed can predict incident depression.

We will also control for important covariates such as alcohol excess, smoking, blood pressure, cardiovascular disease and subthreshold depressive symptoms.



## **CHAPTER 2:**

# Methodology and The Irish Longitudinal Study on Ageing



## **2.1 Key Findings**

- TILDA was designed to investigate how the health, social and economic circumstances of the older Irish population interact in the determination of 'healthy' ageing.
- These studies use data from TILDA waves 1 to 3.
- Measures performed at the TILDA health assessment include continuous measurement of orthostatic blood pressure during active stand, with parallel frontal lobe perfusion measured by near-infrared spectroscopy (NIRS) and gait analysis by spatiotemporal analysis.
- A subset of participants also underwent brain MRI at wave 3.
- Depressive symptoms were assessed using the Centre for Epidemiological Studies Depression Scale (CES-D).
- The 20-item CES-D was performed at wave1, with a cut-off score of 16 indicative of clinically significant depressive symptoms.
- The 8-item CES-D was performed at waves 2 and 3 in order to reduce respondent burnout and fatigue.
- We conducted a validation study that identified a cut-off score of 9 as indicating clinically significant depressive symptoms on the 8-item CES-D.

## **2.2 The Irish Longitudinal Study on Ageing**

TILDA is a prospective, nationally representative study of community-dwelling Irish residents aged 50 and over. It is the most ambitious and comprehensive study of ageing ever carried out in Ireland and was designed to investigate how the health, social and economic circumstances of the older Irish population interact in the determination of 'healthy' ageing.

TILDA was designed following extensive international consultation, incorporating lessons learned in the conduct of similar studies in other countries and ensuring comparability of data with other well established international longitudinal studies of ageing (e.g., the English Longitudinal Study on Ageing , the Survey of Health, Ageing and Retirement in Europe and the Health and Retirement Survey in the US).

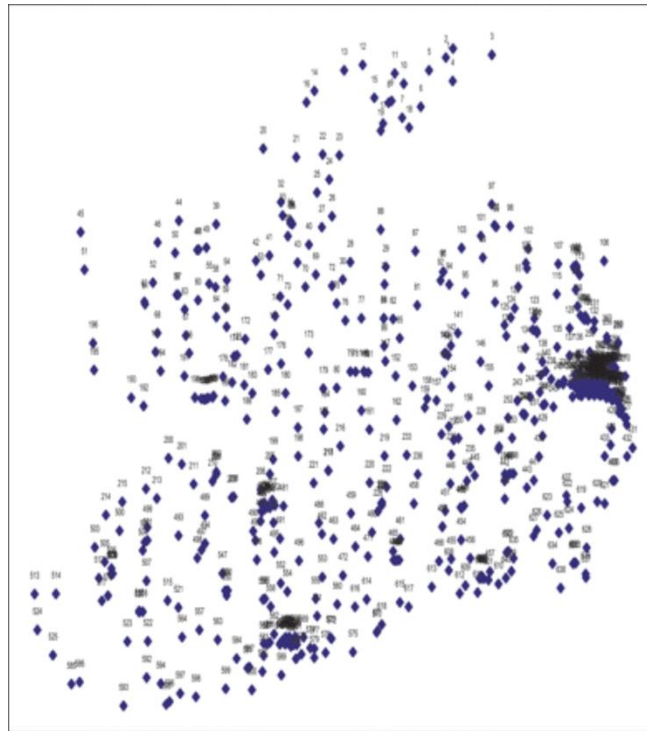
Since 2009, interviewers have collected data on all aspects of the lives of older people in Ireland, including economic (pensions, employment, income and assets, etc.), health (physical, mental, service needs and usage, etc.) and social aspects (contact with friends and kin, formal and informal care, social participation. etc.).

### *Study Sampling*

To generate the original TILDA sample, a stratified clustered procedure was used to randomly sample postal addresses from the Irish Geo-Directory (a listing of all residential addresses in the Republic of Ireland)(117).

All postal addresses in Ireland were assigned to one of 3155 geographic clusters, and a sample of 640 of these clusters was selected, stratified by socio-economic group and geography to maintain a population representative sample. Figure 2.1 demonstrates the location of these clusters across Ireland. Clusters were selected with a probability proportional to the number of individuals aged 50 and over in each cluster. Forty households were selected from each cluster and each of the selected addresses was visited by an interviewer, who attempted to ascertain the eligibility of the address, to contact a household member and determine whether any individuals aged 50 or over lived at that address(118).

**Figure 2.1: Map of selected addresses at TILDA Wave 1, location of 640 clusters**



All individuals aged 50 or over in each selected household and their partners (even if aged less than 50 themselves) were invited to be included in the study. Successful interviews were obtained in 6,279 households, yielding a response rate of 62%.

Participants with a history of dementia, based on a prior doctor's diagnosis, were excluded at wave 1.

#### *Study Components*

There are three components to data collection: (i) a computer-assisted personal interview (CAPI) administered by trained social interviewers in the participants' own homes; (ii) a self-completion questionnaire (SCQ) completed in the participants' own time; and (iii) a comprehensive health assessment delivered by trained research nurses in a dedicated health centre, or a modified version delivered in the participant's home(119). The CAPI and SCQ are included at each wave, while the health assessment is conducted at every second wave. Wave 3 included brain MRI for a sub-sample of participants.

The CAPI and the SCQ gather detailed information on educational attainment, economic status, and self-reported health including hearing, vision, chronic diseases and cognitive function. Lifestyle behaviour information includes smoking behaviour, exercise, alcohol consumption, sleep, functional disabilities and use of healthcare. It also includes a detailed neuropsychiatric assessment including measures of depression, anxiety, and personality type. Detailed medication and supplement use is recorded during the interview and cross-checked with the Health Service Executive pharmacy database.

The health assessment measurements are conducted by trained research nurses in a dedicated health assessment centre or in the participant's home. This assessment includes measures of the key domains that are known to change with age, including cognition, cardiovascular function, mobility, vision, bone health, anthropometry and health biomarkers. Anthropometric measures include height, weight, body mass index (BMI), grip strength, heel ultrasound and measures of sensory function (visual acuity and eye health). A comprehensive and extensive cognitive examination battery includes global cognitive function (Montreal Cognitive Assessment (MOCA), Mini Mental State Examination (MMSE)), executive function (colour trail tasks, letter fluency, word fluency, visual reasoning), processing speed (colour trail task 1, cognitive and motor reaction time), attention (SART mean and variability measures), memory (picture recall, picture recognition, immediate recall, delayed recall and self-reported memory).

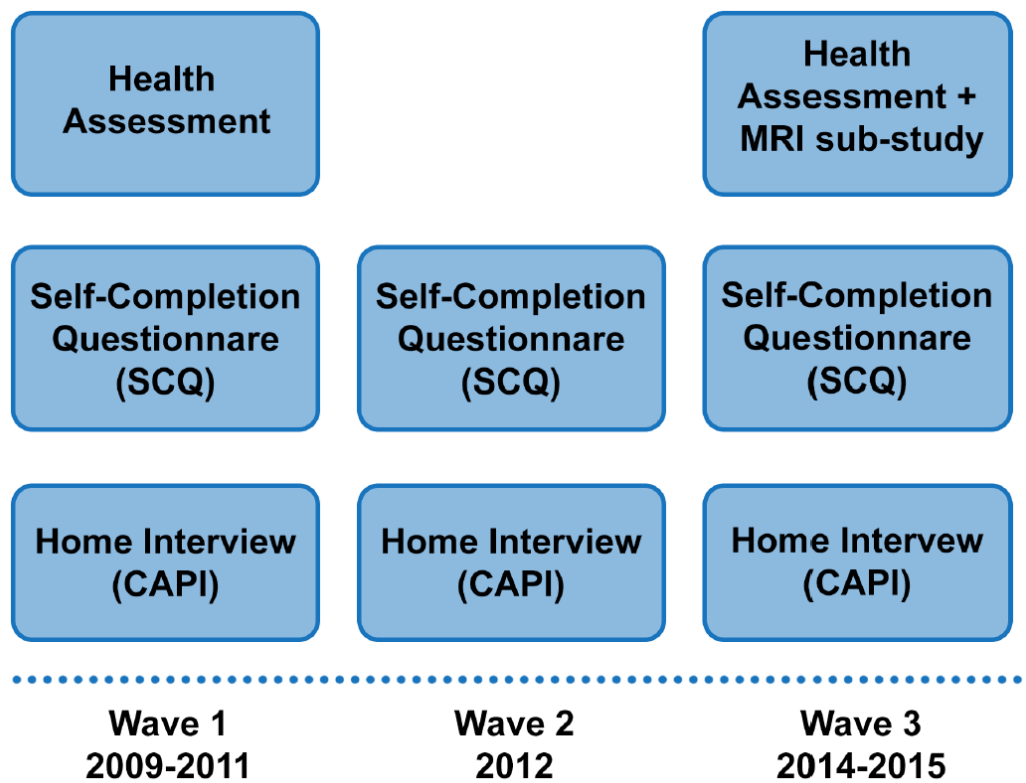
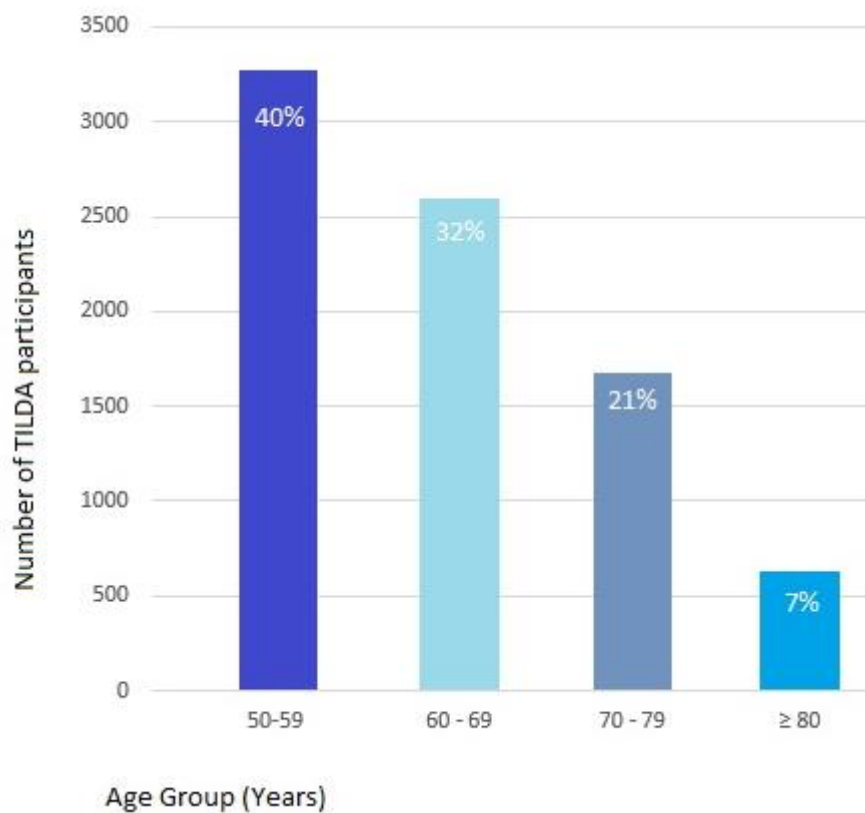
Baseline interviews on 8504 participants took place between October 2009 and February 2011; 85% and 72% of these participants completed the SCQ and health assessment, respectively.

#### *Longitudinal Follow-Up*

Wave 1 was conducted between 2009 and 2011; Wave 2 was conducted in 2012 and Wave 3 was conducted between 2014 and 2015. Figure 2.2 demonstrates the study components completed at each wave. The attrition rate between waves 1 and 3 was 15%, with 6,566 participants included at wave 3. 82% and 85% of participants at wave 3 completed the health assessment and SCQ respectively(120). Figure 2.3 demonstrates the age break-down for TILDA participants at Wave 1.

#### *Ethics*

The TILDA study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki. All healthcare assessments were carried out by trained research nurses.

**Figure 2.2: Timeline for TILDA Waves and Study Components****Figure 2.3: Histogram of age distribution of TILDA cohort at Wave 1**

### **2.3 TILDA Measures**

Some specific measures completed during the TILDA health assessment are particularly relevant to this project.

#### *Depressive Symptoms*

Depressive symptoms were assessed at wave 1 using the 20-item Centre for Epidemiological Studies Depression Scale (CES-D-20). The CES-D-20 is a 20-item scale, with response values are 4-point Likert scales, with range 0 to 3, yielding a total possible score of 60 (121). The CES-D has been validated in an older population, and a value of 16 or more has been shown to have a sensitivity of 92% and a specificity of 87% for diagnosis of depression (122). A score  $\geq 16$  was therefore used to define those with clinically significant depressive symptoms at wave 1 (123).

At waves 2 and 3 the 8-item Centre for Epidemiological Studies Depression Scale (CES-D-8) was used to screen for depression. The CES-D-8 was introduced in the TILDA study at waves 2 and 3 in order to reduce the time taken to conduct participant assessments, as well as to reduce respondent burden and fatigue, and previous work has confirmed its reliability in comparison to the CES-D-20 in terms of internal consistency and factor structure within the TILDA cohort (124).

We conducted a further validation study using the TILDA cohort in order to ascertain a cut-off score to define cases of clinically significant depressive symptoms (see 2.4 below). A score of  $\geq 9$  on the CES-D-8 was therefore used to define cases of clinically significant depressive symptoms (125).

#### *Orthostatic Blood Pressure*

Orthostatic BP was measured by active stand using a Finometer® Midi(126). Participants lay in the supine position for 10 minutes in a quiet room, before standing in a timely manner ( $<5$  seconds), and were aided by a research nurse to mobilize as necessary. After standing, systolic BP, diastolic BP, and heart rate were monitored for a further 120 seconds. Throughout the recording, subjects stood quietly. After the 2 minute period, subjects were asked to report occurrence of orthostatic symptoms (dizziness, light-headedness, or unsteadiness).

OH at 30 seconds (OH-30) was defined as a drop in systolic BP  $\geq 20$  mmHg or drop in diastolic BP  $\geq 10$  mmHg at 30 seconds compared to baseline BP(78). At wave 1, time-point values were 5-second moving averages, i.e. the 30 second time point was the average of 27.5 to 32.5 seconds. 30 seconds was chosen as the cut-off point post stand for several reasons. A recent large study has demonstrated that measurements of OH performed within 60 seconds of standing were the most strongly related to dizziness and adverse outcomes such as syncope, injury or death(127). Furthermore, a prior study looking at normative changes in phasic BP in the TILDA cohort established that an initial BP drop immediately after standing is common but non-recovery of BP should be considered abnormal by 30 seconds(126).

### *Near-Infra Red Spectroscopy*

Real-time Frontal lobe cerebral oxygenation was measured by the ArtinisPortalite System, a portable continuous wave NIRS system, which uses spatially resolved spectroscopy, reporting absolute values, developed to measure cerebral perfusion(128).

The NIRS technique is based on the property of human tissue being relatively transparent to light in the near infra-red spectrum; by measuring changes in light absorption at different wavelengths, the oxygenation of tissue can be monitored continuously(129, 130).

An optical sensor is placed on the participant's forehead, on the equivalent of the FP1 position in the international 10-20 electrode system, to measure changes in frontal lobe oxyhemoglobin and deoxyhemoglobin continuously. Tissue Saturation Index (TSI) was the primary measure used in this study, and is defined as  $(\text{oxyhemoglobin}) / (\text{oxyhemoglobin} + \text{deoxyhemoglobin}) \times 100$  and expressed as a percentage(131).

Continuous orthostatic BP was measured in parallel with this by active stand. Figure 2.3 demonstrates the set-up for this with the Finometer® applied to the finger and the NIRS device applied to the forehead.

**Figure 2.4: Active Stand using Finometer® and NIRS device**



*Notes: Finometer device on index finger of left hand with NIRS device applied to forehead.*

### *Brain Magnetic Resonance Imaging*

At wave 3, a subset of participants underwent brain MRI. Participants were sampled on a random basis. Participants meeting exclusion criteria, e.g. pacemakers, cerebral aneurysm clips or other MRI contraindications, were excluded prior to selection. In total, 501 MRI scans were completed with a mean delay between the health assessment and MRI of 62 days.

All imaging was performed using a 3T MRI scanner (Achieva, Philips, Netherlands) equipped with 32-channel head coil.

### *Gait*

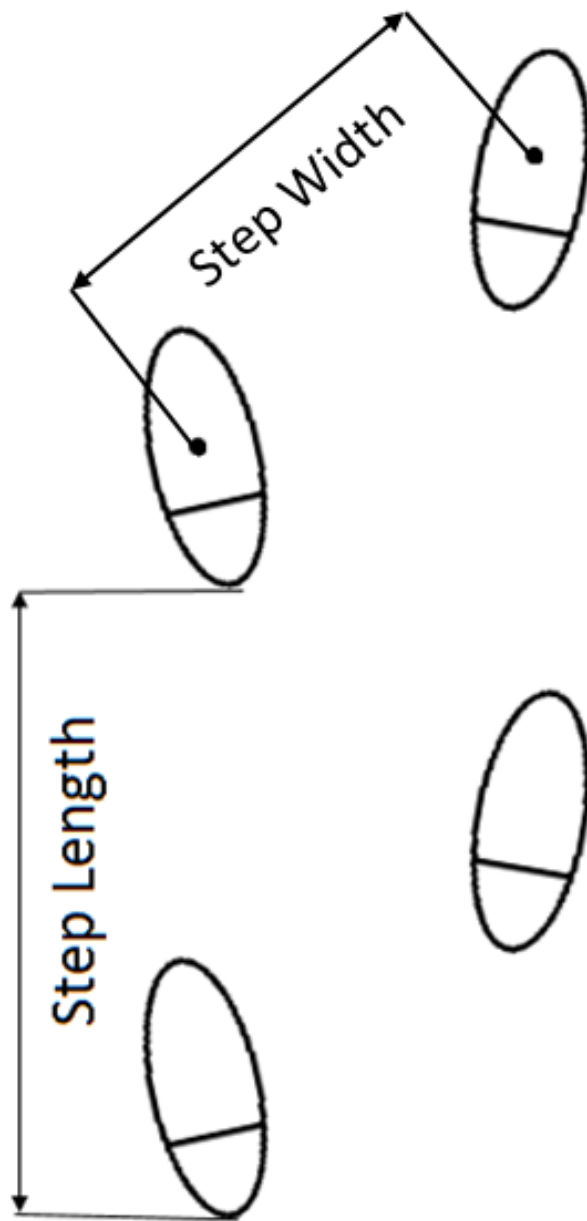
Gait was assessed using both the TUG and by spatiotemporal gait analysis.

The TUG involves measuring the time taken for a participant to rise from a chair, walk 3 metres, turn around and then walk back to the chair and sit down(132). The TUG is a reliable screening assessment for gait disturbance all levels, as well as a predictor of falls risk (133), correlating well with both gait speed and the Berg Balance Scale (134).The TUG was administered at baseline and at waves 2 and 3. Participants with a score of 12 seconds or more were considered to have gait disturbance (135).

Spatiotemporal gait analysis was provided by the GAITRite system, a computerized mat with pressure-sensors(136).Participants started walking 2.5 metres before the mat and stopped 2 metres after the mat to allow for acceleration and deceleration. They completed two walks in each of three conditions: at usual walking pace; walking while carrying out a manual task (holding a glass of water) and walking while carrying out a cognitive task (reciting alternate letters of the alphabet, i.e. A-C-E, etc.). Data from the two walks in each condition were averaged, e.g. the two 'normal' walks were combined to yield one overall variable for normal walking; similarly the two manual task walks were averaged and so on, and the following gait variables were obtained: gait speed, step length, step width and double support phase.

Gait speed is defined as the distance covered by the body per unit time, and is measured in cm/second. Step length is the distance between corresponding successive points of heel contact of the opposite foot and is measured in cm. Step width is the side-to-side distance measured between the midline midpoint of one foot to the midline midpoint of the opposite foot and is measured in cm. Double support phase is the time spent with both feet in contact with the floor, expressed as a percentage of the total gait cycle. See figure 2.4.

**Figure 2.5: Step length and Step Width**



*Notes:*

*Step Width and Step Length measured using GAITRite.*

## **2.4 Validation of 8-item CES-D**

### *Abstract*

#### Background:

The aim of this study was to validate the CES-D-8 against the CES-D-20 in a large sample of community-dwelling older people.

#### Methods:

Scales were compared for correlation and internal consistency. The ideal cut-off score for the CES-D-8 was determined by comparing scores ranging from 7-12 on the CES-D-8 to CES-D-20.

#### Results:

8,033 participants were included. The spearman co-efficient between the scales was 0.8980 indicating high degree of correlation. At a score of 9/24, the sensitivity and specificity of the CES-D-8 were 98% and 83% respectively. The Cohen's kappa for a score of 9 was 0.7855, indicating strong agreement and the ROC area was 0.88.

#### Conclusion:

When compared to the CES-D-20, the CES-D-8 is a valid and reliable measure of depressive symptoms in community-dwelling older people, and a score of 9 can be used to identify those with clinically significant symptoms.

## *Introduction*

The CES-D is one of the most commonly employed scales used to identify depression in large population studies involving older people (123). It is free to use and has been validated against in an older cohort against structured diagnostic interviews (137, 138).

However, concerns that the CES-D-20 is too time consuming and onerous, especially when embedded within large surveys involving older people, have led to the development of short forms of the scale. While the 10-item CES-D has been studied widely (139-141), the CES-D-8 is now increasingly employed in large international studies, including the European Social Survey and the Health and Retirement Study (142, 143). Previous work has confirmed the reliability of the CES-D-8 in comparison to the CES-D-20 in terms of internal consistency and factor structure, as well as correlations with disability and perceived stress, but as yet, no appropriate cut-off value to define depression cases via the CES-D-8 has been identified (124).

The aim of this study therefore is to validate the shortened CES-D-8 scale against the original CES-D-20 in a large sample of community-dwelling older people, in order to identify an appropriate cut-off value to define cases with clinically significant depressive symptoms.

## *Methods*

### *Study design*

We analysed data from waves 1 and 3 of TILDA, a study of a nationally representative sample of community dwelling adults aged 50 years and over (117). Participants were included if they underwent a complete assessment at wave 1, including a CES-D, as well as collection of other biological and social data.

### *CES-D*

The CES-D-20 consists of 20 items on a likert scale, yielding a total score of from 0 to 3 for each item (144). A score of 16 or more on the CES-D-20 is used to define clinically significant depressive symptoms (123).

The CES-D-8 consists of 8 items taken from this original CES-D-20. The range of the CES-D-8 is therefore 0-24. The CES-D-8 was repeated at wave 3 (4 year follow-up) to assess retest reliability.

### *Other Measures*

Relevant biological and sociological data were also collected by self-report at wave 1, including marital status, third level educational attainment, cardiovascular disease (myocardial infarction, angina, cardiac arrhythmia, or cardiac failure), chronic pain, functional impairment, diabetes and prior stroke.

### *Statistical Analysis*

Correlation between the two scales was assessed using Spearman's rank correlation coefficient. This was used in preference to Pearson's correlation as the CES-D scales are ordinal and results are not normally distributed. Spearman's correlation was also used to assess retest reliability at 4-year follow-up.

Cronbach's alpha was used to measure internal consistency of the scale. Factor analysis with varimax rotation was used to demonstrate the latent structure of the scale.

Due to the clustered nature of household sampling in TILDA, a cross-validation approach was used whereby analyses were repeated on smaller samples containing one participant from each cluster, and results were compared. For example, when analysing all clusters with a minimum of 5 households, we initially selected clusters that comprised at a minimum 6 unique respondent households. Next, we drew a random sample of 5 participants from that cluster – since each sampled participant was an inhabitant from a unique household, the sample did not include any cohabiting respondents (in order to reduce bias from within-household correlation of data). We then took the first sampled individual from each cluster (cluster N= here) as an observation and re-ran analysis across the subset of n= [here] individuals. We then repeated this process four further times, allowing each remaining sampled individual to serve as a data point for the cluster they were sampled from. In this way, the analysis provided multiple estimates of Cronbach's alpha, Spearman's rho and the factor structure that allowed the reliability of data to be verified across multiple samples from separate clusters.

For the full sample analysis, the appropriate cut-off score for the CES-D-8 was determined by comparing scores ranging from 7 to 12 against the CES-D-20 cut-off score of 16. Sensitivity, specificity, agreement and receiver operator characteristics were estimated for each of these potential cut-off values. Agreement was measured by percent agreement calculation, as well as by Cohen's kappa statistic.

In order to confirm that depression defined by the CES-D-8 had similar associations to depression defined by the CES-D-20 with respect to variables of interest, binary logistic regression models, reporting odds ratios (OR), were used and compared. This analysis was completed for the full sample analysed.

## Results

8,033 participants were included in the study. 10% (774/8,033) scored  $\geq 16$  on the CES-D-20 and were therefore defined as having clinically significant depressive symptoms.

The baseline characteristics of the study sample are shown in table 2.1.

**Table 2.1: Baseline characteristics of study sample**

|                                  | Not Depressed (n=7,259) | Depressed (n=774)  |                                    |
|----------------------------------|-------------------------|--------------------|------------------------------------|
| <b>Mean age in years(95% CI)</b> | 63.9 (63.7 – 64.1)      | 62.5 (61.8 – 63.1) | t=3.9057, p <0.001                 |
| <b>Female (%)</b>                | 53%                     | 67%                | X <sup>2</sup> =60.3108, p<0.001   |
| <b>Married (%)</b>               | 71%                     | 54%                | X <sup>2</sup> =93.1594, p <0.001  |
| <b>Third Level Education (%)</b> | 30%                     | 23%                | X <sup>2</sup> =15.0575, p <0.001  |
| <b>Functional Impairment (%)</b> | 6%                      | 22%                | X <sup>2</sup> =285.3378, p <0.001 |
| <b>Chronic Pain (%)</b>          | 18%                     | 47%                | X <sup>2</sup> =385.9011, p<0.001  |
| <b>Cardiac Disease (%)</b>       | 43%                     | 50%                | X <sup>2</sup> =15.0216, p<0.001   |
| <b>Prior Stroke (%)</b>          | 1%                      | 3%                 | X <sup>2</sup> =20.0271, p<0.001   |
| <b>Diabetes (%)</b>              | 8%                      | 10%                | X <sup>2</sup> =5.1679, p=0.023    |

Notes:

*Depression diagnosis based on a score  $\geq 16$  on 20-item Centre for Epidemiological Studies Depression Scale.*

*Categorical variables analysed by chi-square test, binary variables analysed using student t-test.*

*Abbreviations: CI = confidence interval*

*Functional impairment is defined as one or more impairments in instrumental activities of daily living, including cleaning and maintaining the house, managing money, moving within the community and preparing meal.*

*Chronic pain, prior stroke and diabetes are defined by self-report of these conditions.*

*Cardiovascular Disease is defined as self-report of angina, congestive cardiac failure, arrhythmia or myocardial infarction.*

### Agreement between scales

The spearman correlation co-efficient between the CES-D-20 and the CES-D-8 was 0.8980 (p Value <0.001), indicating a high degree of correlation between the scales. The CES-D-20 and CES-D-8 both also showed excellent internal consistency with a Cronbach alpha of 0.8757 and 0.8127 respectively.

The random samples in our cross-validation analysis showed a range of values for Cronbach's alpha all of which were close to or above 0.8, indicating high consistency. Similarly the range of values obtained for Spearman's rho were all close to 0.9. See table 2.2.

**Table 2.2: Results from cross-validation using samples derived from unique clusters.**

| Analysis of 20 groups each containing 58 participants from unique clusters   |                        |                       |
|------------------------------------------------------------------------------|------------------------|-----------------------|
|                                                                              | <u>Cronbach Alpha</u>  | <u>Spearman Rho</u>   |
| Mean (95% CI)                                                                | 0.787265 (0.76 – 0.81) | 0.88791 (0.87 – 0.91) |
| Median                                                                       | 0.78285                | 0.8947                |
| IQR                                                                          | 0.0708                 | 0.0652                |
| Analysis of 10 groups, each containing 365 participants from unique clusters |                        |                       |
| Mean (95% CI)                                                                | 0.80431 (0.79 – 0.82)  | 0.89676 (0.89 – 0.91) |
| Median                                                                       | 0.8035                 | 0.89945               |
| IQR                                                                          | 0.0392                 | 0.0172                |
| Analysis of 5 groups, each containing 520 participants from unique clusters  |                        |                       |
| Mean (95% CI)                                                                | 0.8201 (0.80 – 0.84)   | 0.89710 (0.89 – 0.90) |
| Median                                                                       | 0.8235                 | 0.8966                |
| IQR                                                                          | 0.0138                 | 0.0017                |

Notes:

CI = confidence interval; IQR = interquartile range.

## Factor Analysis

Factor analysis revealed the internal structure of the CES-D-8. Two factors with eigenvalues  $\geq 1$  were identified, and they accounted for 58% of the total variance of the data. The 6 'negative affect' items of the CES-D-8 loaded on to Factor 1, while the remaining two 'positive affect' items loaded on to Factor 2. See table 2.3. Factor analysis remained consistent when analysed iteratively using participants selected as a random sub-sample from each cluster (see methods).

**Table 2.3: Factor analysis of CES-D-8**

| <u>Factor</u>                                | <u>Eigenvalue</u> | <u>Variation</u> |
|----------------------------------------------|-------------------|------------------|
| <b>Factor 1</b>                              | 2.91              | 0.36             |
| <b>Factor 2</b>                              | 1.76              | 0.22             |
| <b>Factor Loading</b>                        |                   |                  |
| <u>CES-D-8 Item</u>                          | <u>Factor 1</u>   | <u>Factor 2</u>  |
| <b>I felt depressed</b>                      | 0.7022            | -0.3196          |
| <b>I felt everything I did was an effort</b> | 0.7507            | -0.1775          |
| <b>My sleep was restless</b>                 | 0.5726            | -0.1158          |
| <b>I was happy</b>                           | -0.1882           | 0.8435           |
| <b>I felt lonely</b>                         | 0.6454            | -0.2504          |
| <b>I enjoyed life</b>                        | -0.1615           | 0.8592           |
| <b>I felt sad</b>                            | 0.7002            | -0.2745          |
| <b>I could not get 'going'</b>               | 0.7475            | -0.1530          |

Notes:

Abbreviations: CES-D-8= 8-item Centre for Epidemiological Studies Depression Scale.

## Cut-Off Scores

Table 2.4 shows the performance of the CES-D-8 using different cut-off scores compared to the CES-D 20 (with a cut-off score for 16) for diagnosis of clinically relevant depressive symptoms. At a cut-off score of 9/24, the sensitivity and specificity of the 8-item CES-D were 98% and 83% respectively. The Cohen's kappa for a cut-off score of 9 was 0.7855, suggestive of strong agreement and the ROC area was adequate at 0.88.

**Table 2.4: Performance of different cut-off scores of CES-D-8 against CES-D-20 with cut-off score 16**

| Cut-off Score | Prevalence        | Sensitivity | Specificity | % Agreement | Kappa  | ROC Area (95% CI)  |
|---------------|-------------------|-------------|-------------|-------------|--------|--------------------|
| ≥ 7           | 15% (1,196/8,033) | 99%         | 61%         | 93.7        | 0.7091 | 0.94 (0.93 – 0.95) |
| ≥ 8           | 12% (958/8,033)   | 99%         | 71%         | 95.3        | 0.7557 | 0.92 (0.91 – 0.93) |
| ≥ 9           | 9% (733/8,033)    | 98%         | 83%         | 96.4        | 0.7855 | 0.88 (0.87 – 0.90) |
| ≥ 10          | 7% (554/8,033)    | 96%         | 90%         | 95.9        | 0.7331 | 0.82 (0.80 – 0.84) |
| ≥ 11          | 5% (429/8,033)    | 95%         | 96%         | 95.3        | 0.6617 | 0.77 (0.75 – 0.78) |

Notes: Abbreviations: CES-D-8 = 8-item Centre for Epidemiological Studies Depression Scale; CES-D-20 = 20-item Centre for Epidemiological Studies Depression Scale; % Agreement = Percentage agreement between CES-D8 and CES-D-20; Kappa = Cohen's kappa statistic; ROC = receiver operating characteristic; CI = confidence interval.

Table 2.5 shows binary logistic regression models, comparing the relationship of some variables of interest with depression diagnosis by CES-D-20 (at a cut off score of 16) and CES-D-8 (at a cut off score of 9). Results are broadly similar across scales, with the CES-D-8 demonstrating similar relationships with social and biological factors such as sex, educational attainment and chronic medical conditions.

**Table 2.5: Linear regression, comparing odds ratios for predictor variables for depression by CES-D-20 and CES-D-8**

|                     | Depression by CES-D-20 (Score ≥ 16) |         |       | Depression by CES-D-8 (Score ≥ 9) |         |       |
|---------------------|-------------------------------------|---------|-------|-----------------------------------|---------|-------|
|                     | OR (95% CI)                         | P Value | z     | OR (95% CI)                       | P Value | z     |
| Age ≥ 75 years      | 0.41 (0.32 – 0.53)                  | <0.001  | -7.02 | 0.47 (0.37 – 0.60)                | <0.001  | -6.06 |
| Female              | 1.58 (1.34 – 1.87)                  | <0.001  | 5.46  | 1.56 (1.32 – 1.84)                | <0.001  | 5.14  |
| Married             | 0.49 (0.42 – 0.58)                  | <0.001  | -8.50 | 0.52 (0.44 – 0.61)                | <0.001  | -7.74 |
| 3rd Level Education | 0.78 (0.65 – 0.94)                  | 0.007   | -2.68 | 0.82 (0.68 – 0.98)                | 0.033   | -2.13 |
| Functional Imp.     | 2.91 (2.31 – 3.65)                  | <0.001  | 9.13  | 3.29 (2.62 – 4.14)                | <0.001  | 10.24 |
| Chronic Pain        | 3.22 (2.72 – 3.80)                  | <0.001  | 13.76 | 3.00 (2.53 – 3.560)               | <0.001  | 12.62 |
| Cardiac Disease     | 1.14 (0.97 – 1.34)                  | 0.117   | 1.57  | 1.17 (0.99 – 1.38)                | 0.061   | 1.87  |
| Stroke              | 1.67 (1.02 – 2.73)                  | 0.040   | 2.06  | 1.49 (0.90 – 2.47)                | 0.118   | 1.56  |
| Diabetes            | 1.13 (0.86 – 1.49)                  | 0.368   | 0.90  | 1.30 (0.99 – 1.70)                | 0.060   | 1.88  |

Notes:

N= 8,030

CES-D-20 = 20-item Centre for Epidemiological Studies Depression Scale; CES-D-8 = 8-item Centre for Epidemiological Studies Depression Scale; OR = odds ratio; CI = confidence interval; Functional Imp. = Functional Impairment.

Functional impairment is defined as one or more impairments in instrumental activities of daily living, including cleaning and maintaining the house, managing money, moving within the community and preparing meal.

Chronic pain, prior stroke and diabetes are defined by self-report of these conditions. Cardiovascular Disease is defined as self-report of angina, congestive cardiac failure, arrhythmia or myocardial infarction.

### Test Retest Reliability

Three quarters (6,013/8,033) of the study sample had the CES-D-8 repeated at 4 year follow-up. The Spearman's correlation coefficient for the CES-D-8 performed at baseline and at 4 years was 0.4239 ( $p$  Value < 0.001), suggesting moderate correlation.

### *Discussion*

This study demonstrates that the CES-D-8 correlates well with the CES-D-20 when administered to a cohort of community-dwelling older adults.

At a cut-off score of 9 the CES-D-8 accurately identifies clinically significant depressive symptoms in this cohort when validated against the CES-D-20 with a sensitivity and specificity of 98% and 83% respectively. Logistic regression models offer further validation, with similar OR demonstrated for variables of interest, such as older age or chronic medical conditions, when comparing the CES-D-8 and CES-D-20 as dependent variables.

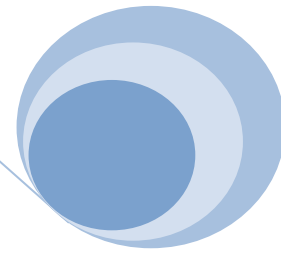
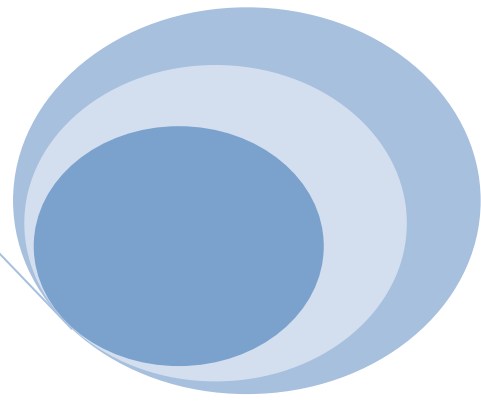
The CES-D-8 has previously been shown to have measurement equivalence across different ages, gender and countries (143, 145) and specifically in older people (146). However, while cut-off scores of 16 and 10 have been established for the CES-D-20 and CES-D-10 (139) respectively indicating a threshold for clinically significant depressive symptoms, this is the first study to identify an appropriate cut-off score to define cases of clinically significant depressive symptoms using the CES-D-8.

Validated shortened scales allow more rapid assessment and reduce respondent burden in large surveys. While it is often preferable to analyse continuous data from scales such as these, using a defined cut-off score to dichotomize cases into either a depressed or non-depressed group can also be useful as it mirrors decision-making in clinical practice, and allows us to estimate incidence and prevalence figures.

We also show that the internal structure of the CES-D-8 is similar to that of the CES-D-10, with two factors explaining almost 60% of the variance in the data (139). This is consistent with previous comparisons of factor structure between the CES-D-8 and CES-D-20 (124).

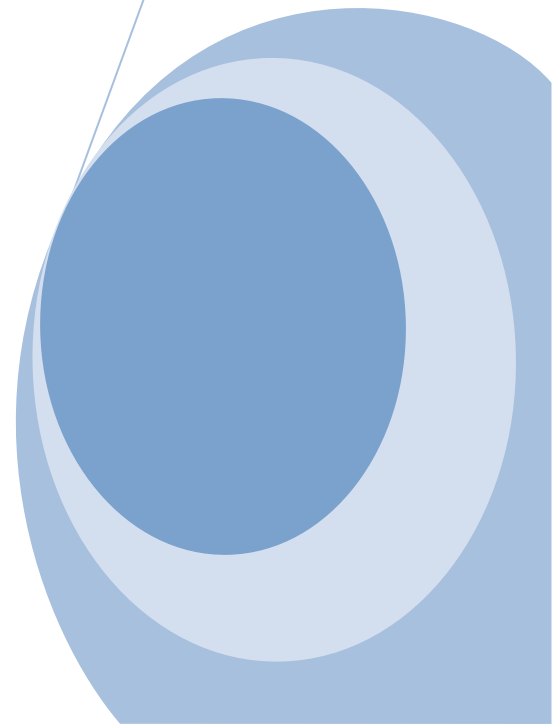
There are some limitations to this study which must be noted. While the CES-D-20 has previously been validated against a structured psychiatric interview, we did not compare the CES-D-8 to this gold standard and a further study validating the CES-D-8 against clinically diagnosed depression would be welcome.

In conclusion, this study demonstrates that, when compared to the 20-item CES-D, the 8-item CES-D is a valid and reliable measure of depression symptoms in community-dwelling older adults, and that a cut-off score of 9 can be used to identify those with clinically significant symptoms.



## **CHAPTER 3:**

# Systematic Review: The Association between Hypotension and Late Life Depression



### **3.1 Key Findings**

- **Cross-sectional studies to date, although limited in their ability to attribute causality, have demonstrated a consistent relationship between LLD and systemic hypotension.**
- **Studies examining the longitudinal relationship between lower systemic BP and LLD are less consistent however.**
- **These inconsistencies can at least partially be explained by marked methodological differences between longitudinal studies, making it difficult to generalise and pool results.**
- **As well as systemic hypotension, small studies have demonstrated a cross-sectional association between OH and LLD, although no longitudinal studies have examined this relationship as yet.**
- **Several factors may explain an association between lower BP and depression, including cerebral hypoperfusion, as well as the impact of chronic medical illnesses on mood and BP.**
- **Robust longitudinal studies controlling for important covariates such as cardiovascular disease and other chronic diseases are therefore important in order to better understand the link between BP, cerebral perfusion and depression in later life.**
- **This study was published in the Journal of the American Medical Director's Association (JAMDA): DOI 10.1016/j.jamda.2016.06.027.**

### **3.2 Abstract**

#### *Background*

LLD, defined as depressive illness in people aged 60 years or older, is more complex than depression presenting in earlier life, with different clinical features and a poorer response to therapy. Different biological factors underlie LLD and hypotension may be an important modifiable risk factor. The aim of this systematic review is to clarify the relationship between hypotension and LLD.

#### *Methods*

A systematic search was conducted in PubMed and Embase for articles published up to December 31, 2015. Key search terms were “depression,” “depressive disorder,” “hypotension,” and “blood pressure.” Studies were included if they were published as a primary research paper in a peer-reviewed journal, involved participants with a mean age of 60 years or more, and examined the relationship between hypotension and depression.

#### *Results*

The initial combined search retrieved 2268 non-duplicate articles. Of these, 116 full texts were assessed for eligibility, of which 19 were included in this systematic review.

Nine cross-sectional studies examined the association between hypotension and LLD, with 8/9 indicating a positive association between the 2. Five cross-sectional studies examined the relationship between OH and LLD, with each study finding a positive association between the 2. Five longitudinal studies examined the relationship between hypotension and LLD, with discordant findings between studies. There were no longitudinal studies examining the relationship between OH and LLD.

#### *Conclusion*

This systematic review found that cross-sectional studies demonstrated a consistent relationship between hypotension and LLD, but longitudinal data to date is less consistent, with discordant findings. There are several methodological limitations of published longitudinal data that may explain these differences, including differences in age at enrolment, depression and BP assessment, and controlling for covariates.

Further longitudinal studies to clarify the role of these potentially modifiable factors in the development of this complex illness are essential.

### **3.3 Background**

One of the most welcome developments in our lifetime is that older people are now living significantly longer, healthier lives. The global share of older people (aged 60 years or over) increased from 9.2% 1990 to 11.7% in 2013, and the number of older people worldwide is expected to more than double, from 841 million people in 2013 to more than 2 billion by 2050 (147). The majority of these older people live independently. This represents one of the success stories of modern times; however, such marked demographic shifts do not come without significant challenges. One such challenge is the increasing prevalence of neuropsychiatric disorders of later life, including LLD.

Given the strong cardiovascular basis of LLD, one would expect to find a close relationship with BP control and, in parallel, with dementia, there is an increasing body of evidence to suggest that hypotension and cerebral hypoperfusion may be an important factor in development of LLD(33). This review addresses the relationship between hypotension and depression in later life but in advance of that, we examine some important definitions and terminology surrounding both conditions.

#### *Late Life Depression*

LLD, defined as depressive illness with onset after 60 years or with onset before 60 years and persisting after the age of 60 years(148), is common, especially in those with significant medical comorbidities and functional disability (149). Depression can intensify these functional limitations (150), and carries with it significant levels of morbidity and mortality (151), as well as further functional limitations, independent of underlying illnesses (152). The incidence of LLD ranges from 0.2 to 14.1 per 100 person-years for a major depressive episode and 6.8 per 100 person-years for a subclinical depressive episode (12), with an estimated prevalence of 15% in people over 65 years (153). In TILDA, over 8% of a population-representative sample of older participants were found to have clinically relevant depressive symptoms on the CES-D (154). With projected demographic changes, it is likely that the prevalence of depression in later life will increase significantly over the coming years and become an even more central public health issue.

Depression in older people is a more complex illness than depression presenting in earlier life (155). Clinical features of LLD differ to earlier onset depression, with a higher likelihood of cognitive impairment, and executive dysfunction, which has been associated with a lower likelihood of remission of depressive symptoms (156). In addition, underlying medical comorbidities, such as heart disease and frailty, add to this complexity. As well as intrinsic factors, extrinsic influences also contribute to this high prevalence of depressive illness in later life. Although later life is generally a time of reasonably good health and happiness, it is clear that it can also be a time of loss, bereavement, and social isolation for a minority of older people(21).

A meta-analysis has shown that after 24 months follow-up following the diagnosis of LLD, 50% of surviving participants remained depressed (157). This is supported by a more recent longitudinal study demonstrating a chronic or relapsing course in approximately one-half of the cases diagnosed (158). Suicide rates are higher among older adults than younger adults,

and suicide is more closely associated with depression in this group (155). Depression also tends to present differently in older adults, with less dysphoria and guilt, and more complaints of somatic symptoms, anhedonia, fatigue, sleep disturbance, and psychomotor retardation (155).

A majority of research in this area concurs that LLD has a markedly different phenotype to EOD. As well as the different social factors involved which confer vulnerability to low mood, it is also likely that different biological factors underlie depression in the older person. One such factor that has received much attention is the vascular basis of depression in later life, as well as the structural brain changes associated with this (33, 35). This concept began to emerge when it was noted that patients with LLD had higher rates of cerebrovascular disease, reflected by cerebral white matter disease, than patients with earlier onset depression (159). This has led to attempts to clarify the role played by cardiovascular risk factors, such as BP, in the development of depression in later life.

### *Hypotension*

#### Definition

There is no widely accepted definition of what value constitutes hypotension in the older patient, and instead of a “one size fits all” approach, BP targets are becoming increasingly individualized, considering both the age and fitness of the patient. International guidelines suggest that in general BP less than 120/80 mm Hg is “normal” (160) but in an older population there is an increasing trend toward less strict targets for BP control (93) and values of 140–150 mm Hg for systolic BP (sBP) may be considered optimal in certain circumstances in this setting.

The recent SPRINT study, however, demonstrated a reduction in cardiovascular deaths and vascular events combined in a subgroup of patients 75 years of age and over, and this may have important implications for lower therapeutic targets in older persons in subsequent BP guidelines (161), despite concerns around the relatively strict exclusion criteria used (162).

Furthermore, the cut-off values for hypotension are predominantly based on static BP values, and we must remain cognizant that BP is a highly dynamic variable, with significant variability and diurnal variation, which does not lend itself to the isolated measurements traditionally employed in clinical practice. When we consider that the heart beats over 100,000 times per day, the beat-to-beat variability of BP is such that these individual readings provide only a crude estimate of average overall BP.

#### Hypotensive syndromes

The term hypotension is broad and encompasses several hypotensive subtypes, with differing clinical features and relevance in the older person. Persistent hypotension is present both supine and standing and is best demonstrated on a 24-hour ambulatory BP monitor.

OH is defined as a drop in sBP by at least 20 mm Hg or diastolic BP (dBP) by at least 10 mm Hg within 3 minutes of standing, with or without symptoms of orthostatic intolerance (78). OH is further subclassified into initial orthostatic hypotension (IOH), where symptoms occur within

30 seconds of standing; classic OH where symptoms occur between 30 seconds and 3 minutes from standing and delayed OH, with symptoms between 3 and 30 minutes after standing and characterized by a prolonged prodrome, frequently followed by sudden syncope(163).

Postprandial hypotension (PPH) is defined as a drop of 20 mm Hg or more in SBP within 2 hours of the start of a meal or when the absolute level of SBP following a meal falls below 90 mm Hg where preprandial SBP is over 100 mm Hg (164). It can occur both sitting and supine, more commonly after breakfast, and is thought to be related to an inability to compensate for hypotension caused by increased bowel blood flow after eating (165).

#### *BP measurement*

The multiplicity of non-invasive techniques used to measure BP may also introduce inconsistency into study findings. Despite the technological advances in medical assessment over the last 100 years, the auscultatory method of BP measurement, using a sphygmomanometer remains in common use. The Korotkoff method continues to be the most widely used technique for measuring BP using a sphygmomanometer, but it tends to give values for systolic pressure that are lower than the true intra-arterial pressure, and diastolic values that are higher(166). Findings are also operator-dependent and can be subject to inaccuracies such as terminal digit preference (167).

The oscillometric method of BP measurement is commonly used in automated devices, including ambulatory BP monitors and is based on the finding that the point of maximal oscillation when deflating a sphygmomanometer cuff corresponds to the mean intra-arterial pressure. An algorithm is then used to determine sBP and dBP(168). These algorithms are proprietary and differ from one another, meaning that commercial devices cannot be compared or standardized (169). The oscillometric method requires less skill than the auscultatory method and cuff placement is less critical, however, there are concerns that automated measurement to BP, particularly dBP, in patients with arrhythmias such as atrial fibrillation may be inaccurate (170).

Ambulatory BP is a fully automated BP recording, with multiple measurements over a defined period of time, usually 24 hours. During a typical monitoring session, BP is measured every 15 to 30 minutes over 24 hours including both awake and sleeping hours, ideally on a workday, with the total number of readings varying between 50 and 100 (171).

Non-invasive beat-to-beat BP is based on the vascular unloading technique (172). It allows real-time continuous tracking of BP and gives waveform measurements similar to those seen in invasive intra-arterial monitoring (173). It, therefore, captures dynamic BP shifts that are missed by other techniques and is of particular utility when performing active stands, tilt table testing, and carotid sinus massage. Commercially available kits include Finapres(174) and Finometer (175)and employ a finger cuff.

### **3.4 Review Methodology**

A systematic search was conducted in order to clarify the relationship between hypotension and LLD. Our review methodology and reporting followed standard guidance (176).

#### *Search Strategy*

In collaboration with a clinical librarian, a systematic search was conducted in PubMed and Embase for articles published up to December 31, 2015. A customized search strategy was conducted for each database. A manual search of references in the selected articles was also conducted to identify additional studies. Key search terms were “depression,” “depressive disorder,” “hypotension,” and “blood pressure.”

Our clinical question was “Does hypotension, either systemic or orthostatic, predispose to the development of depression in older people?”

Based on the PICO (Population, Intervention, Comparison, Outcome) model our clinical question had 4 elements: (1)Population: Participants aged 60 years and over, can be community- or hospital-based, with hypotension, defined either by a cut-off value or as a percentile value based on the overall mean of the study group. No depression at baseline.(2) Interventions and (3) Comparisons: Controls are participants with similar baseline characteristics with either normal BP or hypertension. We included observational, (i.e., non-interventional trials only). (4)Outcome: Diagnosis of depressive illness, defined either based on structured neuropsychological assessment or using a validated assessment tool.

For depression, key search terms used were “depression” AND “depressive disorder,” OR “late onset,” “late life,” “geriatric,” “senile,” “elderly,” and “hypotension.” For hypotension, we searched “hypotension” OR “blood pressure” OR “orthostatic” OR “orthostasis” OR “postprandial hypotension.”

Two reviewers (RB and SK) first independently screened titles and abstracts for inclusion and then read the full text of the eligible articles found during this first selection. In case of differences between the 2 reviewers, a third independent reviewer was consulted (RAK).

We identified 1131 records from Medline and a further 1136 nonduplicate records from Embase. We also searched references from all full texts reviewed and identified 1 further record, yielding a total of 2268 records.

Search protocols are outlined in Section 3.7.

#### *Inclusion/exclusion criteria*

Studies were included if they were published as a primary research paper in a peer-reviewed journal, involved participants with a mean age of 60 years or more, and examined the relationship between hypotension and depression.

Articles were excluded if the sample comprised a specific disease defined population (e.g., persons with diabetes); if they were reviews, case reports, or conference abstracts; and if they

were not published in English. If 2 or more articles had included the same populations, only 1 was included.

#### *Data extraction/quality assessment*

Data collected included study design and setting, study population, method for BP assessment, method for depression assessment, study covariates, and outcomes. Study quality was assessed by the same reviewers (RB and SK) using a modified version of the National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (177). No studies were excluded based on quality, but quality of studies was considered during the critical review.

Study Quality Assessment protocol is outlined in section 3.8.

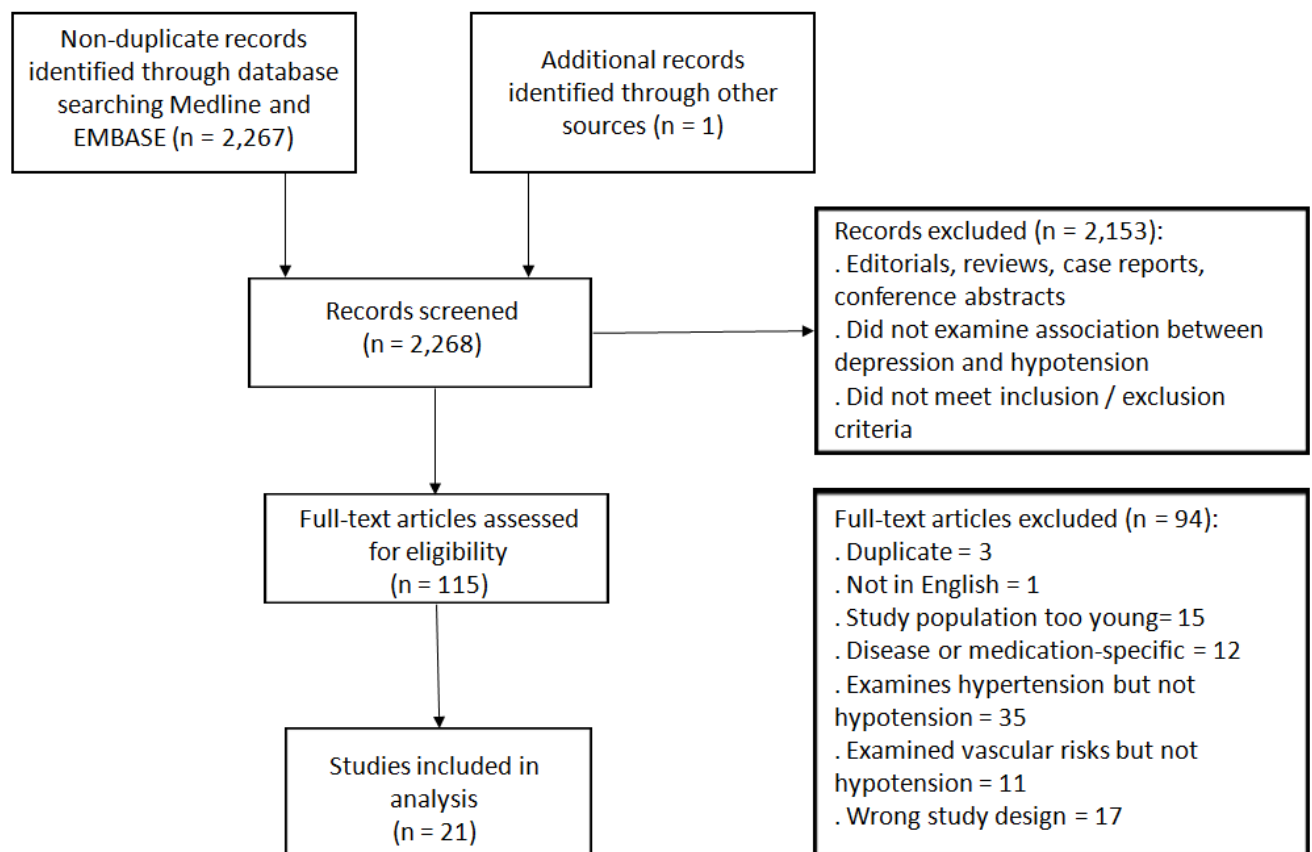
#### *Data synthesis/analysis*

As included studies were heterogeneous in design and assessment methods, a descriptive approach was used to summarize study characteristics and outcomes. No statistical pooling was conducted.

### 3.5 Results

After removing duplicates, the initial combined search retrieved 2268 journal articles. Of these, 116 full texts were assessed for eligibility, of which 19 were included in this systematic review (See figure 3.1). Fourteen of these studies examined the relationship between hypotension and depression in older people, whereas 5 studied orthostatic BP syndromes (OH and PPH).

**Figure 3.1: Flow-sheet of study screening, extraction and inclusion/exclusion**



### *Methodological Considerations*

#### BP measurement

Of the 14 hypotension studies, 71% (10/14) used a mean value derived from 2 clinic or office-based BP readings, whereas a single study used the mean value of 3 readings. The remaining 3 studies used a single BP reading only or did not define how many BP readings were used.

Forty-three percent (6/14) of these used automated BP measurement, whereas 29% (4/14) used manual measurements based on sphygmomanometer, and a further 7% (1/14) used a combination of both manual and automated BP readings. Three hypotension studies (21%) did not define whether readings were automated or manual.

BP values were analysed either as a continuous variable or as a categorically defined quartile/cut-off value. As shown in tables 3.1 and 3.2, the definition of what constitutes hypotension differed considerably between studies.

Of the OH/PPH studies, 60% (3/5) used active stand with beat-to-beat BP measurements, whereas the remaining 2 studies (40%) used automated orthostatic BP measurements.

#### Depression assessment

All of the hypotension studies (14/14) used a validated screening tool to detect depression, with or without additional self-report of depressive disorder or identification of antidepressant use to further define depression. The most commonly used of these tools was the CES-D, used in one-third (5/14) of the hypotension studies, followed by the Geriatric Depression Scale (GDS) (4/14 studies).

Of the 5 OH/PPH studies, a single study used a structured psychiatric interview to confirm depression, whereas 2 studies used both a structured interview and a screening tool combined (GDS).

#### Covariates

The range of covariates included in the studies is shown in tables 3.1 and 3.2.

Less than half (7/15) of the hypotension studies controlled for cardiovascular disease in their analyses, while the majority (13/15) controlled for antihypertensive use.

Two thirds of the hypotension studies (10/15) controlled for the use of antidepressant medication, while each of the 5 OH/PPH studies either controlled for or excluded participants taking antidepressants.

### *Cross-Sectional Studies: Hypotension*

As shown in table 3.1, nine cross-sectional studies examined the association between hypotension and LLD, with 8 of these studies finding an association between lower BP values and depressive symptoms (178-186). Some studies also demonstrated a relationship between

low BP and specific depressive symptomology(183-185), with hypotension associated with endorsement of lower positive affect scores rather than higher negative affect.

#### *Cross-Sectional Studies: Orthostatic Hypotension*

Five cross-sectional studies examined the relationship between OH/PPH and LLD(89, 187-190). These studies demonstrated either a higher drop in orthostatic BP in participants with depression (187-189) or a higher depressive symptom burden in participants with symptomatic OH(89, 190).

#### *Longitudinal Studies: Hypotension*

As shown in table 3.2, five longitudinal studies met inclusion/exclusion criteria(191-195)

#### *3.5.5 Longitudinal Studies: Orthostatic Hypotension*

There were no longitudinal studies that examined the link between OH and LLD.

**Table 3.1: Cross-Sectional Studies Examining the Relationship between Depression and Low BP in Older People**

| Author/Journal                                                                                | Study Setting                                                                                                                             | Participants                                                                            | BP Assessment                                                                                                            | Depression Assessment                                                                                                                                                                               | Covariates         | Main Results                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Gould and Beaudreau (2013)</b><br><br><b>International Journal of Geriatric Psychiatry</b> | Michigan.<br><br>Nationally representative.<br>Population-based.<br>Participants recruited from 2006 wave of Health and Retirement Study. | 4179 community-dwelling participants, aged over 50 years.<br><br>Mean age 68.6 years.   | Mean value of 3 seated automated oscillometric BP recordings.<br>Hypotension defined as sBP<90 mm Hg or dBP<60 mm Hg.    | 8-item CES-D using the following questions: depressed, everything was an effort, restless sleep, happy, lonely, enjoyed life, sad, and could not get going.<br><br>Analysed as continuous variable. | 1, 4, 7, 9, 10, 12 | Participants with both systolic and diastolic hypotension had higher mean scores on CES-D compared with normotensive or hypertensive participants.<br><br>Depressive symptoms predicted low dBP (OR = 0.88(95% CI:0.81-0.96)) in ordinal regression analysis adjusted for demographic characteristics, health conditions, and heart and antihypertensive medications. |
| <b>Imai, et al (2013)</b><br><br><b>Journal of the American Geriatrics Society</b>            | Tosa, Japan.<br><br>Population-based.<br>Participants recruited from annual health examination program.                                   | 134 participants, aged 80 years and over.<br><br>Mean age 84.5 years.                   | Mean value of 2 consecutive seated BP measurements.<br>Not noted if manual or automated.<br>Analysed continuously.       | 15-item GDS.<br><br>Analysed continuously.                                                                                                                                                          | 1, 2, 3, 9, 10     | No significant associations between GDS and sBP(correlation coefficient $r = 0.017$ , $p=0.84$ ) or GDS score and dBP ( $r = -0.12$ , $p=0.17$ ) in simple or quadratic regression.                                                                                                                                                                                   |
| <b>Rosset, et al (2013)</b><br><br><b>Journal of the American Geriatrics Society</b>          | Ribeirao Preto and Caxias do Sul, Brazil.<br><br>Community-based population study.                                                        | 272 community-dwelling older people aged 80 years and over.<br><br>Mean age 84.7 years. | Mean value of 2 independent BP measures.<br>Not noted if supine/seated or if manual/automated.<br>Analysed continuously. | 15-item GDS.<br><br>Analysed continuously.                                                                                                                                                          | 1, 2               | Inverse linear regression line best fit relationship between dBP and GDS score (coefficient of determination $r^2= 0.031$ , $p=0.004$ ).<br>Quadratic regression curve best represented relationship between sBP and GDS score ( $r^2= 0.036$ , $P =0.009$ ).                                                                                                         |

**Table 3.1 (cont'd): Cross-Sectional Studies Examining the Relationship between Depression and Low BP in Older People**

| Author/Journal                                                         | Study Setting                                                                                            | Participants                                                                                              | BP Assessment                                                                                                                                      | Depression Assessment                                                                                                                                                                                                                                                                                                                                             | Covariates                     | Main Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ng, et al (2010)</b><br><br><b>The American Journal of Medicine</b> | Singapore.<br><br>Population-based Singapore Longitudinal Aging Study, recruited by door-to-door census. | 2611 community-dwelling participants, aged 55 years and over.<br><br>Mean age 66.1 years.                 | Mean value of 2 seated BP readings using automated oscillometric method.<br><br>Hypotension defined as < 120 mm Hg systolic, < 75 mm Hg diastolic. | Translated version of 15-item GDS.<br><br>Cut-off score of 5 used to define depression.<br><br>Face-to-face interviews performed by trained multilingual research nurses using both English and Chinese versions based on participant preference.                                                                                                                 | 1, 2, 3, 4, 5, 6, 8, 9, 11, 12 | In multiple regression models, sBP ( $\beta = -0.012$ , $p < 0.001$ ) and dBP ( $\beta = 0.01$ , $p = 0.007$ ) were negatively associated with GDS scores.<br><br>In participants not using antihypertensive medications, lower sBP ( $\beta = -0.011$ , $p = 0.007$ ) and dBP ( $\beta = -0.019$ , $p = 0.012$ ) significantly associated with higher scores on GDS after adjusting for covariates. Among treated hypertensive participants, low sBP ( $\beta = -0.013$ , $p = 0.011$ ) and low sBP and/or dBP but not low dBP ( $\beta = -0.014$ , $p = 0.14$ ) were independently associated with increased odds of depressive symptoms. |
| <b>Lenoir, et al (2008)</b><br><br><b>Journal of Hypertension</b>      | Bordeaux, Dijon and Montpellier, France.<br><br>Community-based 3 city longitudinal study.               | 9294 community-dwelling participants randomly recruited from electoral rolls.<br><br>Mean age 73.7 years. | Mean value of 2 automated seated BP readings.<br><br>BP analysed as a continuous variable.                                                         | (i) Self-report history of depression.<br>(ii) MINI, a brief structured psychiatric interview consisting of 11 questions.<br>(iii) 20-item CES-D used to assess depressive symptomology.<br>Cut-off values for depression used were 22 in females, 16 in males.<br>"Depressive" participants were those defined as having depression by 1 of the 3 above methods. | 1, 2, 3, 5, 6, 7, 9, 10        | Both men and women with depression had lower means BP (men 148.2 vs. 151.8 mm Hg, $p = 0.002$ ; women 141.7 vs. 144.7 mm Hg, $P < 0.0001$ ) and dBP (men 83.0 vs. 84.7 mm Hg, $p = 0.003$ ; women 80.7 vs. 81.4 mm Hg, $p < 0.02$ ) values than non-depressed controls.<br><br>When analysed separately, each of the 3 markers of depression were associated with lower values of sBP and dBP. Relationship between sBP/dBP and depressive status stronger in psychotropic drug nonusers than users, but no statistically significant interaction was found.                                                                                |

**Table 3.1 (cont'd): Cross-Sectional Studies Examining the Relationship between Depression and Low BP in Older People**

| Author/Journal                                                                              | Study Setting                                                                                                               | Participants                                                                         | BP Assessment                                                                                                                                                 | Depression Assessment                                                                                                   | Covariates                                                                             | Main Results                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Jorm (2001)</b><br><br><b>British Journal of Psychiatry</b>                              | Canberra and Queanbeyan, Australia.<br><br>Community-based survey from wave 3 of longitudinal study.                        | 340 community-dwelling participants, aged 77-99 years.<br><br>Mean age not reported. | Mean value of 2 automated BP readings.<br>Did not state if readings were supine/seated.<br>Hypotension defined as < 120 mm Hg systolic, < 75 mm Hg diastolic. | Anxiety and Depression symptoms scales.<br><br>PANAS.<br><br>20 words describing emotions: 10 positive and 10 negative. | 1, 2, 4, 5, 6, 9, 11, 12.<br><br>Did not control for use of antidepressant medication. | Lower dBP but not sBP was weakly associated with higher depression scores (unstandardized $\beta = 0.55$ , $P = 0.031$ ). Lower dBP was strongly inversely associated with lower positive affect scores ( $\beta = -3.21$ , $p = 0.0002$ ) and not associated with negative affect scores. Number of participants with low sBP too low to assess association with positive affect scores. |
| <b>Stroup-Benham, et al (2000)</b><br><br><b>Journal of the American Geriatrics Society</b> | Texas, New Mexico, Arizona, Colorado, and California.<br><br>Population-based. Multistage area probability sampling design. | 2723 community-dwelling Mexican Americans.<br><br>Mean age 72.6 years.               | Mean value of 2 manual seated BP readings using sphygmomanometer.<br>Hypotension defined as <120 mm Hg systolic or <75 mm Hg diastolic.                       | 20-item CES-D.<br><br>Cut-off score of 16 used to detect depression.                                                    | 1, 2, 4, 7, 9, 10                                                                      | Participants with low BP had higher mean CES-D scores compared with normotensives (11.39 +/- 0.61 vs. 9.92 +/- 0.48, $p < 0.05$ ). The presence of low BP associated with a greater likelihood of scoring in the depressed range on CES-D.                                                                                                                                                |
| <b>Barrett-Connor, et al (1994)</b><br><br><b>British Medical Journal</b>                   | Rancho Bernardo, California.<br><br>Population-based.                                                                       | 594 men, aged 60-89 years.<br><br>Mean age not reported.                             | Mean value of 2 manual seated readings using sphygmomanometer.<br>Hypotension defined as <120 mm Hg systolic, <75 mm Hg diastolic.                            | 18-item, self-administered BDI Score.<br><br>Cut-off score of 13 used to detect depression.                             | 1, 3, 5, 6, 8, 9, 10, 12                                                               | Participants with lower dBP had higher scores on BDI Score ( $\beta = -0.9711$ , $p < 0.01$ ) compared with normotensives after adjusting for covariates. Participants with low sBP did not have higher overall scores on Beck Depression Inventory Score but scored significantly higher in fatigue, pessimism and lack of satisfaction.                                                 |

*Notes:*

*Abbreviations: BP = blood pressure; sBP =systolic blood pressure; dBP = diastolic blood pressure; CES-D = Centre for Epidemiological Studies Depression Scale; OR = odds ratio; CI = confidence interval; GDS = Geriatric Depression Scale; MINI = Mini International Neuropsychiatric Interview; PANAS = Positive and Negative Affect Scales; BDI = Beck Depression Inventory.*

*Covariates: 1 = age, sex; 2 = educational status; 3 = body mass index/weight; 4 = marital status; 5 = alcohol use; 6 = cigarette smoking; 7 = vascular disease; 8 = activity levels; 9 = antihypertensive medication use; 10 = antidepressant medication use; 11 = functional status; 12 = chronic disease.*

**Table 3.2: Longitudinal Studies Examining the Relationship between Depression and Low BP in Older People**

| Author/Journal                                                                    | Study Setting                                                                                                                    | Participants                                                                                                                                                                                                                                                             | BP Assessment                                                                                                                                                                                                                  | Depression Assessment                                                                                                                                                                                                                         | Covariates                  | Main Results                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Tikhonoff, et al (2014)</b><br><b>Journal of Hypertension.</b>                 | England, Scotland and Wales.                                                                                                     | 1,683 community-dwelling participants aged 60-64 years at final assessment<br><br>Mean age not reported.<br><br>Followed from age 36 years (i.e., 24 years follow-up).                                                                                                   | Mean value of 2 seated BP readings.<br>At ages 36 and 43 years BP measured manually using Sphygmomanometer and at ages 53 and 60-64 years.<br><br>Automated oscillometric method used.                                         | Short version of the PSE used at age 36.<br>At age 43 years, the 20-item PSFS was used, with a cut-off of 23 indicating depression.<br>At ages 53 and 60-64 years, the 28-item GHQ was used, with a cut-off score of 5 indicating depression. | 1, 2, 5, 6, 7, 8, 9, 10, 12 | The presence of case-level symptoms of depression at follow-up time points was associated with lower sBP values at age 60-64 years (-2.46 mm Hg; 95% CI -4.39 to -0.52) after controlling for lifestyle factors and antihypertensive use.<br><br>A similar but weaker negative association was also observed for dBP.<br><br>Suggests that recurrent episodes of depression may have an accumulative effect on lowering BP in later life. |
| <b>Gao, et al (2013)</b><br><b>International Journal of Geriatric Psychiatry.</b> | Indianapolis, Indiana.<br><br>Participants aged 60 years and over recruited from primary care.<br><br>No depression at baseline. | 2581 participants.<br>Mean age not reported.<br>Followed until diagnosis of depression or last date of contact with health system.<br>Mean times from enrolment to endpoint for depression and no depression groups were 7.2 +/- 4.6 and 7.9 +/- 5.8 years respectively. | BP readings taken in primary care. Mean number of BP readings 21 per patient.<br><br>No information regarding seated/supine or manual/ automated.<br><br>Provides information on BP prior to diagnosis of incident depression. | Participants screened initially with 20-item CES-D to ensure no depression at baseline.<br><br>Subsequent diagnosis of depression based on primary care diagnosis.                                                                            | 1, 3, 6, 12                 | Participants in incident depression group had lower sBP at enrolment than those without depression (p = 0.0057). SBP of those with incident depression increased significantly more prior to this diagnosis than in those without depression (p < 0.0001).<br><br>No significant main effects or interactions were found when dBP used as dependent variable                                                                              |

**Table 3.2 (cont'd): Longitudinal Studies Examining the Relationship between Depression and Low BP in Older People**

| Author/Journal                                                                              | Study Setting                                                                                                             | Participants                                                                                      | BP Assessment                                                                                                                                                                                                                                    | Depression Assessment                                                                                                                                                                  | Covariates            | Main Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Siennicki-Lantz, et al (2013)</b><br><br><b>American Journal of Geriatric Psychiatry</b> | Malmo, Sweden.<br><br>Population-based sample of men born in 1914.                                                        | 171 community-based males.<br><br>Seen initially at age 68 years and followed-up at age 81 years. | SBP measured manually using sphygmomanometer in supine position at age 65 years after 15 minutes rest and in sitting position at age 81 years.<br>Hypertension defined as BP > 160 mm Hg.                                                        | 20-item ZSDS applied by research psychologist at age 81 years.<br><br>Participants divided into 2 groups, "High ZSDS score" based on tertile with highest scores on scale (ZSDS < 38). | 1, 3, 5, 6, 7, 9, 12  | At age 81 years, frequency of hypertension lower in "High ZSDS" group (30% vs. 50%, $p = 0.023$ ). Antihypertensive use equal in both groups at age 81 years.<br><br>Decreasing sBP more frequent in the "High ZSDS" group than in low-score group (41% vs. 23%, $df = 1$ , $p < 0.05$ ). Difference in SBP negatively correlated with ZSDS score (Pearson $r = -0.256$ , $df = 162$ , $p < 0.005$ ).<br>Participants who were hypertensive at 68 years, and whose sBP decreased over time, had higher ZSDS scores than those with increasing sBP (38.2 $\pm$ 7.5 vs. 35.2 $\pm$ 8.1; $df = 95$ , $p < 0.05$ ). |
| <b>Paterniti, et al (2000)</b><br><br><b>British Journal of Psychiatry</b>                  | Nantes, France.<br><br>Population-based, part of EVA longitudinal study. Study population recruited from electoral rolls. | 1389 community dwelling older participants, mean age 65 years.<br><br>Followed-up at 2 years.     | Mean value of 2 automated readings. Not noted if patients were seated or supine. Change in BP defined as difference between value at baseline and at 2-year follow-up. Low BP and drop in BP defined as those with values in the first quartile. | 20-item CES-D.<br><br>Cut-off scores to define depression were 16 and 22, respectively, for males and females.                                                                         | 1, 3, 5, 6, 9, 10, 12 | Low DBP at baseline was a borderline significant risk factor for depression at two-year follow-up (Adjusted OR = 1.9 (95% CI: 1.0 - 3.6)). The association between low sBP and depression was not statistically significant (Adjusted OR = 1.3 (95% CI: 0.7 - 2.6)). There was no association between high depressive symptomology at baseline and subsequent low BP.<br>Participants with a greater drop in DBP had a higher likelihood of being depressed at follow-up (Adjusted OR 2.6 (95% CI: 1.2 - 5.7)).                                                                                                 |

**Table 3.2 (cont'd): Longitudinal Studies Examining the Relationship between Depression and Low BP in Older People**

| Author/Journal                     | Study Setting                                       | Participants                                                                     | BP Assessment                                                      | Depression Assessment                                                                                         | Covariates | Main Results                                                                                                                                                                                    |
|------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Gilmore, et al (1995)</b>       | Liverpool, England.                                 | 701 community-dwelling                                                           | Mean value of 3 manual sitting BP readings using sphygmomanometer. | GMS community version and History and aetiology schedule analysed using AGECAT diagnostic computer algorithm. | 1, 9, 10   | Men with dBP greater than 85 mm Hg were significantly less likely to be diagnosed with depression than men with low or normal dBP and were significantly less likely to be cases 3 years later. |
| <b>Acta Psychiatrica Scandania</b> | Community-based longitudinal Liverpool CHitC study. | participants with mean age 73 years at enrolment.<br><br>Followed-up at 3 years. | Low BP defined as < 120 mm HG systolic or <75 mm Hg diastolic.     |                                                                                                               |            | Does not support association between low BP and depression but suggests possible protective role of high BP.                                                                                    |

Notes:

Abbreviations: BP = blood pressure; sBP =systolic blood pressure; dBP = diastolic blood pressure; PSFS = Psychiatric Symptom Frequency Scales;GHQ = General Health Questionnaire, CES-D = Centre for Epidemiological Studies Depression Scale; OR = odds ratio; CI = confidence interval; GDS = Geriatric Depression Scale; PSE = Present State Examination; ZSDS = Zung Self-Rating Depression Scale; GMS = Geriatric Mental State; Chit C= Continuing Health in the Community.

Covariates: 1 = age, sex; 2 = educational status; 3 = body mass index/weight; 4 = marital status; 5 = alcohol use; 6 = cigarette smoking; 7 = vascular disease; 8 = activity levels; 9 = antihypertensive medication use; 10 = antidepressant medication use; 11 = functional status; 12 = chronic disease.

**Table 3.3: Cross-Sectional Studies Examining the Relationship between Depression and Orthostatic Hypotension in Older People**

| Author/Journal                                                               | Study Setting                                                                                                                              | Participants                                                                                                                        | BP Assessment                                                                                                                                                                         | Depression Assessment                                                                                                                                                                                   | Antidepressants                                                                                                                 | Main Results                                                                                                                                                                                                                                                   |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>O'Regan, et al (2013)</b><br><br><b>BMC Psychiatry</b>                    | The Irish Longitudinal Study on Ageing.<br><br>Nationally representative population sample.                                                | 3144 community-dwelling Participants over 60 years.<br><br>Mean age 69.3 years.                                                     | Oscillometric sit-to-stand orthostatic stress test. OH defined as reduction of sBP of at least 20mmHg or dBP of 10 mm Hg with (symptomatic OH) or without symptoms (Asymptomatic OH). | Based on 20-item CES-D, with cut-off of 16 used to define depression.                                                                                                                                   | Participants taking antidepressants were excluded from analysis.                                                                | Participants with symptomatic OH had highest mean CES-D score (8.6 +/- 1.6) when compared with participants with asymptomatic OH (5.6 +/- 0.48) and participants with no OH (5.2 +/- 0.14) and this difference was significant for both comparisons (p<0.001). |
| <b>Colloby, et al (2011)</b><br><br><b>The British Journal of Psychiatry</b> | Newcastle, UK. Recruited participants with history of depression from local psychiatry service. Healthy controls recruited from community. | 68 community dwelling adults aged ≥60 years: 38 with lifetime diagnosis of depression and 30 controls. Mean age 74.2 years.         | Active Stand.<br><br>Beat-to-beat BP recorded noninvasively using digital photoplethysmographic device.                                                                               | Participants in depressed group required to fulfil DSM-IV criteria for lifetime diagnosis of major depressive episode. Neuropsychiatric assessment conducted. Mean GDS 11.6 +/- 7.9 in depressed group. | 32/38 patients taking antidepressants. Authors report no significant correlation between antidepressants and BP drop.           | Degree of drop in sBP significantly greater in depressed group (21.3 +/- 13.1 mm Hg vs. 14.3 +/- 8.5 mm Hg, p=0.01).<br><br>No significant difference in dBP drop between groups.                                                                              |
| <b>Vasudev, et al (2010)</b><br><br><b>Journal of Affective Disorders</b>    | Newcastle, UK. Recruited participants with history of depression from local psychiatry service. Healthy controls recruited from community. | 73 community dwelling people aged 60 years and over, 41 with lifetime diagnosis of depression and 32 controls. Mean age 74.3 years. | Active Stand.<br><br>Beat-to-beat BP recorded noninvasively using digital photoplethysmographic device.                                                                               | Participants in depressed group required to fulfil DSM-IV criteria for lifetime diagnosis of major depressive episode. Neuropsychiatric assessment conducted. Mean GDS 12.9 +/- 8.6 in depressed group. | No significant effect of venlafaxine (n=13, ANOVA, p=0.303) or duloxetine (n=4, ANOVA, P=0.457) on sBP drop in depressed group. | More significant drop in sBP in depressed group (21.53 +/- 14.95 mm Hg vs. 14.84 +/- 8.46 mm Hg, p=0.019), but no difference in dBP drop.<br><br>Linear regression showed best predictor of SBP drop was a diagnosis of depression.                            |

**Table 3.3 (cont'd): Cross-Sectional Studies Examining the Relationship between Depression and Orthostatic Hypotension in Older People**

| Author/Journal                                                                         | Study Setting                                                                                                           | Participants                                                                                                                                   | BP Assessment                                                                                                            | Depression Assessment                                                                                                  | Antidepressants                                                                                                                                                                                                                                                            | Main Results                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Richardson, et al (2009)</b><br><br><b>American Journal of Geriatric Psychiatry</b> | Newcastle, UK.<br><br>Recruited participants with known depression from community, as well as controls.                 | 34 community-dwelling people aged 60 years and over, 17 with depression, 17 with no history of depressive illness.<br><br>Mean age 76.5 years. | Active Stand. Beat-to-beat BP recorded noninvasively using digital photoplethysmographic device.                         | DSM-IV major depressive disorder was diagnosed by referring senior psychiatrists and confirmed at interview by author. | 13/17 participants in depressed group on antidepressants. When compared with depressed patients on antidepressants, the 4 depressed participants not taking antidepressants had similar drop in sBP (42 mm Hg vs. 47 mm Hg) and larger drop in dBP (46 mmHg vs. 22 mm Hg). | 16/17 (94%) of depressed group had OH, compared with 11/17 (65%) of controls ( $X^2 = 4.5$ , $df = 1$ , $p = 0.034$ ).<br><br>The degree of sBP drop was highly significantly greater in the depressed participants (45.76 +/- 24.64 mm Hg vs. 19.94 +/- 10.84 mm Hg, $p = 0.001$ ) and more depressed participants reported clinical symptoms of OH on standing. |
| <b>Schwartz, et al (2007)</b><br><br><b>Experimental Aging Research</b>                | Chicago, Illinois. Participants recruited from adult day healthcare program located in Veterans Affairs Medical Center. | 17 participants with no history of depression / Dementia. Not taking antidepressants. Mean age 69.9 years.                                     | BP measured in supine position with manual sphygmomanometer at intervals of 5-15 minutes pre and post high calorie meal. | 20-item ZSDS, with clinical depression indicated by a score of >30.                                                    | Participants taking antidepressants were excluded.                                                                                                                                                                                                                         | Larger drop in postprandial sBP positively associated with higher somatic depression scores ( $r = 0.49$ , $p < 0.05$ ). Direction of association between sBP and affective component was negative and not significant ( $r = -0.16$ , $p = 0.54$ ).                                                                                                              |

Notes: Abbreviations: BP = blood pressure; sBP = systolic blood pressure; dBP = diastolic blood pressure; OH = orthostatic hypotension; CES-D = Centre for Epidemiological Studies Depression Scale; DSM = Diagnostic and Statistical Manual of Mental Disorder; ZSDS = Zung Self-Rating Depression Scale.

### **3.6 Discussion**

Cross-sectional studies to date, although limited in their ability to attribute causality, have demonstrated a consistent relationship between hypotension and LLD. Only 1 cross-sectional study failed to demonstrate this association, however despite involving an exclusively “oldest old” population, only 7 participants in the study had a SBP < 100 mm Hg(180).

There is also a growing body of research indicating a cross-sectional association between OH and depression in later life. Each of the 5 studies identified a positive association between OH and LLD. In addition, there is some evidence that pre-treatment OH may influence treatment response in older patients with LLD(196, 197). However, as yet, there is no longitudinal data examining this relationship.

The prospective relationship between LLD and hypotension remains less clear, however, with longitudinal studies providing less consistent results. These inconsistencies can at least partially be explained by marked methodological differences between longitudinal studies, which make it difficult to generalize and pool results. Although all of the studies we identified involved older participants, age at enrolment varied widely between studies, essentially meaning that participants were studied at very different life time points. For example, the mean age at enrolment for 1 study was 36 years(194), which means that cases of EOD would be included in the analysis. When we consider that early onset and late onset depression are 2 very different disease entities, it is clear that this will impact on study results. The number of years of follow-up in the longitudinal studies we identified ranged from 2 to 24 across these studies.

In addition to the cross-sectional studies, we found that, longitudinal studies also varied considerably with regard to assessment of both depression and hypotension and controlling for confounding factors.

#### *Depression Assessment*

The hypotension studies invariably employed validated screening tools such as the CES-D to define cases of depression. These tools were developed to identify populations at risk of developing depression and were not intended to be used as diagnostic tools. However, in the setting of large population-based studies, performance of a structured psychiatric interview is often impractical or impossible, and the high sensitivity and specificity of these tools mean they are a reliable alternative to a structured interview in the setting of epidemiologic studies of this nature. In addition, several of these instruments have been validated in an older population(198). The CES-D has a sensitivity of 92% and a specificity of 87% for diagnosis of LLD, whereas the GDS has a sensitivity of 100% and a specificity of 84%.(122)The Beck Depression Inventory is also validated for use in an older population, with a sensitivity and specificity of 88 % and 82%, respectively(199).

Several differences exist between these screening tools however. For example, although the CES-D contains statements such as “my sleep was restless” and “I felt tired all the time,” the GDS focuses primarily on the neuropsychiatric symptoms of depression and less on somatic symptoms(200).There have been concerns expressed that such inclusion of somatic concerns

may artificially inflate the CES-D scores for older or chronic pain populations(144).In effect, what is classified as depression or an increasing burden of depressive symptoms in one study may not necessarily be reflected in another study using a different screening tool. In addition, in older people, depression is often characterized less by pervasive low mood than features such as anhedonia and as such, lower “positive affect” instead of more than higher negative affect(201). It also appears that hypotension is more closely associated with these aspects of positive affect. The assessment of positive affect is often less prominent in screening tools for depression, and these instruments may only weakly tap into the psychological characteristics associated with hypotension(184).

Another complexity with studying depression in older persons is the difficulty involved in capturing the life course of the illness. Depression with age of onset in the eighth decade of life is likely to be very different from depression developing in early to middle age and persisting to late life but both are termed LLD, and untangling the differences between these entities in population studies is challenging.

Structured psychiatric interview with diagnosis based on the Statistical Manual of Mental Disorders, 4th Edition criteria remains the gold standard for depression diagnosis. Three of the 5 OH/PPH studies included participants with a diagnosis of depression based on this but, as noted previously, numbers in these studies were low. One cross-sectional study used a combination of the CES-D, self-report of depression, as well as a modified psychiatric interview, to detect depression in the study population(182).This method would seem preferable, as given the fluctuating course depression in later life can take, affected by social issues, as well as physical illness, it endeavours to capture past history of depression, as well as current symptomology and undiagnosed depressive illness.

#### *BP Measurement*

There were marked variations in BP measurement protocols between studies. All of the hypotension studies we identified used static BP measurements only with no study to date using ambulatory BP values. The limitations of this method are clear, providing a snapshot of BP control only and not reflecting diurnal variation of BP or nocturnal BP changes(202).Ambulatory BP monitoring has been shown to have stronger predictive power for stroke risk than a screening BP measurement(203),as well as for mortality(204).

Several studies used cut-off values to define hypotension, with sBP<120 mm Hg and dBP<90 mm Hg most commonly used. However, for studies of older people specifically, it may be better to use a percentile value based on the mean of the study population rather than a defined lower cut-off given that increasing evidence suggests that standard guidelines for BP thresholds may not be appropriate for use in this group of patients(205, 206).

Only 3 of the studies we identified used beat-to-beat BP monitoring to identify OH. The remaining 2 studies employed automated BP measurements. Although these lying and standing measurements have a high degree of specificity in detecting OH, they lack adequate sensitivity compared with this gold standard.

#### *Covariates*

Hypotension can be an end-point for several diverse disease processes in the older person, including congestive heart failure(207)and lung disease(208).Rates of depression are also significantly higher in older persons with more profound chronic medical illness(24). Some have argued that both depression and BP are markers of poor physical health and that this mediated the relationship between the two conditions(209). Hypotension in older persons has been associated with a higher mortality risk, but this association is attenuated when medical illnesses are controlled(210). As a result, controlling for comorbidities is essential in studies examining the relationship between depression and BP in later life but this can be complex.

Only 9 of 14 hypotension studies controlled for chronic medical illnesses, and even then, there was marked heterogeneity regarding the methods used to capture comorbid illness, ranging from a questionnaire requesting self-report a range of medical conditions to focusing on 1 or 2 specific illnesses. Each of the studies used a different method to account for medical comorbidity.

The effect of antidepressant medication on BP and cardiac autonomic control directs a requirement to control for their use in studies of this nature. Although most of the studies controlled for this, all of the OH studies that employed active stand and beat-to-beat BP values involved a majority of participants taking antidepressants, and whereas the authors analysed the subgroup of patients not taking antidepressants separately, any conclusion that can be drawn from these analyses are limited by the very small number of participants involved.

### *Conclusions*

It is clear that depression in later life represents a distinct entity to mood disorders presenting in earlier life. Factors which add to the complexity of LLD include medical comorbidities and physical frailty, coexisting cognitive impairment, and social isolation. Another important factor that may distinguish LLD from earlier onset depression is the association with BP.

While cross-sectional studies have demonstrated a consistent relationship between hypotension and LLD, longitudinal research to establish the direction of this relationship has so far shown conflicting results. There are several methodological differences between published longitudinal data that may explain these discordant findings. Alternatively, it may be that the association, as for depression and cardiovascular disease, is bidirectional in nature.

As well as hypotension, it also appears that neurocardiovascular instability, demonstrated by OH may also be related to LLD, however, no longitudinal studies examining this relationship have been completed to date.

Several factors exist that may mediate the observed cross-sectional association between hypotension and depression among older adults, including cerebral hypoperfusion, as well as the impact of the chronic medical illness on mood and BP. Further longitudinal studies robustly controlling for factors such as these are essential.

LLD currently affects 1 in 8 older adults and with projected future demographic changes, in conjunction with the detrimental effect depression can have on the independence of older people; the burden of depression in this cohort is likely to increase significantly in the near future. Despite this the underlying aetiology of depression in older people is still not fully

understood. Further longitudinal studies to clarify the role of these potentially modifiable factors in the development of this complex illness are essential.

### **3.7 Search Protocols**

Medline Search Protocol:

1. Depression/
2. Depressive Disorder/
3. Mood Disorder/
4. elderly.mp
5. late life.mp
6. geriatric.mp
7. old age.mp
8. senile.mp
9. late onset.mp
10. 1 or 2 or 3
11. 4 or 5 or 6 or 7 or 8 or 9
12. 10 or 11
13. Blood Pressure/
14. Hypotension/
15. low blood pressure.mp
16. Hypotension, orthostatic/
17. post prandial.mp
18. hypotensive.mp
19. 13 or 14 or 15 or 16 or 17 or 18
20. 12 and 19

Embase search protocol:

1. 'depression'/exp OR Depression
2. depressive AND disorder
3. mood AND disorder

4. #1 OR #2 OR #3 AND([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim)

5. hypotension

6. blood AND pressure

7. Orthostatic AND hypotension

8. post AND prandial

9. hypotensive

10. #5 OR #6 OR #7 OR #8 OR #9

11. #4 AND #10

### **3.8 Study Quality Assessment**

We used an abbreviated version of the National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (<http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort>) to assess study quality. We did not exclude any studies based on their quality, but we considered this when compiling our critical review. See table 3.4.

For cross-sectional studies we used the following 6 items:

- (1) Was the study population clearly specified and defined?
- (2) Were all the participants selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
- (3) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
- (4) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
- (5) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
- (6) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Each question was answered yes/no by the reviewers (RB and SK), yielding a score out of 6 for each of the cross-sectional studies we identified.

For longitudinal studies, we included the 6 items used in assessment of cross-sectional studies, as well as the following additional items:

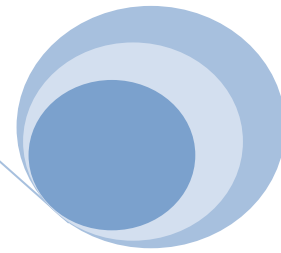
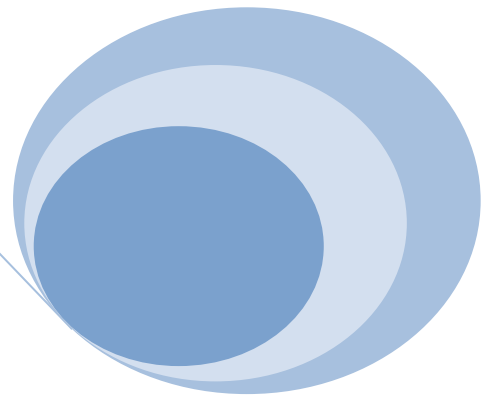
- (7) For analysis in this article,, were the exposure(s) of interest measured prior to the outcome(s) being measured?
- (8) Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
- (9) Was loss to follow-up after baseline 20% or less?

Each question was answered yes/no by the reviewers (RB and SK), yielding a score out of 9 for each of the longitudinal studies we identified.

**Table 3.4: Modified National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies Score for Included Studies**

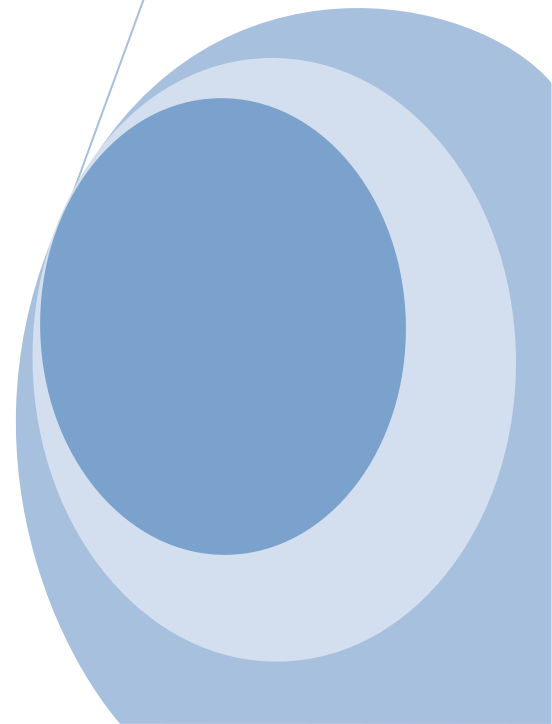
| Article (Year)                | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | Score |
|-------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|
| Gould and Beaudreau (2013)    | ✓   | ✓   | ✓   | ✓   | X   | ✓   |     |     |     | 5/6   |
| Imai, et al (2013)            | X   | ✓   | ✓   | X   | ✓   | X   |     |     |     | 3/6   |
| Rosset, et al (2013)          | ✓   | ✓   | ✓   | X   | ✓   | X   |     |     |     | 4/6   |
| Ng, et al (2010)              | ✓   | ✓   | X   | ✓   | ✓   | ✓   |     |     |     | 5/6   |
| Kim, et al (2010)             | ✓   | ✓   | X   | ✓   | ✓   | ✓   |     |     |     | 5/6   |
| Lenoir, et al (2008)          | ✓   | ✓   | ✓   | ✓   | ✓   | ✓   |     |     |     | 6/6   |
| Jorm (2001)                   | X   | ✓   | X   | X   | X   | X   |     |     |     | 1/6   |
| Stroup-Benham, et al (2000)   | ✓   | ✓   | X   | ✓   | ✓   | ✓   |     |     |     | 5/6   |
| Barrett-Connor, et al (1994)  | ✓   | ✓   | X   | ✓   | X   | X   |     |     |     | 3/6   |
| O Regan, et al (2013)         | ✓   | ✓   | ✓   | X   | ✓   | ✓   |     |     |     | 5/6   |
| Colloby, et al (2011)         | ✓   | X   | ✓   | ✓   | ✓   | X   |     |     |     | 4/6   |
| Vasudev, et al (2010)         | ✓   | X   | ✓   | ✓   | ✓   | X   |     |     |     | 4/6   |
| Richardson, et al (2009)      | ✓   | X   | ✓   | ✓   | ✓   | X   |     |     |     | 4/6   |
| Schwartz, et al (2007)        | ✓   | ✓   | X   | X   | ✓   | X   |     |     |     | 3/6   |
| Tikhonoff, et al (2014)       | X   | ✓   | X   | ✓   | X   | ✓   | ✓   | ✓   | X   | 5/9   |
| Gao, et al (2013)             | X   | ✓   | ✓   | X   | X   | X   | ✓   | ✓   | ✓   | 5/9   |
| Siennicki-Lantz, et al (2013) | X   | ✓   | ✓   | X   | X   | X   | ✓   | ✓   | X   | 4/9   |
| Paterniti, et al (2000)       | ✓   | ✓   | X   | X   | ✓   | X   | ✓   | ✓   | ✓   | 6/9   |
| Gilmore, et al (1995)         | X   | ✓   | X   |     | X   | X   | ✓   | ✓   | X   | 4/9   |

Notes: (1) Was the study population clearly specified and defined? (2) Were all the participants selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (3) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? (4) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (5) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (6) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? (7) For analysis in this article, were the exposure(s) of interest measured prior to the outcome(s) being measured? (8) Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (9) Was loss to follow-up after baseline 20% or less?



## **CHAPTER 4:**

### **Study 1: The Longitudinal Association between lower Blood Pressure and incident Depressive Symptoms**



#### **4.1 Key Findings**

- Over 4% of non-depressed participants aged  $\geq 50$  years met criteria for incident depressive symptoms at 2-year follow-up.
- Participants with incident depressive symptoms had an average sBP almost 4 mm Hg lower at initial assessment when compared to those who did not develop depression.
- SBP values less than 130 mm Hg were associated with a 40% increased risk of incident depressive symptoms at follow-up in regression models.
- Analysis was adjusted for important covariates such as frailty, cardiovascular disease, chronic disease and functional impairment.
- Lower sBP may therefore represent a potentially modifiable risk factor for depression in later life.
- These findings are important given recent large international studies advocating more aggressive BP control in older people.
- This study was published in Age and Ageing: DOI [10.1093/ageing/afx033](https://doi.org/10.1093/ageing/afx033).

## **4.2 Abstract**

### *Background*

Hypotension is now recognised as a risk factor for syncope, cardiovascular events and mortality, but it may also represent a risk factor for LLD. The aim of this study was to clarify the longitudinal relationship between hypotension and incident depressive symptoms.

### *Methods*

This is a longitudinal study involving community-dwelling participants aged  $\geq 50$  years, using data from TILDA. The CES-D was administered at baseline and at follow-up 2 years later. BP was measured at baseline. Participants with a CES-D score  $\geq 16$  at baseline and those taking antidepressants were excluded and considered to have a current diagnosis of depression. A score of  $\geq 16$  at follow-up was used to define incident depression.

### *Results*

4,525 participants were included and 200 participants had diagnosis of incident depressive symptoms. The depressed group had lower systolic BP at baseline than the non-depressed group ( $132.8 \pm 1.43$  mm Hg vs.  $136.0 \pm 0.30$  mm HG,  $P = 0.025$ ). Logistic regression showed those with systolic BP  $< 130$  mm HG had an unadjusted OR of 1.31 (1.01–1.68) for incident depressive symptoms. This persisted after adjustment for confounding factors.

### *Conclusion*

Systolic BP  $< 130$  mm Hg increased the likelihood of incident depressive symptoms in a cohort of community-dwelling older adults. These findings are important because systolic hypotension may represent a potentially modifiable risk factor for LLD. They are also relevant in the context of BP treatment targets for older people.

### **4.3 Background**

LLD, defined as depression presenting in later life or persisting into later life, is common, affecting 8% of a population-representative sample of older participants in TILDA (154). LLD also represents a distinct clinical entity to depression at an earlier age, with different clinical features and presentations (155), on a background of significant underlying medical complexity such as heart disease and frailty (211, 212). As well as these intrinsic factors, extrinsic influences including social isolation and bereavement also contribute to this high prevalence of depressive illness in later life.

Depression in later life is, therefore, underpinned by different underlying aetiological mechanisms. One such factor is the strong influence of cardiovascular disease, including stroke and heart disease (211). The vascular basis of LLD is now well recognised (213), and initially emerged when it was noted that patients with LLD had higher rates of cerebrovascular disease, reflected by cerebral WMH on MRI studies compared to those with earlier onset depression (159). Given this relationship, one would expect to find a close association with BP control and there is an increasing body of evidence to suggest that hypotension, rather than hypertension in later life, may be an important factor in development of LLD (102).

Hypotension in later life is now recognised as a risk factor for falls and syncope (214), cardiovascular events (215) and all-cause mortality (216). While the potentially detrimental effects of hypotension in later life are reflected by current Joint National Committee guidelines for BP targets in older adults (217), the recent SPRINT trial demonstrated the possible benefits of aggressive BP lowering in a subgroup of older patients and this may have important implications for more aggressive BP target recommendations in future guidelines (161).

The aim of this study is to clarify the longitudinal relationship between hypotension and depressive symptoms. Our hypothesis is that hypotension at baseline increases the risk of incident depression. A specific challenge in studies of this type is that hypotension can represent an end-point for several diverse disease processes in the older person, including heart failure and lung disease (218). Rates of depression are also significantly higher in older persons with more profound chronic medical illness (24) and while both depression and hypotension are markers of poor physical health, this could mediate the relationship between the two (209). Therefore, controlling for the myriad of confounding factors, including physical dependency, frailty and accumulating medical illness, can be complex. The comprehensive TILDA data set allows us to control for these potentially confounding factors however.

#### **4.4 Methods**

This is a longitudinal study in a cohort of community-dwelling participants aged 50 years and over, examining the relationship between baseline BP and incident depressive symptoms at 2-year follow-up.

##### *Study design*

Data were analysed from the 1st and 2nd wave of TILDA, a nationally representative study of community-dwelling older people, collected between 2009 and 2012. The TILDA study design has been outlined previously (117). Briefly, each participant undertakes a CAPI, involving specific questions with a focus on health, social and economic factors. This took place in their home.

Participants are also invited to a health centre for a comprehensive health assessment, involving measures such as gait and orthostatic BP analysis. All assessments are completed by trained nursing staff. Participants with a history of dementia, based on a prior physician diagnosis, were excluded.

The TILDA study received ethical approval from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and informed consent was obtained from all participants.

##### *Depression*

The CES-D was used to measure depressive symptoms. The CES-D is a 20-item scale examining four key factors: depressed affect, absence of positive affect or anhedonia, somatic activity or inactivity and interpersonal challenges (121).

The response values are 4-point Likert scales, with range 0–3, yielding a total possible score of 60, with higher scores indicating greater depressive symptoms.

The CES-D has been validated in an older population, and a value of 16 or more has been shown to have a sensitivity of 92% and a specificity of 87% for diagnosis of LLD (122). The CES-D was administered at baseline and at wave 2 follow-up 2 years later.

Participants with a score of 16 or more on the CES-D at baseline were excluded from the study. Participants were also excluded if they were taking antidepressants. A score of 16 or more at follow-up was used to define incident depressive symptoms.

##### *Blood Pressure*

BP was measured twice by a trained research nurse in the seated position using the OMRON™ digital automatic BP monitor and the mean value of the two BP readings was used for analysis.

#### *Other measures*

Further detailed sociodemographic and biological data were also collected. The CAGE (Cut Down, Angry, Eye Opener, Guilty) questionnaire was administered to screen for alcohol dependency with a score of two or more indicative of same. Functional impairment was defined as having one or more impairment in personal activities of daily living (ADL), including dressing, washing, bathing, eating, getting in and out of bed and using the toilet. Chronic illness burden was assessed by recording the absolute number of chronic illnesses self-reported from the following list: lung disease, arthritis, cancer, liver disease, Parkinson's disease, previous hip or wrist fracture, peptic ulcer disease and cataracts. Frailty status was defined using the fried frailty criteria (219), defining participants as either frail, pre-frail or non-frail. Loneliness was measured using the University of California, Los Angeles (UCLA) Loneliness Scale (220). Cardiovascular disease burden was assessed by self-report of a history of diabetes, stroke, myocardial infarction (MI) or angina. Chronic pain was based on the self-report of moderate to severe pain. Additionally, medication lists were examined for antihypertensive medication use, specifically antidepressant use (Anatomical Therapeutic Classification (ATC) N06A).

#### *Statistical Analysis*

Data were analysed using Stata (Statacorp).

Logistic regression models were used to estimate OR (with 95% confidence intervals (CI)) for sBP<130 mm Hg as a predictor of incident depression. Covariates were chosen a priori, based on their hypothesised role in modifying the relationship between baseline BP and incident depression. Three models were tested. The first model was unadjusted; the second added sociodemographic factors including age, sex, marital status, alcohol excess, smoking status, chronic pain and loneliness; the third model added clinical covariates including frailty, stroke, cardiovascular disease, number of chronic diseases, diabetes and functional impairment.

A p value  $\leq 0.05$  was considered statistically significant.

## 4.5 Results

### *Baseline characteristics*

In total 5,857 participants were aged 50 years and above and completed both a home interview and health assessment, including BP measurement. Of these, 872 participants were excluded because they were prescribed antidepressants or their baseline CES-D score was 16 or more. Four hundred sixty participants did not complete 2-year follow-up, resulting in a study population of 4,525 participants. 13% of participants were aged 75 years or more, 27% were aged 65-74 years and the remaining 60% were aged 50-64 years. See figure 4.1.

**Figure 4.1: Flow Diagram of Study Inclusion / Exclusion**

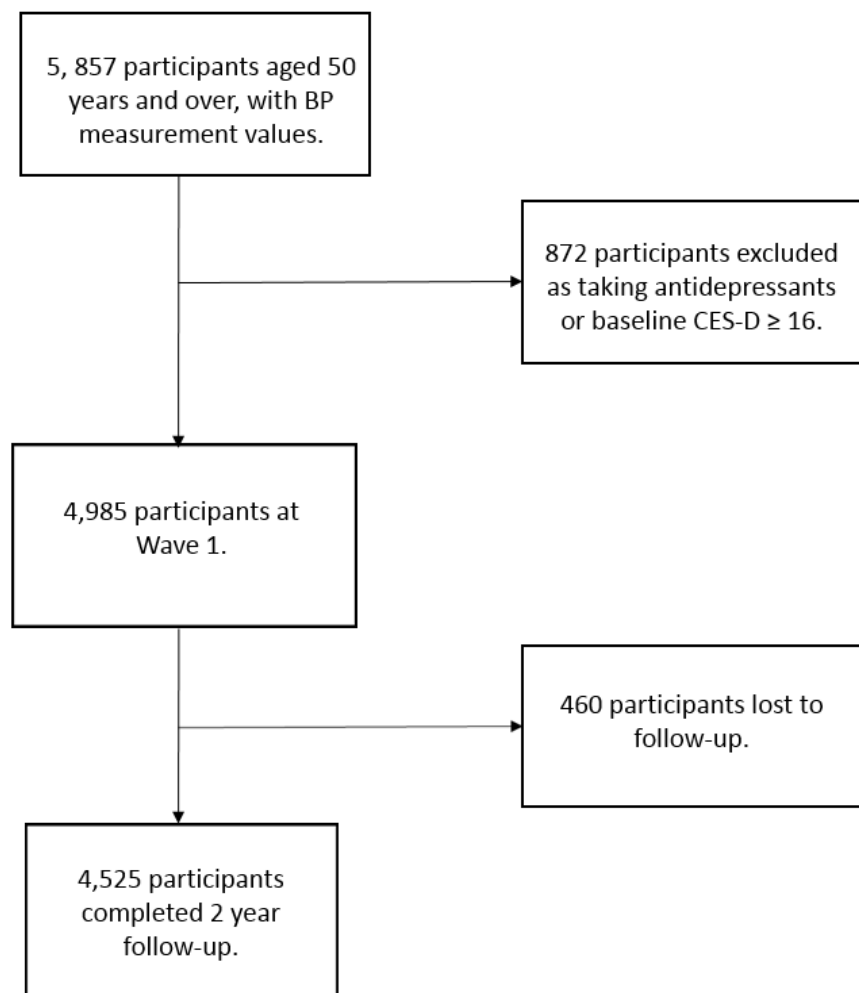


Table 4.1 shows baseline characteristics of both the incident depressive symptoms group and the non-depressed group.

**Table 4.1: Baseline Characteristics by Incident Depressive Symptoms**

|                                        | Incident Depressed<br>(n = 200) | Non-depressed<br>(n = 4,325) | Statistical Test                  |
|----------------------------------------|---------------------------------|------------------------------|-----------------------------------|
| Age (years), mean (SE)                 | 61.1 (0.63)                     | 62.9 (0.14)                  | t = 2.70; p = 0.007               |
| Female sex (%)                         | 61.0                            | 51.7                         | X <sup>2</sup> = 6.69; p = 0.010  |
| <b>Marital status</b>                  |                                 |                              |                                   |
| - Married (%)                          | 69.2                            | 72.7                         | X <sup>2</sup> = 6.79; p = 0.079  |
| - Widowed (%)                          | 12.8                            | 12.3                         |                                   |
| - Never married (%)                    | 8.3                             | 9.1                          |                                   |
| - Separated / divorced (%)             | 9.8                             | 5.9                          |                                   |
| Currently drinks alcohol (%)           | 76.0                            | 77.1                         | X <sup>2</sup> = 0.14; p = 0.710  |
| CAGE score ≥ 2 (%)                     | 17.0                            | 11.8                         | X <sup>2</sup> = 4.45; p = 0.035  |
| <b>Smoking status</b>                  |                                 |                              |                                   |
| - Never smoked (%)                     | 42.5                            | 47.0                         | X <sup>2</sup> = 8.80; p = 0.012  |
| - Ex-smoker (%)                        | 37.0                            | 39.8                         |                                   |
| - Current smoker (%)                   | 20.5                            | 13.2                         |                                   |
| <b>Educational status</b>              |                                 |                              |                                   |
| - Primary Level (%)                    | 29.0                            | 23.3                         | X <sup>2</sup> = 3.58; p = 0.167  |
| - Secondary Level (%)                  | 37.5                            | 41.7                         |                                   |
| - Third Level / Higher (%)             | 33.5                            | 35.0                         |                                   |
| Functional Impairment (%)              | 11.5                            | 6.0                          | X <sup>2</sup> = 10.05; p = 0.002 |
| sBP < 130 mm Hg                        | 50.5                            | 40.9                         | X <sup>2</sup> = 7.30; p = 0.007  |
| Number of chronic illnesses, mean (SE) | 0.9 (0.90)                      | 0.6 (0.01)                   | t = - 4.87; p < 0.001             |
| <b>Frailty status</b>                  |                                 |                              |                                   |
| - Frail (%)                            | 3.1                             | 1.2                          | X <sup>2</sup> = 39.1; p < 0.001  |
| - Pre-frail (%)                        | 41.3                            | 23.6                         |                                   |
| - Non-frail (%)                        | 55.6                            | 75.2                         |                                   |
| <b>Cardiovascular risk factors</b>     |                                 |                              |                                   |
| - Diabetes Mellitus (%)                | 7.5                             | 6.4                          | X <sup>2</sup> = 0.40; p = 0.528  |
| - Previous stroke (%)                  | 1.5                             | 1.2                          | X <sup>2</sup> = 0.17; p = 0.683  |
| - Previous MI (%)                      | 6.5                             | 4.1                          | X <sup>2</sup> = 2.82; p = 0.093  |
| - Angina (%)                           | 4.0                             | 4.5                          | X <sup>2</sup> = 0.10; p = 0.756  |

Notes:

*Incident Depressed group defined as Centre for Epidemiological Studies Depression Scale ≥ 16 at Wave 2.*

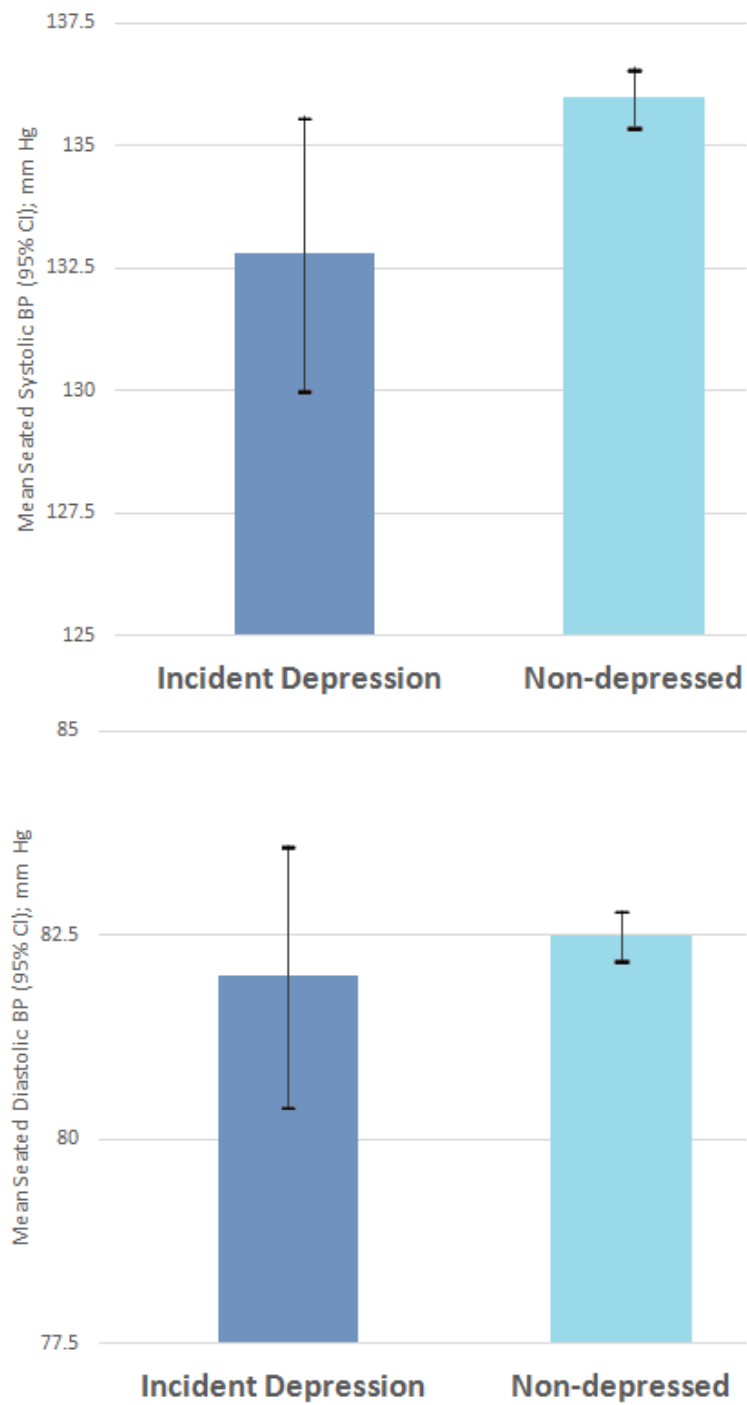
*Student's t-test used for continuous variables; Chi-square test used for categorical variables.*

*Abbreviations: SE = standard error; sBP = systolic Blood Pressure; MI = myocardial infarction.*

*Blood Pressure and Depression*

Figure 4.2 shows the mean baseline BP values of the incident depressive symptoms group compared to the non-depressed group. The incident depressive symptoms group had lower systolic BP at baseline compared to the non-depressed group (132.8 (95% CI: 130.0 – 135.6) mm Hg vs. 136.0 (95% CI: 135.4 – 136.6) mm Hg;  $p = 0.025$ ;  $t = 2.24$ ). There was no statistically significant difference in diastolic BP between the two groups (82.0 (95% CI: 80.4 – 83.6) mm Hg vs. 82.5 (95% CI: 82.2 – 82.8) mm Hg;  $p = 0.564$ ;  $t = 0.578$ ).

**Figure 4.2: Mean Seated Blood Pressure by Incident Depressive Symptoms**



Notes: n = 4,525 (Depressed n =200).

Abbreviations: BP = Blood Pressure; CI = Confidence Interval.

Blood pressure measured twice in seated position using Omron digital cuff and mean of two readings taken. Incident depressive symptoms defined as Centre for Epidemiological Studies Depression Scale  $\geq 16$  at 2-year follow-up.

Logistic regression models demonstrated that participants with systolic BP less than 130 mm Hg at baseline had an increased likelihood of incident depressive symptoms at follow-up, with an unadjusted OR of 1.31 (1.01–1.68).

This effect persisted when analysis was adjusted for sociodemographic factors as well as relevant clinical factors, including cardiovascular disease, other chronic diseases and frailty. See table 4.2.

**Table 4.2: Logistic Regression with Incident Depressive Symptoms as Dependent Variable**

|                                                       | <u>Odds Ratio</u> | <u>95% Confidence Interval</u> | <u>P value</u> |
|-------------------------------------------------------|-------------------|--------------------------------|----------------|
| <b><u>Model 1: Unadjusted</u></b>                     |                   |                                |                |
| sBP< 130 mm Hg <sup>A</sup>                           | 1.48              | 1.11 – 1.96                    | 0.007          |
| <b><u>Model 2: Sociodemographic Factors Added</u></b> |                   |                                |                |
| sBP< 130 mm Hg <sup>A</sup>                           | 1.38              | 1.01 – 1.89                    | 0.041          |
| Female Sex                                            | 1.44              | 1.05 – 1.99                    | 0.025          |
| Age (Years)                                           | 0.98              | 0.96 – 1.0                     | 0.043          |
| Alcohol: CAGE Score <sup>B</sup>                      | 1.44              | 0.95 – 2.18                    | 0.083          |
| Smoker                                                | 1.26              | 0.92 – 1.72                    | 0.143          |
| Chronic pain                                          | 1.22              | 0.87 – 1.71                    | 0.226          |
| Loneliness: UCLA Scale>6 <sup>C</sup>                 | 1.12              | 0.53 – 2.33                    | 0.769          |
| Marital status                                        | 1.07              | 0.92 – 1.26                    | 0.362          |
| <b><u>Model 3: Clinical Factors Added</u></b>         |                   |                                |                |
| sBP< 130 mm Hg <sup>A</sup>                           | 1.38              | 1.00 – 1.90                    | 0.047          |
| Female Sex                                            | 1.48              | 1.06 – 2.07                    | 0.023          |
| Age (Years)                                           | 0.95              | 0.93 – 0.97                    | 0.000          |
| Alcohol: CAGE Score <sup>B</sup>                      | 1.45              | 0.95 – 2.22                    | 0.085          |
| Smoker                                                | 1.18              | 0.86 – 1.62                    | 0.313          |
| Frailty <sup>D</sup>                                  | 2.43              | 1.81 – 3.27                    | 0.000          |
| Cardiovascular Disease <sup>E</sup>                   | 1.18              | 0.65 – 2.13                    | 0.589          |
| Prior Stroke                                          | 0.67              | 0.15 – 2.91                    | 0.591          |
| Chronic Disease Burden <sup>F</sup>                   | 1.23              | 1.08 – 1.40                    | 0.002          |
| Diabetes                                              | 0.72              | 0.38 – 1.38                    | 0.329          |
| ADL Impairment <sup>G</sup>                           | 1.71              | 1.00 – 2.93                    | 0.051          |

Notes:

Abbreviations: sBP = Systolic Blood Pressure; UCLA = University of California, Los Angeles; ADL = activities of daily living.

*A* Systolic Blood Pressure measured twice in seated position using Omron digital cuff by trained research nurse, and mean value of 2 readings taken; *B* Score on Cut Down, Angry, Guilty, Eye Opener Scale for Alcohol Excess; Score > 6 on UCLA loneliness scale, consistent with loneliness; *D* Frailty defined by Fried criteria; *E* Cardiovascular disease defined as self-report of stroke, myocardial infarction or angina; *F* Number of chronic diseases from self-reported list (lung disease, arthritis, cancer, liver disease, Parkinson's disease, previous hip or wrist fracture, peptic ulcer disease and cataracts) as continuous variable; *G* Defined as self-reported impairment in 1 or more personal activities of daily living.

#### **4.6 Discussion**

This study demonstrates that in a cohort of non-depressed older people, lower values for systolic BP increased the likelihood of incident depressive symptoms at 2-year follow-up. The group with incident depressive symptoms was more likely to be female and smokers, and had higher rates of alcohol dependence, chronic disease, functional impairment and frailty. However, the association with lower systolic BP persisted after controlling for these potentially confounding factors.

Cross-sectional studies, while limited in their ability to attribute causality, have demonstrated a consistent relationship between hypotension and depression in later life (102). Longitudinal studies up to now have demonstrated conflicting results however. Paterniti et al demonstrated that low diastolic BP at enrolment predicts future depression, but that depression at baseline did not predict subsequent low BP (191). Tikhonoff et al found that the burden of depressive illness in early and middle age contributes to lower BP in later life (194), while Gao et al showed that the systolic BP of a group of participants aged over 60 years with incident depression increased significantly more prior to this diagnosis than in those without depression (195).

There are marked methodological differences between these studies, which may explain these discordant findings, including age at enrolment, as well as the methods used to assess depressive symptoms and measure BP. No studies to date have controlled for frailty, in addition to functional status.

These findings are important because, despite its prevalence, the aetiological basis of LLD is not yet fully understood and hypotension may represent a potentially modifiable risk factor for LLD. They are also relevant in the context of setting BP treatment targets and guidelines for older people.

There are several potential mechanisms that may underlie this association. Hypotensive episodes lead to a reduction in CBF, causing cerebral hypoperfusion and the development of WMH (221). These WMH can disrupt the frontal-subcortical circuitry resulting in psychomotor retardation, loss of interest and executive dysfunction; hallmarks of LLD (213) and have been shown to be a predictor for severity of depression in older subjects after adjusting for quality of life (222). Alternative mechanisms that may partially explain this observed association include hypocortisolemia occurring in the setting of LLD (223), monoaminergic dysfunction (221) and immune dysregulation (224).

These findings also parallel the association between low BP and dementia, where late life hypotension have been identified as a risk factor<sup>(100)</sup>. This is against the backdrop of overlapping clinical features between LLD and dementia, including the presence of executive dysfunction, and may demonstrate a common aetiological pathway shared between the two when we consider the impact of white matter disease and loss of frontal lobe integrity on neurophysiological status in older people.

The strengths of this study include the fact that data were collected prospectively. The breadth of data collected as part of the TILDA study also allows us to control for factors, such as frailty, which has not previously been possible in longitudinal studies examining this relationship.

There are some weaknesses of this study which must also be considered. A CES-D score of 16 or more was used to define depressive symptoms, rather than the gold standard structured psychiatric interview. The CES-D was developed in order to identify populations at risk of developing depression and was not intended to be used as diagnostic tool; however, in the setting of large population-based studies, performance of a structured psychiatric interview is often impractical or impossible, and the high sensitivity and specificity of the CES-D means it is a reliable alternative to a structured interview in this setting. Additionally, BP values were based on automated oscillometric readings. While this represents the most commonly used method in clinical practice, it provides only a static measurement of BP, a highly dynamic variable, and, therefore, may not be reflective of true 24 h BP average. Additionally, while our study demonstrates a significant association between hypotension and LLD, this should not be assumed to indicate a causal relationship and further studies are required to clarify this.

Depressive symptoms currently affect 1 in 12 older adults. In this study, systolic BP less than 130 mm Hg increased the likelihood of incident depressive symptoms in a cohort of community-dwelling older adults, suggesting that systolic hypotension may represent a potentially modifiable risk factor for LLD. Given projected future demographic changes, in conjunction with the detrimental effect depression can have on the independence of older people, the burden of depression in this cohort is likely to increase significantly in the near future and studies directly testing this hypothesis are warranted. Furthermore, given recent findings directing more aggressive BP treatment in older people, there is also a need for specific studies examining beneficial and adverse effects of BP lowering specifically in an older population.

## **CHAPTER 5:**

### **Study 2: The Longitudinal Association between Orthostatic Hypotension and incident Depressive Symptoms**

### **5.1 Key Findings**

- This is the first study to investigate the longitudinal relationship between OH and depression in older people.
- It involves a large, well-described population-representative sample of older people with a diagnosis of OH based on continuous beat-to-beat readings.
- Symptomatic OH at 30-seconds (sOH-30) post standing was associated with a two-fold increased risk of incident depressive symptoms during 4-year follow-up after controlling for covariates including subthreshold depressive symptoms, alcohol, cognitive impairment and antidepressant use.
- Asymptomatic OH and initial OH did not predict incident depressive symptoms.
- These findings are important as, given the higher burden of cerebral white matter disease in LLD, cerebral hypoperfusion due to OH may be the mechanism for this association, and OH may therefore represent a modifiable risk factor for depression in older people.
- This study was published in Hypertension: DOI [10.1161/HYPERTENSIONAHA.117.10542](https://doi.org/10.1161/HYPERTENSIONAHA.117.10542).

## **5.2 Abstract**

### *Background*

There is an established cross-sectional association between OH and LLD. The aim of this observational study was to clarify the longitudinal association between baseline sOH-30 and incident depressive symptoms in a sample of over 3,000 older people without baseline depression (Mean age 62 years at baseline).

### *Methods*

This study was embedded within TILDA using data from waves 1 to 3, collected between 2009 and 2014. At 2 and 4 year follow-up, a score  $\geq 9$  on the CES-D-8 was used to define incident depression. SOH-30 was defined as a drop in sBP  $\geq 20$ mmHg or diastolic BP  $\geq 10$ mmHg at 30 seconds post standing in conjunction with orthostatic symptoms such as dizziness, using beat-to-beat measurements.

### *Results*

Almost one fifth (prop 18%; 95% CI:16-20%) of the study sample had sOH-30. One tenth (prop. 10%; 95% CI:9-12%) had incident depression. Participants with incident depression were twice as likely to have sOH-30 at baseline compared to those without incident depression (linear regression:13% (95% CI:8-19%) vs. 7% (95% CI:6-8%)). Weighted logistic regression models demonstrated that sOH-30 predicted incident depression with an OR of 1.90 (95% CI:1.15-3.15) after controlling for covariates including subthreshold depression, hypotension, cognitive impairment and antidepressant use. Asymptomatic Orthostatic Hypotension at 30 seconds after standing (aOH-30) and IOH did not predict depression.

### *Conclusion*

This study demonstrates that sOH-30 predicts incident depression in a population-representative sample of older people and may therefore represent a potentially modifiable risk factor for LLD.

### **5.3 Background**

OH is defined as a sustained drop in sBP by at least 20 mmHg or diastolic BP by at least 10 mmHg within 3 minutes of standing (78, 225). OH is common, affecting one in five people aged 65 years old or older and this prevalence increases with further advancing age(79).

Normally, when we stand from a seated or lying position, blood pools in the legs, causing a drop in venous return, cardiac filling pressure, cardiac output and systemic BP. This drop in BP causes activation of baroreceptors, which act to normalise BP by increasing sympathetic outflow and reducing parasympathetic activity, resulting in peripheral vasoconstriction and tachycardia(80).In later life, this baroreflex can become less sensitive, leading to prolonged times to stabilise BP and resulting in OH(81).Prolonged hypotension can cause cerebral hypoperfusion and OH increases the risk of conditions related to cerebral perfusion deficits, including dementia, falls and stroke(86-88).

Cerebral hypoperfusion has been implicated in LLD(33, 70).Decline in CBF is associated with increased depressive symptoms in older people with chronic cardiovascular disease(71, 72).Reduced CBF measured by TCD predicts incident depression in a sample of almost 1,500 older people(73).In a cohort with Parkinson's disease, SPECT demonstrated cerebral perfusion deficits in fronto-temporo-limbic regions in depressed participants compared to non-depressed controls(74).

Studies in LLD have also demonstrated increased burden of cerebral white matter disease, specifically strategic WMH (42), which can be caused by ischaemic insults due to cerebral hypoperfusion(66, 226).WMH are more common and severe in older people with depression (44)and higher burden of WMH is predictive of increased severity of depressive symptoms, as well as poorer response to treatment in older people(37, 222).Conditions predisposing to cerebral hypoperfusion and resultant WMH may therefore represent modifiable risk factors for LLD. Initial studies with some methodological limitations have demonstrated a cross-sectional association between OH and LLD but a longitudinal relationship has yet to be investigated(89, 102, 187).

A further orthostatic BP pattern, IOH has also been described and is defined as a transient BP drop within 15 seconds of standing, of more than 40 mmHg systolic BP and/or more than 20 mmHg diastolic BP, with symptoms of cerebral hypoperfusion(227). Typically BP has recovered within 30 seconds of standing. IOH is a common benign cause of dizziness and syncope in younger people but can also be seen in older adults, particularly those taking medications that

may interfere with BP recovery after standing(228). Prior evidence from TILDA has shown that IOH does not predict unexplained or injurious falls within the TILDA cohort of older people however(88).The role of IOH in incident depression has not yet been investigated.

An important limitation of many studies of OH is the method used to measure orthostatic BP(102).Non-invasive beat to beat BP measurement by active stand using a finometer is a more sensitive diagnostic test for OH as it allows real-time continuous tracking of BP, and gives waveform measurements similar to those seen in invasive intra-arterial monitoring(173).It captures dynamic BP changes that are often missed with other techniques(90).

Our hypothesis was that OH may represent a modifiable risk factor for depression in later life and the aim of this study therefore, is to clarify if OH and IOH, divided into symptomatic and asymptomatic based on the presence or absence of orthostatic symptoms, measured with continuous BP values, predicts incident depressive symptoms in a cohort of community-dwelling older people.

## **5.4 Methods**

### *Ethics*

The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki. All assessments were carried out by trained research nurses.

Anonymised data and materials have been made publicly available at the Irish Social Science Data Archive based in University College Dublin, and the Interuniversity Consortium for Political and Social Research (ICPSR) based in the University of Michigan and can be accessed at [www.tilda.ie](http://www.tilda.ie).

### *Study Design*

This study is embedded within TILDA, a large population-based study of a nationally representative sample of community dwelling older adults aged 50 years and over, with an initial study population of over 8,000 participants.

The TILDA study design has been outlined previously(117). We analysed data from the first, second and third wave of TILDA collected between 2009 and 2015. Participants were included in this study if they were aged 50 years or more, and underwent a complete health assessment at wave 1 including measurement of orthostatic BP and screening for depression. Participants were excluded if they did not complete 4-year follow-up, including assessment of mood at both wave 2 and wave 3. Participants were also excluded at wave 1 if they had a pre-existing diagnosis of dementia.

This is a longitudinal study establishing whether OH at baseline (wave 1), measured at 30 seconds post standing, is a predictor of incident depressive symptoms by 4-year follow-up. Therefore, participants with depression at wave 1 were excluded. The remaining participants were screened for depressive symptoms at waves 2 and 3.

### *Orthostatic Hypotension*

Orthostatic BP was measured by active stand using a Finometer® Midi as described previously(126). The Finometer® device has been validated against British Hypertension Society protocol and the criteria of the Association for the Advancement of Medical Instrumentation for measurement of finger BP noninvasively on a beat-to-beat basis(175).

While clinical practice has generally shifted towards use of continuous BP measurement for OH rather than sphygmomanometer-based readings, it must be noted that these measurements also show low to moderate reliability and natural variation at short-term follow-up(229). Furthermore, while continuous BP measurement is validated extensively as a reliable method to track changes in BP, due to differences between arterial waveforms at the finger compared to central arteries, finger systolic BP may be higher than invasive brachial BP while finger diastolic BP may be lower(227).

Briefly, participants lay in the supine position for 10 minutes in a quiet room, before standing in a timely manner (<5 seconds), and were aided by a research nurse to mobilize as necessary. After standing, systolic BP, diastolic BP, and heart rate were monitored for a further 120 seconds. Throughout the recording, subjects stood quietly. After the 2 minute period, subjects were asked to report occurrence of orthostatic symptoms (dizziness, light-headedness, or unsteadiness).

OH at 30 seconds (OH-30) was defined as a drop in systolic BP  $\geq 20$  mmHg or drop in diastolic BP  $\geq 10$  mmHg at 30 seconds compared to baseline BP. Time-point values were 5-second moving averages, i.e. the 30 second time point was the average of 27.5 to 32.5 seconds. SOH-30 was defined as OH at 30 seconds with associated orthostatic symptoms. AOH-30 was defined as OH at 30 seconds without associated orthostatic symptoms. 30 seconds was chosen as the cut-off point post stand for several reasons. A recent large study has demonstrated that measurements of OH performed within 60 seconds of standing were the most strongly related to dizziness and adverse outcomes such as syncope, injury or death(127). Furthermore, a prior study looking at normative changes in phasic BP in the TILDA cohort established that an initial BP drop immediately after standing is common but non-recovery of BP should be considered abnormal by 30 seconds(88).

IOH was defined as a drop in systolic BP  $> 40$  mm Hg or a drop in diastolic BP  $> 20$  mmHg at 10 seconds post standing compared to baseline BP with full recovery of BP to baseline BP value or higher by 30 seconds. Symptomatic initial orthostatic hypotension (sIOH) was defined as IOH with associated orthostatic symptoms.

### *Depression*

Depressive symptoms were assessed at wave 1 using the 20-item CES-D-20. A score  $\geq 16$  was used to define clinically significant depressive symptoms (123). Participants with depression at wave 1 were excluded from the study.

At waves 2 and 3 the CES-D-8 was used to screen for depression. The CES-D-8 was introduced in the TILDA study at waves 2 and 3 in order to reduce the time taken to conduct participant assessments, as well as to reduce respondent burden and fatigue, and previous work has confirmed its reliability in comparison to the CES-D-20 in terms of internal consistency and factor structure within the TILDA cohort(124). A score of  $\geq 9$  on this scale was used to define clinically significant depressive symptoms and participants with a CES-D-8 score  $\geq 9$  at either wave 2 or 3 were defined as having incident depressive symptoms (125).

### *Other Measures*

Detailed social and biological data were collected at wave 1. Functional impairment was defined as impairment in one or more instrumental ADL, which includes cleaning and maintaining the house, managing money, moving within the community and preparing meals. Alcohol abuse was defined as a score of 2 or more on the CAGE Alcohol Scale. Gait was assessed using the TUG, where a score of 12 seconds or more was considered abnormal(135). BP was measured twice in a seated position by a trained research nurse using the OMRON™ digital automatic BP monitor and the mean value was used for analysis. Cardiac disease was defined as self-report of prior MI, cardiac failure or cardiac arrhythmia. Self-report was also elicited for prior stroke, diabetes and Parkinson's disease, as well as recent unintentional weight loss of 10 pounds or more. Participants were asked about physical activity within the last week and those who were inactive for the full 7 days were defined as having low physical activity, compared to moderate (active 1-3 days) and high (active 4 or more days) physical activity levels. Medication records were examined for antihypertensive use, specifically those with Anatomic Therapeutic Chemical (ATC) Classification C02, C03, C07, C08, or C09) and antidepressant use (ATC N06A). Cognitive impairment was defined as a MMSE Score  $\leq 24$ .

### *Statistical Analysis*

Data were analysed using Stata (Statacorp).

Cross-sectional analysis was weighted. Weights were estimated by comparing the counts of individuals in the sample across age, sex and highest level of educational attainment, marital status and urban or rural dwelling, with the counts in the population with the same characteristics using information from the Central Statistics Office of Ireland 2011 Census. Differences in baseline binary demographic and clinical variables between study groups were therefore presented as weighted prevalence estimates using proportional estimation.

Continuous variables were analysed by linear regression with study group as a predictor. In order to correct for non-normality of the distribution, reciprocal transformation was applied to the TUG variables as they demonstrated a highly positive skew. Marginal mean values calculated post-estimation and data was presented by recalculating as  $1/(\text{marginal mean})$ .

Additionally, attrition weights were applied to the longitudinal analysis. These weights corrected for the difference in attrition rates over subgroups and reduced the bias caused by this difference in attrition rates. These weights are calculated based on the reciprocal of the probability of a wave 1 health assessment respondent completing a CAPI at waves 2 and 3.

Logistic regression models were used to estimate OR (with 95% CI) for sOH-30 as a predictor of incident depression. Covariates were chosen a priori, based on their hypothesised role in modifying the relationship between baseline OH and incident depression.

Based on these regression models, average marginal effects were calculated for relevant predictor variables post-estimation. Per subject, each nominal predictor of interest was first assigned its base category level value whilst holding values of all other variables in the regression model for that subject constant; the probability of outcome was calculated. The process was then repeated, assigning the predictor of interest to its next value. The difference between the calculated probabilities for the levels of the predictor variable was the marginal effect; the average marginal effect for the sample was calculated as the mean of these values over the different levels of the predictor of interest.

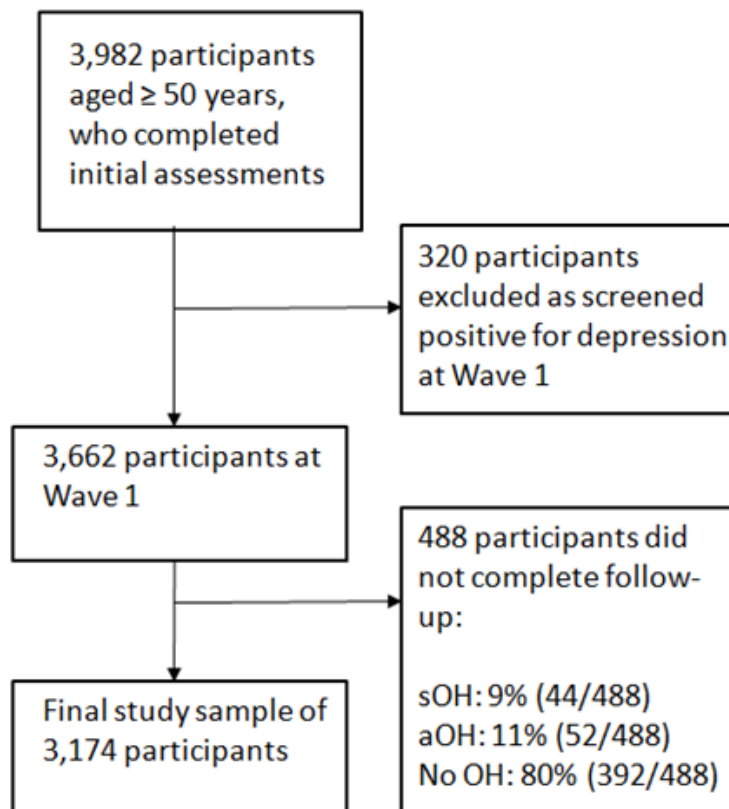
In order to ensure findings were not related to antidepressant use, subgroups of participants taking antidepressant medication were excluded from the analysis and logistic regression models were rerun in order to ensure that findings were not significantly different when these groups were omitted. Similarly, analysis was rerun excluding participants with an MMSE <28 in order to ensure that findings were not affected by those with early or undetected cognitive impairment.

A p value  $\leq 0.05$  was considered statistically significant.

## 5.5 Results

3,982 participants met initial criteria for inclusion at wave 1. A further 8% of this group screened positive for depression at wave 1 (CES-D-20 score  $\geq 16$ ) and were therefore excluded from the study, yielding an initial study sample of 3,662 participants. 13% (488/3,662) of this group did not complete 4-year follow-up, leaving a final study sample of 3,174 participants. 8% of study participants were aged 75 years or more, 27% were aged 65-74 years and 65% were aged 50-64 years. See figure 5.1 for flow diagram of study recruitment and attrition.

**Figure 5.1: Flow Diagram of Study Recruitment**



Over one sixth (prop. 18%; 95% CI: 16-20%) of the study sample had OH-30 and over 40% (prop. 42%; 95% CI: 38-47%) of these were symptomatic. The baseline characteristics of the study sample by diagnosis of OH-30 are shown in table 5.1. Participants with OH-30 were older and more likely to be female, functionally impaired, have a history of falls and prescribed antidepressant and antihypertensive medication.

**Table 5.1: Baseline Characteristics of study sample by Diagnosis of OH-30 at Wave 1**

| <b>Baseline Characteristic</b>                           | <b>No OH-30<br/>n = 2,643</b> | <b>Asymptomatic OH-30<br/>n =305</b> | <b>Symptomatic OH-30<br/>n = 226</b> |
|----------------------------------------------------------|-------------------------------|--------------------------------------|--------------------------------------|
| <b>Age, (Mean) years (95% CI)</b>                        | 61.4 (60.9 – 61.8)            | 67.3 (66.0 – 68.6)                   | 66.6 (65.2 – 68.0)                   |
| <b>Females, Prop. (95% CI)</b>                           | 0.48 (0.46 – 0.50)            | 0.61 (0.54 – 0.67)                   | 0.56 (0.49 – 0.63)                   |
| <b>Third Level Education, Prop. (95% CI)</b>             | 0.26 (0.25 – 0.28)            | 0.21 (0.17 – 0.26)                   | 0.25 (0.20 – 0.31)                   |
| <b>Married, Prop. (95% CI)</b>                           | 0.74 (0.72 – 0.77)            | 0.67 (0.61 – 0.73)                   | 0.66 (0.58 – 0.73)                   |
| <b>Alcohol Abuse, Prop. (95% CI)<sup>A</sup></b>         | 0.14 (0.12 – 0.15)            | 0.11 (0.07 – 0.14)                   | 0.13 (0.08 – 0.18)                   |
| <b>≥1 IADL Impairment, Prop. (95% CI)<sup>B</sup></b>    | 0.03 (0.02 – 0.04)            | 0.04 (0.01 – 0.07)                   | 0.06 (0.02 – 0.10)                   |
| <b>TUG, (Mean) seconds (95% CI)</b>                      | 8.2 (8.2– 8.3)                | 8.8(8.6– 9.0)                        | 8.9(8.6– 9.1)                        |
| <b>Falls in last 12 months, Prop. (95% CI)</b>           | 0.18 (0.17 – 0.20)            | 0.22 (0.17 – 0.27)                   | 0.30 (0.23 – 0.37)                   |
| <b>Weight Loss &gt; 10 lbs., Prop. (95% CI)</b>          | 0.05 (0.04 – 0.06)            | 0.07 (0.04 – 0.11)                   | 0.07 (0.03 – 0.12)                   |
| <b>Low physical activity, Prop. (95% CI)<sup>C</sup></b> | 0.69 (0.67 – 0.71)            | 0.74 (0.68 – 0.79)                   | 0.74 (0.68 – 0.80)                   |
| <b>Systolic BP, mmHg (95% CI)<sup>D</sup></b>            | 134.4 (133.6 – 135.2)         | 140.3 (137.8 – 142.8)                | 136.5 (133.7 – 139.4)                |
| <b>Diastolic BP, mmHg (95% CI)<sup>D</sup></b>           | 82.6 (82.1 – 83.0)            | 82.1 (80.7 – 83.6)                   | 81.0 (79.4 – 82.7)                   |
| <b>Cardiac Disease:</b>                                  |                               |                                      |                                      |
| - Myocardial Infarct, Prop. (95% CI)                     | 0.04 (0.03 – 0.05)            | 0.03 (0.01 – 0.06)                   | 0.06 (0.02 – 0.10)                   |
| - Cardiac Failure, Prop. (95% CI)                        | 0.01 (0.00 – 0.01)            | 0.01 (0.00 – 0.01)                   | 0.03 (0.00 – 0.05)                   |
| - Cardiac Arrhythmia, Prop. (95% CI)                     | 0.06 (0.05 – 0.07)            | 0.14 (0.09 – 0.19)                   | 0.12 (0.08 – 0.17)                   |
| <b>Prior stroke, Prop. (95% CI)</b>                      | 0.01 (0.00 – 0.01)            | 0.02 (0.00 – 0.04)                   | 0.01 (0.00 – 0.02)                   |
| <b>Diabetes, Prop. (95% CI)</b>                          | 0.07 (0.05 – 0.08)            | 0.09 (0.05 – 0.13)                   | 0.09 (0.05 – 0.14)                   |
| <b>Parkinson's Disease, Prop. (95% CI)</b>               | 0.00 (0.00 – 0.01)            | 0.00 (0.00 – 0.01)                   | 0.00 (0.00 – 0.02)                   |
| <b>Antihypertensive Use, Prop. (95% CI)<sup>E</sup></b>  | 0.31 (0.29 – 0.33)            | 0.45 (0.38 – 0.51)                   | 0.39 (0.32 – 0.46)                   |
| <b>Antidepressant Use, Prop. (95% CI)</b>                | 0.03 (0.03 – 0.04)            | 0.07 (0.04 – 0.11)                   | 0.12 (0.07 – 0.17)                   |
| <b>Cognitive Impairment, Prop. (95% CI)<sup>F</sup></b>  | 0.03 (0.02 – 0.04)            | 0.04 (0.01 – 0.06)                   | 0.06 (0.02 – 0.10)                   |

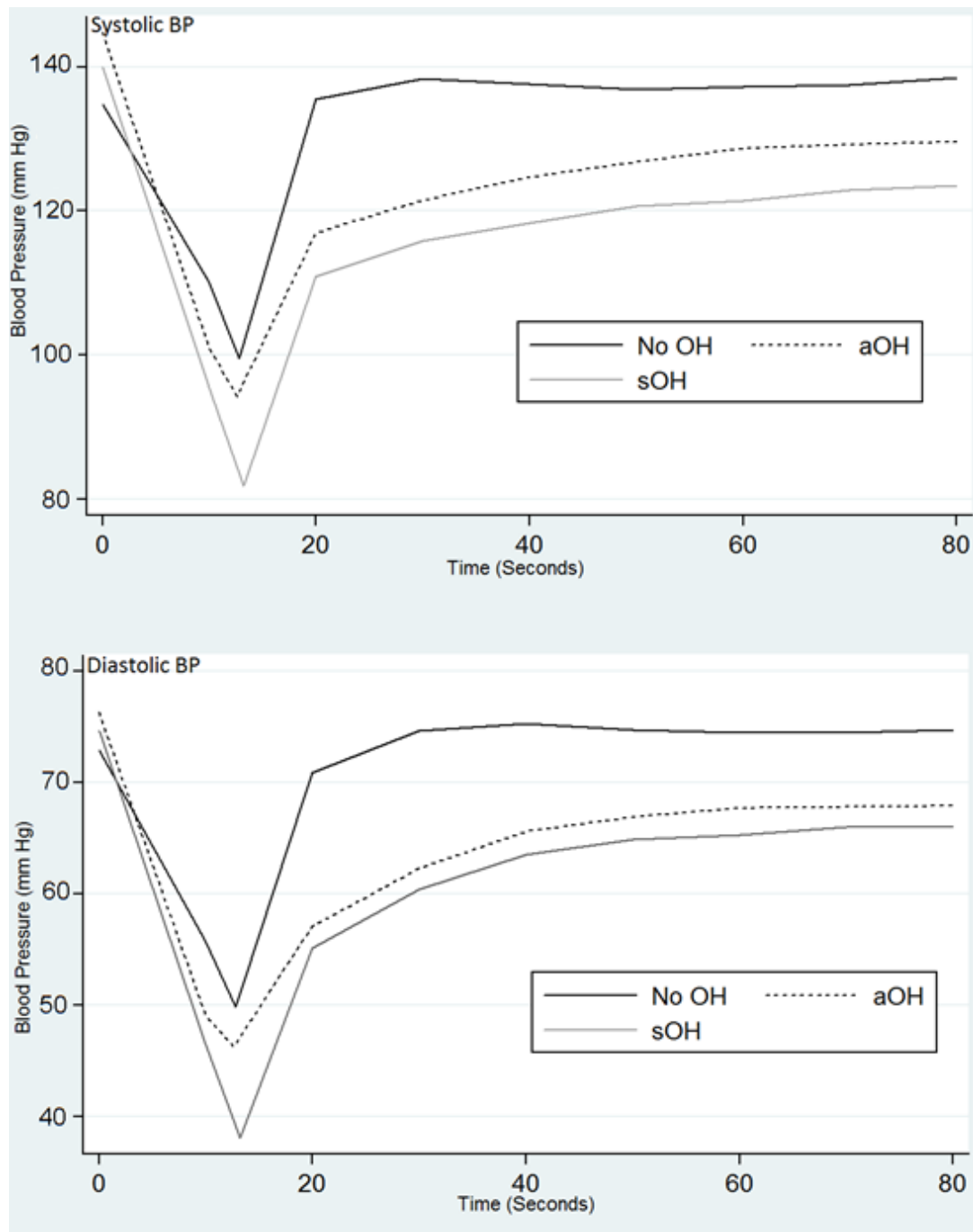
*Notes: Differences in categorical variables presented as weighted prevalence estimates using proportional estimation; Continuous variables were analysed by linear regression with study group as a predictor.*

*Abbreviations: OH-30 = Orthostatic hypotension at 30 seconds post stand during active stand test; Prop. = proportion; CI = confidence interval; IADL = instrumental activities of daily living; TUG = Timed Up and Go Test; lbs. = pounds; BP = blood pressure.*

*A Alcohol Abuse defined as a score ≥ 2 on the CAGE Alcohol Scale. B IADL impairment includes impairments in cleaning and maintaining the house, managing money, moving within the community and preparing meal. C Low physical activity defined as no physical activity on any day in the last week. D Blood pressure was measured twice with sphygmomanometer in seated position and the average of two readings was used. E Antihypertensive use defined as being prescribed any antihypertensive medication with Anatomical Therapeutic Chemical (ATC) Classification Codes C02, C03, C07, C08 and C09. F Cognitive Impairment defined as Mini Mental State Examination Score less than 24.*

In terms of differences between those with sOH-30 and aOH-30, participants with sOH-30 had a lower systolic BP nadir (Linear regression: 80.7 (95% CI: 68.7 – 92.7) mmHg vs. 94.3 (95% CI: 91.1 – 97.4) mmHg) and diastolic BP nadir (Linear regression: 37.5 (95% CI: 26.4 – 48.7) mmHg vs. 46.3 (95% CI: 44.5 – 48.1) mmHg) during active stand testing compared to the aOH-30 group. Participants with sOH-30 were also more likely to have an initial drop (i.e. at 10 seconds post standing) in systolic BP greater than 40 mmHg compared to those with aOH-30 (61% (95% CI: 55 – 68%) vs. 58% (95% CI: 52 – 64%)). There were similar rates of cardiovascular disease and antihypertensive use between groups. See figure 5.2.

**Figure 5.2: Mean Blood Pressure values from Active Stand comparing Symptomatic and Asymptomatic OH-30 groups to Non-OH-30 group**



Notes:

Abbreviations: BP = blood pressure; OH-30 = orthostatic hypotension at 30 seconds post standing; sOH = symptomatic orthostatic hypotension at 30 seconds post standing; aOH = asymptomatic orthostatic hypotension at 30 seconds post standing.

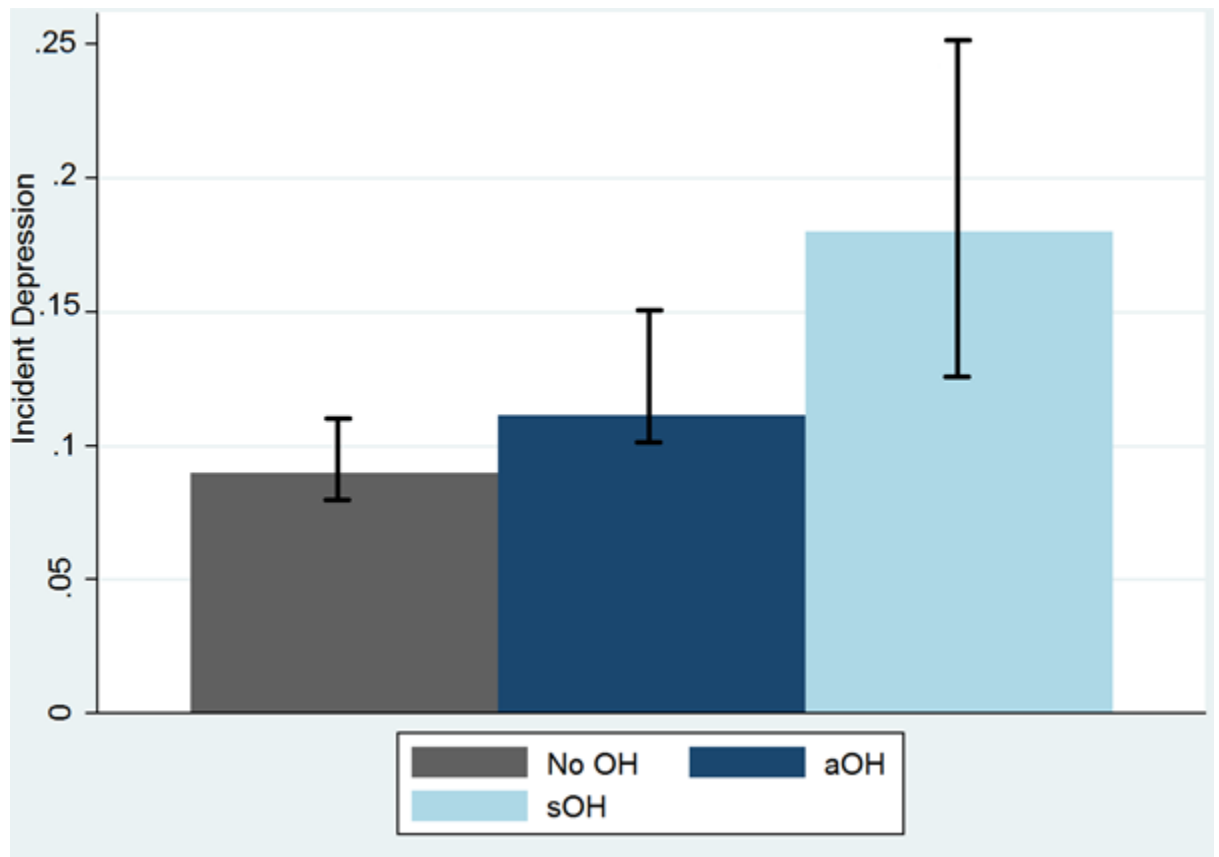
Time = seconds post stand during active stand test.

*Does OH-30 at Wave 1 predict incident depression?*

One tenth (prop. 10%; 95% CI: 9-12%) of the study sample had incident depressive symptoms by 4-year follow-up, i.e. CES-D-8 $\geq$ 9 at either wave 2 or 3. This includes 138 participants with depressive symptoms at wave 2, and a further 162 at wave 3.

Participants with incident depressive symptoms were almost twice as likely to have sOH-30 at wave 1 compared to those without significant depressive symptoms (Linear regression: 13% (95% CI: 8-19%) vs. 7% (95% CI: 6-8%)). Proportions of participants with incident depressive symptoms by OH-30 group are shown in figure 5.3.

**Figure 5.3: Proportion of participants (with 95% confidence intervals) with Incident Depressive Symptoms by OH-30 Group**



Notes:  $n=3,174$  (No OH-30=2,643; aOH-30=305; sOH-30=226)

Differences in incident depression presented as weighted prevalence estimates using proportional estimation.

OH-30 = orthostatic hypotension at 30 seconds post standing at wave 1; aOH = asymptomatic orthostatic hypotension at 30 seconds post standing; sOH = symptomatic orthostatic hypotension at 30 seconds post standing.

Incident depression defined as 8-item Centre for Epidemiological Studies Depression Scale  $\geq 9$  at wave 2 or wave 3.

Weighted logistic regression models demonstrated that sOH-30 predicted incident depressive symptoms with an OR of 1.92(95% CI: 1.18-3.11) after controlling for covariates. Other significant predictors of incident depression were female gender, high-normal CES-D scores and current antidepressant use. AOH-30 did not predict incident depression. See table 5.2.

**Table 5.2: Logistic Regression reporting Odds Ratios (OR) for association between Symptomatic Orthostatic Hypotension at Wave 1 and Incident Depressive Symptoms**

| Incident Depressive Symptoms   | OR (Weighted) | p Value | t     | 95% CI      | OR (Unweighted) with 95% CI |
|--------------------------------|---------------|---------|-------|-------------|-----------------------------|
| <b>Model 1:</b>                |               |         |       |             |                             |
| sOH-30 at Wave 1 <sup>A</sup>  | 2.13          | 0.002   | 3.15  | 1.33 – 3.42 | 2.02 (1.39 – 2.95)          |
| aOH-30 at Wave 1 <sup>B</sup>  | 1.19          | 0.443   | 0.77  | 0.76 – 1.85 | 1.13 (0.76 – 1.68)          |
| <b>Model 2:</b>                |               |         |       |             |                             |
| sOH-30 at Wave 1 <sup>A</sup>  | 2.07          | 0.004   | 2.88  | 1.26 – 3.41 | 1.95 (1.31 – 2.92)          |
| aOH-30 at Wave 1 <sup>B</sup>  | 1.13          | 0.600   | 0.52  | 0.72 – 1.78 | 1.05 (0.69 – 1.60)          |
| <b>Age:</b>                    |               |         |       |             |                             |
| - Age 65 – 74 years            | 0.71          | 0.064   | -1.85 | 0.50 – 1.02 | 0.81 (0.60 – 1.11)          |
| - Age ≥ 75 years               | 1.07          | 0.804   | 0.25  | 0.63 – 1.82 | 1.06 (0.66 – 1.69)          |
| Female sex                     | 1.49          | 0.009   | 2.63  | 1.11 – 2.00 | 1.57 (1.20 – 2.05)          |
| <b>Educational Attainment:</b> |               |         |       |             |                             |
| - Secondary                    | 0.65          | 0.017   | -2.39 | 0.45 – 0.92 | 0.68 (0.49 – 0.95)          |
| - Tertiary                     | 0.65          | 0.028   | -2.20 | 0.45 – 0.96 | 0.72 (0.52 – 1.01)          |
| <b>Marital Status:</b>         |               |         |       |             |                             |
| - Single                       | 0.78          | 0.347   | -0.94 | 0.49 – 1.29 | 0.90 (0.55 – 1.47)          |
| - Separated/Divorced           | 1.46          | 0.139   | 1.48  | 0.88 – 2.42 | 1.29 (0.81 – 2.05)          |
| - Widowed                      | 0.99          | 0.976   | -0.03 | 0.57 – 1.72 | 1.02 (0.66 – 1.59)          |
| <b>CES-D:</b>                  |               |         |       |             |                             |
| - 6-10                         | 2.24          | <0.001  | 4.63  | 1.59 – 3.15 | 2.32 (1.73 – 3.10)          |
| - 11-15                        | 5.78          | <0.001  | 8.60  | 3.87 – 8.62 | 5.87 (4.24 – 8.11)          |
| <b>CAGE Score:</b>             |               |         |       |             |                             |
| - CAGE=1                       | 0.92          | 0.750   | -0.32 | 0.57 – 1.50 | 0.85 (0.56 – 1.29)          |
| - CAGE=2                       | 1.31          | 0.259   | 1.13  | 0.82 – 1.12 | 1.25 (0.83 – 1.89)          |
| - CAGE=3                       | 1.65          | 0.111   | 1.60  | 0.89 – 3.05 | 1.66 (0.96 – 2.88)          |
| - CAGE=4                       | 0.46          | 0.337   | -0.96 | 0.09 – 2.25 | 1.04 (0.23 – 4.74)          |

**Table 5.2 (cont'd): Logistic Regression reporting Odds Ratios (OR) for association between Symptomatic Orthostatic Hypotension at Wave 1 and Incident Depressive Symptoms**

| Incident Depressive Symptoms      | OR (Weighted) | p Value | t     | 95% CI       | OR (Unweighted) with 95% CI |
|-----------------------------------|---------------|---------|-------|--------------|-----------------------------|
| <b>Model 3:</b>                   |               |         |       |              |                             |
| sOH-30 at Wave 1 <sup>A</sup>     | 1.91          | 0.009   | 2.62  | 1.18 – 3.09  | 1.79 (1.19 – 2.70)          |
| aOH-30 at Wave 1 <sup>B</sup>     | 1.10          | 0.673   | 0.42  | 0.70 – 1.75  | 1.00 (0.66 – 1.54)          |
| <b>Age:</b>                       |               |         |       |              |                             |
| - Age 65 – 74 years               | 0.66          | 0.024   | -2.26 | 0.45 – 0.95  | 0.75 (0.55 – 1.03)          |
| - Age ≥ 75 years                  | 0.85          | 0.568   | -0.57 | 0.48 – 1.50  | 0.87 (0.53 – 1.43)          |
| Female sex                        | 1.40          | 0.037   | 2.09  | 1.02 – 1.91  | 1.51 (1.15 – 1.99)          |
| <b>Educational Attainment:</b>    |               |         |       |              |                             |
| - Secondary                       | 0.67          | 0.033   | -2.14 | 0.46 – 0.97  | 0.73 (0.52 – 1.02)          |
| - Tertiary                        | 0.73          | 0.105   | -1.62 | 0.49 – 1.07  | 0.81 (0.53 – 1.43)          |
| <b>Marital Status:</b>            |               |         |       |              |                             |
| - Single                          | 0.77          | 0.274   | -1.10 | 0.47 – 1.24  | 0.86 (0.53 – 1.42)          |
| - Separated/Divorced              | 1.40          | 0.202   | 1.28  | 0.83 – 2.36  | 1.29 (0.81 – 2.07)          |
| - Widowed                         | 1.01          | 0.985   | 0.02  | 0.57 – 1.77  | 1.04 (0.66 – 1.62)          |
| <b>CES-D:</b>                     |               |         |       |              |                             |
| -6-10                             | 2.02          | <0.001  | 4.03  | 1.44 – 2.91  | 2.16 (1.61 – 2.91)          |
| -11-15                            | 5.44          | <0.001  | 7.96  | 3.58 – 8.25  | 5.49 (3.95 – 7.64)          |
| <b>CAGE Score:</b>                |               |         |       |              |                             |
| - CAGE=1                          | 0.87          | 0.588   | -0.54 | 0.51 – 1.46  | 0.81 (0.53 – 1.24)          |
| - CAGE=2                          | 1.29          | 0.309   | 1.02  | 0.79 – 2.12  | 1.22 (0.80 – 1.86)          |
| - CAGE=3                          | 1.67          | 0.112   | 1.59  | 0.89 – 3.13  | 1.71 (0.98 – 2.98)          |
| - CAGE=4                          | 0.36          | 0.249   | -1.15 | 0.07 – 2.03  | 0.92 (0.20 – 4.29)          |
| Weight loss >10 lbs.              | 2.02          | 0.007   | 2.70  | 1.21 – 3.36  | 1.82 (1.15 – 2.89)          |
| I-ADL Impairment <sup>C</sup>     | 0.70          | 0.442   | -0.77 | 0.28 – 1.74  | 0.72 (0.36 – 1.46)          |
| Gait Abnormality <sup>D</sup>     | 1.44          | 0.349   | 0.94  | 0.67 – 3.08  | 1.55 (0.85 – 2.82)          |
| Cardiac Disease <sup>E</sup>      | 1.24          | 0.141   | 1.47  | 0.93 – 1.66  | 1.17 (0.90 – 1.52)          |
| Hypotension <sup>F</sup>          | 1.38          | 0.510   | 0.66  | 0.53 – 3.61  | 1.11 (0.54 – 2.26)          |
| Stroke                            | 0.62          | 0.556   | -0.59 | 0.13 – 3.01  | 0.58 (0.13 – 2.57)          |
| Diabetes                          | 1.06          | 0.823   | 0.22  | 0.63 – 1.79  | 1.39 (0.87 – 2.22)          |
| Parkinson's Disease               | 4.10          | 0.173   | 1.36  | 0.54 – 31.26 | 4.08 (0.72 – 23.04)         |
| Antidepressant Use                | 1.87          | 0.037   | 2.10  | 1.04 – 3.35  | 1.97 (1.23 – 3.15)          |
| Cognitive Impairment <sup>G</sup> | 1.22          | 0.646   | 0.46  | 0.52 – 2.91  | 1.30 (0.60 – 2.81)          |

Notes: N = 3,174.

Abbreviations: sOH-30 = symptomatic orthostatic hypotension at 30 seconds; aOH-30 = asymptomatic orthostatic hypotension at 30 seconds; OR = Odds Ratio; CI = confidence interval; CES-D = Centre for Epidemiological Studies Depression Scale; lbs. = pounds; I-ADL = instrumental activities of daily living.

For age, reference value is age 50-65 years. For educational attainment, reference value is primary level education. For marital status, reference value is married. For CES-D, reference value is CES-D score 0-6. For CAGE score, reference value is CAGE score=0.

*A Drop in systolic blood pressure  $\geq 20$  mmHg or diastolic blood pressure  $\geq 10$  mmHG from baseline at 30 seconds post standing during active stand test with associated orthostatic symptoms. B Drop in systolic blood pressure  $\geq 20$  mmHg or diastolic blood pressure  $\geq 10$  mmHG from baseline at 30 seconds post standing during active stand test without associated orthostatic symptoms. C Impairment in cleaning and maintaining the house, managing money, moving within the community or preparing meal by self-report. D Timed Up and Go Test Score  $\geq 12$  seconds. E Self-report of prior myocardial infarction, cardiac arrhythmia, congestive heart failure or hypertension. F Blood pressure measured in seated position of systolic  $< 100$  mmHg or diastolic  $< 60$  mmHg. G Mini Mental State Examination score  $\leq 24$ .*

Average marginal effects, calculated post-estimation, demonstrated that the average marginal probability of incident depressive symptoms in participants with sOH-30 was 0.16 (95% CI: 0.11 – 0.21;  $z=5.84$ ;  $p < 0.001$ ), compared to 0.10 (95% CI: 0.08 – 0.11) and 0.10 (95% CI: 0.07 – 0.14) for those with both no OH-30 and aOH-30 respectively. The  $dy/dx$  for the sOH group (with the No OH-30 group as a reference) was therefore 0.06 (95% CI: 0.01 – 0.12;  $z=2.25$ ;  $p = 0.025$ ) suggesting that the probability of developing incident depressive symptoms in those with sOH-30 at baseline is 6% higher than in those without OH-30.

#### *Subgroup Analysis*

For OH-30 as a predictor of incident depressive symptoms, separate analyses were also performed excluding participants taking antidepressants ( $n=132$ ), as well as those with  $MMSE < 28$  ( $n=468$ ) and results were not attenuated significantly. See table 5.3.

**Table 5.3: Logistic regression reporting odds ratios (with 95% confidence interval) of Symptomatic Orthostatic Hypotension predicting Incident Depressive Symptoms**

| <b>Odds Ratio for sOH-30 predicting incident depression when subgroups excluded.</b> |                                               |                                                |                                              |
|--------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------|----------------------------------------------|
|                                                                                      | <b><u>Model 1</u></b>                         | <b><u>Model 2</u></b>                          | <b><u>Model 3</u></b>                        |
| <b><i>Excluding Antidepressant Users (n = 3,042)</i></b>                             | OR 1.74 (1.14 – 2.65)<br>p 0.010; $z = 2.56$  | OR 1.72 (1.09 – 2.69)<br>p 0.019; $z = 2.35$   | OR 1.65 (1.05 – 2.61)<br>p 0.031; $z = 2.15$ |
| <b><i>Excluding participants with MMSE &lt; 28 (n= 2,706)</i></b>                    | OR 2.13 (1.40 – 3.23)<br>p <0.001; $z = 3.54$ | OR 2.01 (1.29 – 3.15)<br>p = 0.002; $z = 3.07$ | OR 1.86 (1.18 – 2.94)<br>p 0.008; $z = 2.66$ |

*Abbreviations: sOH-30= symptomatic orthostatic hypotension at 30 seconds post standing; OR = odds ratio; MMSE = Mini Mental State Examination.*

*Model 1 is unadjusted. Model 2 controls for age, gender, marital status, CAGE score and baseline depression scores. Model 3 controls for Model 2 covariates, as well as functional impairment, gait abnormalities, heart disease, low blood pressure, weight loss, physical activity, stroke, diabetes, Parkinson's disease, antidepressant use and cognitive impairment.*

*Does IOH at Wave 1 predict incident depression?*

Almost half (prop. 46%; 95% CI: 44-48%) of the study sample had IOH, with 40% of these participants having sIOH. The baseline characteristics of the study sample by diagnosis of IOH are shown in table 5.4. There was no significant age or sex difference across groups defined by diagnosis of IOH.

**Table 5.4: Baseline Characteristics of study sample by diagnosis of IOH at Wave 1**

| Baseline Characteristic                            | No IOH<br>n = 1,717   | Asymptomatic<br>IOH<br>n =849 | Symptomatic<br>IOH<br>n = 608 |
|----------------------------------------------------|-----------------------|-------------------------------|-------------------------------|
| Age, (Mean) years (95% CI)                         | 61.6 (61.1 – 62.2)    | 63.7 (62.9 – 64.5)            | 62.8 (61.9 – 63.7)            |
| Females, Prop. (95% CI)                            | 0.50 (0.47 – 0.52)    | 0.52 (0.49 – 0.56)            | 0.47 (0.42 – 0.51)            |
| Third Level Education, Prop. (95% CI)              | 0.26 (0.23 – 0.28)    | 0.25 (0.22 – 0.28)            | 0.28 (0.24 – 0.31)            |
| Married, Prop. (95% CI)                            | 0.74 (0.72 – 0.77)    | 0.72 (0.68 – 0.75)            | 0.71 (0.66 – 0.75)            |
| Alcohol Abuse, Prop. (95% CI) <sup>A</sup>         | 0.14 (0.12 – 0.16)    | 0.12 (0.09 – 0.14)            | 0.14 (0.11 – 0.16)            |
| ≥1 IADL Impairment, Prop. (95% CI) <sup>B</sup>    | 0.03 (0.02 – 0.04)    | 0.02 (0.01 – 0.04)            | 0.05 (0.03 – 0.07)            |
| TUG, (Mean) seconds (95% CI)                       | 8.3 (8.2– 8.4)        | 8.4 (8.3– 8.5)                | 8.4(8.2– 8.5)                 |
| Falls in last 12 months, Prop. (95% CI)            | 0.19 (0.17 – 0.21)    | 0.20 (0.17 – 0.24)            | 0.21 (0.18 – 0.25)            |
| Weight Loss > 10 lbs, Prop. (95% CI)               | 0.05 (0.04 – 0.06)    | 0.07 (0.04 – 0.11)            | 0.07 (0.03 – 0.12)            |
| Low physical activity, Prop. (95% CI) <sup>C</sup> | 0.71 (0.69 – 0.74)    | 0.67 (0.63 – 0.70)            | 0.70 (0.66 – 0.74)            |
| Systolic BP, mmHg (95% CI) <sup>D</sup>            | 133.7 (132.7 – 134.8) | 134.3 (132.8 – 135.9)         | 138.7 (137.4 – 140.4)         |
| Diastolic BP, mmHg (95% CI) <sup>D</sup>           | 82.4 (81.8 – 83.0)    | 83.4 (82.5 – 84.3)            | 81.0 (80.2 – 81.8)            |
| Delayed recovery of BP II                          | 0.06 (0.05 – 0.07)    | 0.33 (0.29 – 0.36)            | 0.31 (0.27 – 0.35)            |
| <b>Cardiac Disease:</b>                            |                       |                               |                               |
| Myocardial Infarct, Prop. (95% CI)Cardiac          | 0.04 (0.03 – 0.05)    | 0.04 (0.02 – 0.05)            | 0.06 (0.03 – 0.08)            |
| Failure, Prop. (95% CI)Cardiac Arrhythmia,         | 0.01 (0.00 – 0.01)    | 0.00 (0.00 – 0.01)            | 0.03 (0.00 – 0.05)            |
| Prop. (95% CI)                                     | 0.06 (0.05 – 0.07)    | 0.10 (0.08 – 0.13)            | 0.08 (0.05 – 0.10)            |
| Prior stroke, Prop. (95% CI)                       | 0.01 (0.00 – 0.01)    | 0.01 (0.00 – 0.02)            | 0.01 (0.00 – 0.01)            |
| Diabetes, Prop. (95% CI)                           | 0.07 (0.06 – 0.08)    | 0.07 (0.05 – 0.09)            | 0.07 (0.05 – 0.10)            |
| Parkinson's Disease, Prop. (95% CI)                | 0.00 (0.00 – 0.01)    | 0.00 (0.00 – 0.01)            | 0.01 (0.00 – 0.02)            |
| Antihypertensive Use, Prop. (95% CI) <sup>E</sup>  | 0.32 (0.30 – 0.35)    | 0.33 (0.29 – 0.36)            | 0.35 (0.31 – 0.39)            |
| Antidepressant Use, Prop. (95% CI)                 | 0.03 (0.02 – 0.04)    | 0.05 (0.03 – 0.07)            | 0.06 (0.04 – 0.08)            |
| Cognitive Impairment, Prop. (95% CI) <sup>F</sup>  | 0.03 (0.02 – 0.05)    | 0.03 (0.01 – 0.04)            | 0.04 (0.02 – 0.06)            |

Notes:

Differences in categorical variables presented as weighted prevalence estimates using proportional estimation; Continuous variables were analysed by linear regression with study group as a predictor.

Abbreviations: IOH= Initial orthostatic hypotension; Prop. = proportion; CI = confidence interval; IADL = instrumental activities of daily living; TUG = Timed Up and Go Test; lbs = pounds; BP = blood pressure.

*A Alcohol Abuse defined as a score  $\geq 2$  on the CAGE Alcohol Scale. B IADL impairment includes impairments in cleaning and maintaining the house, managing money, moving within the community and preparing meal. C Low physical activity defined as no physical activity on any day in the last week. D Blood pressure was measured twice with sphygmomanometer in seated position and the average of two readings was used. E Delayed recovery is defined as systolic BP  $\leq 20$  mmHg or diastolic BP  $\leq 10$  mmHg than baseline BP at 30 seconds post standing during Active Stand test. F Antihypertensive use defined as being prescribed any antihypertensive medication with Anatomical Therapeutic Chemical (ATC) Classification Codes C02, C03, C07, C08 and C09. G Cognitive Impairment defined as Mini Mental State Examination Score less than 24.*

Weighted logistic regression models demonstrated that neither sIOH nor asymptomatic IOH predicted incident depressive symptoms. See table 5.5.

**Table 5.5: Logistic Regression reporting Odds Ratios (OR) for association between Initial Orthostatic Hypotension at Wave 1 and incident Depressive Symptoms**

| <u>Incident Depression</u>  | <u>OR (Weighted)</u> | <u>p Value</u> | <u>t</u> | <u>95% CI</u> | <u>OR (Unweighted) with 95% CI</u> |
|-----------------------------|----------------------|----------------|----------|---------------|------------------------------------|
| <b>Model 1:</b>             |                      |                |          |               |                                    |
| sIOH at Wave 1 <sup>A</sup> | 0.96                 | 0.819          | -0.23    | 0.66 – 1.39   | 0.91 (0.66 – 1.24)                 |
| aIOH at Wave 1 <sup>B</sup> | 0.85                 | 0.331          | -0.97    | 0.61 – 1.18   | 0.81 (0.61 – 1.09)                 |
| <b>Model 2:</b>             |                      |                |          |               |                                    |
| sIOH at Wave 1 <sup>A</sup> | 0.98                 | 0.904          | -0.12    | 0.67 – 1.43   | 0.91 (0.65 – 1.26)                 |
| aIOH at Wave 1 <sup>B</sup> | 0.87                 | 0.428          | -0.79    | 0.63 – 1.22   | 0.82 (0.61 – 1.11)                 |
| <b>Model 3:</b>             |                      |                |          |               |                                    |
| sIOH at Wave 1 <sup>A</sup> | 0.94                 | 0.750          | -0.32    | 0.65 – 1.36   | 0.88 (0.63 – 1.23)                 |
| aIOH at Wave 1 <sup>B</sup> | 0.89                 | 0.500          | -0.67    | 0.63 – 1.25   | 0.82 (0.61 – 1.11)                 |

Notes: N = 3,174.

Model 1 is unadjusted. Model 2 controls for age, gender, marital status, CAGE score and baseline depression scores. Model 3 controls for Model 2 covariates, as well as functional impairment, gait abnormalities, heart disease, low blood pressure, weight loss, physical activity, stroke, diabetes, Parkinson's disease, antidepressant use and cognitive impairment.

Abbreviations: sIOH = symptomatic initial orthostatic hypotension at 10 seconds; aIOH = asymptomatic initial orthostatic hypotension at 10 seconds; OR = Odds Ratio; CI = confidence interval.

A Drop in systolic blood pressure >40 mmHg or diastolic blood pressure >20 mmHG from baseline at 10 seconds post standing during active stand test with associated orthostatic symptoms. B Drop in systolic blood pressure >40 mmHg or diastolic blood pressure >20 mmHG from baseline at 30 seconds post standing during active stand test without associated orthostatic symptoms.

## **5.6 Discussion**

This study shows that in a large sample of non-depressed community-dwelling older people, participants with sOH-30 after standing had a twofold higher risk of incident clinically significant depressive symptoms during 4-year follow-up after controlling for covariates including cognitive impairment and antidepressant use. Average marginal effects scores demonstrate that, in a group of otherwise average individuals, sOH-30 at baseline increases the probability of incident depressive symptoms by 6%.

This is the first longitudinal study to investigate the relationship between OH and depressive symptoms (102). Our findings are supported by prior studies which identified a cross-sectional association between finometer-defined OH and LLD but were limited by small numbers and high prevalence of current antidepressant use amongst participants (187, 188). A larger cross-sectional study of the TILDA cohort also identified an association between current depression and symptomatic OH diagnosed with sphygmomanometer-based BP data (89).

While our findings are not sufficient to imply causation, OH-related cerebral hypoperfusion may represent the mechanism for this association. Orthostatic drops in BP are associated with higher burden of frontal WMH in older people with depression (189). Several studies have demonstrated loss of frontal lobe integrity in LLD (9, 33, 230). The frontal lobe is relatively sensitive to hypoperfusion (231) and age-related changes in cerebral perfusion are most marked in this region (77), increasing the likelihood that reductions in CBF due to OH would lead to loss of white matter integrity there. Damage to the frontal-subcortical pathway, which links the frontal lobe to the subcortex, can result in executive dysfunction as well as psychomotor retardation, loss of interest, and functional impairment, hallmarks of depression in later life (213). Prior studies have also identified an association between other conditions potentially caused by low BP and deficits in cerebral perfusion, including stroke, syncope and unexplained falls (13, 76, 232).

AOH-30 did not predict depression. There were no significant differences between those with sOH-30 and aOH-30 in terms of age, gender, cardiovascular disease or use of culprit medications. However the sOH-30 group had a lower nadir BP on active stand testing, as well as a more prolonged BP recovery, reflecting a greater degree of hypotensive burden, causing orthostatic symptoms, and potentially increasing the risk of cerebral hypoperfusion (99). IOH also did not predict incident depression. This is not surprising given prior evidence demonstrating that IOH does not increase the risk of falls in the same TILDA population (88).

and that while the IOH group had a profound initial drop in BP, in almost two thirds of participants with IOH BP had recovered to baseline by 30 seconds after standing.

After exclusion for baseline depression by CES-D, almost 9% of participants with OH-30 were prescribed antidepressants, three times more than those without OH-30. Antidepressants, particularly tricyclic antidepressants, increase the risk of OH and are prescribed regularly for indications other than depression, such as chronic pain or anxiety(233). We therefore reran our regression analyses to demonstrate that our findings were not significantly attenuated when antidepressant users were excluded. It is apparent therefore that this association is independent of antidepressant use.

Our findings also mirror those seen in studies of OH and dementia, where OH has also been shown to predict incident dementia in older people(86). There is a complex relationship between depression and dementia in later life with recent research suggesting that LLD represents a prodromal phase prior to the onset of clinically significant cognitive deficits(234). This is supported by the overlapping clinical features between LLD and early dementia, particularly vascular dementia, including executive dysfunction and apathy and our study suggests a potentially shared mechanistic pathway(213).

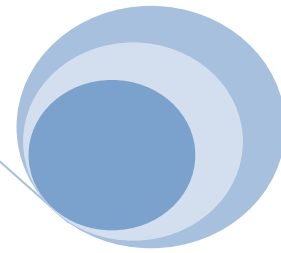
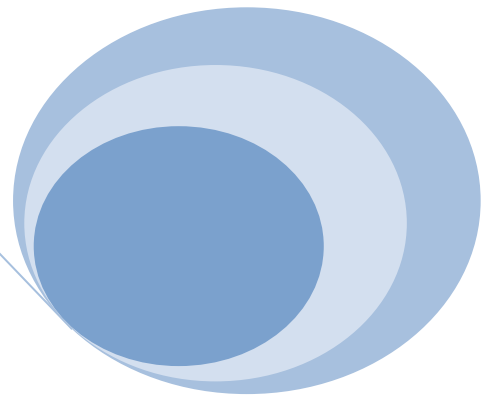
This study has some limitations which must be noted. Incident depression was defined by 8-item CES-D and not by gold standard psychiatric interview. The shortform CES-D-8 has been validated against the CES-D-20 within the TILDA population however(124). Several variables, including cardiovascular disease, are based on self-report and may therefore be limited by recall bias(235).

Additionally, while participants with pre-existing clinically diagnosed dementia were excluded at wave 1 from the TILDA study, it is well recognised that cognitive impairment is often undetected and under diagnosed(236). Furthermore, an MMSE cut-off score of 24, which we used in this study, may not be sensitive enough to detect cognitive impairment in a well older population(237). We therefore performed our regression analysis excluding all participants with MMSE<28 and sOH-30 remained a significant predictor of depression.

The strengths of this study include the large study sample, with detailed social and biological data, allowing us to robustly control for important covariates, as well as the continuous measurement of orthostatic BP, which is unique for a study of this scale.

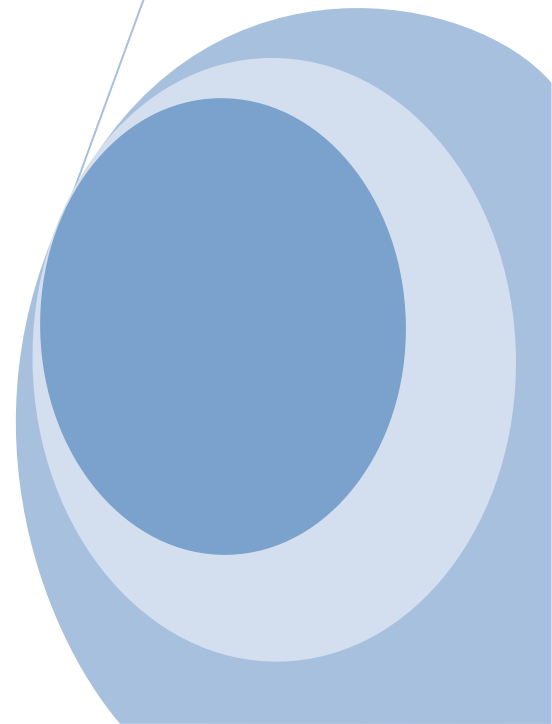
Depression confers significant disability on the older person, as well as an increased mortality risk(148). These findings are important because OH may therefore represent a potentially

modifiable risk factor for LLD. 40% of participants with OH-30 in this study were prescribed antihypertensive therapy; while almost one tenth were prescribed antidepressant medication, despite the absence of clinically significant depressive symptoms at baseline. Treatment of OH in the first instance often involves discontinuation of culprit medications(225). Increased awareness of the risks of over-treatment of BP in older people and resultant hypotension is imperative especially in the context of recent large international research advocating more aggressive BP lowering in this group(161).



## **CHAPTER 6:**

Study 3: How does Blood Pressure  
affect Frontal Lobe perfusion in  
Depressed Older People?



### **6.1 Key Findings**

- This study shows that older participants with depressive symptoms had lower frontal lobe perfusion measured by NIRS after standing, and that depressive symptoms were associated with a more significant drop in frontal lobe perfusion at both 30, 60 and 90 seconds.
- Findings remained robust after controlling for important covariates including prior stroke, heart disease and cognitive impairment.
- Further analyses found that this association was only persistent across time points in those with systolic BP < 120 mm Hg, suggesting that lower systolic BP in depressed individuals may be the predominant driver of this association.
- Given the recognised longitudinal association between lower BP and depression in older people, this may represent a potential therapeutic target for prevention of depression.
- This study also shows that it is feasible for a large population of older people to undergo bedside testing with NIRS for cerebral perfusion analysis. NIRS is non-invasive, portable and given the results we have demonstrated, could therefore potentially be used as a biomarker in LLD.
- This study was published in the British Journal of Psychiatry: DOI [10.1192/bjp.2018.288](https://doi.org/10.1192/bjp.2018.288).

## **6.2 Abstract**

### *Background*

Deficits in frontal lobe perfusion have been demonstrated in LLD, however studies to date have generally involved small numbers, used neuroimaging rather than bedside testing and have not controlled for important covariates. The aim of this study is to examine the association between depressive symptoms and frontal lobe perfusion during standing, in a large cohort of community-dwelling older people.

### *Methods*

Participants aged  $\geq 50$  years underwent continuous measurement of orthostatic BP by finometry and frontal lobe perfusion by NIRS. Depressive symptoms were assessed by the 8-item CES-D. Real-time frontal lobe cerebral oxygenation was measured by the Portalite System, detecting changes in frontal lobe perfusion and reporting a % TSI.

### *Results*

Almost 8% (209/2,616) had clinically significant depressive symptoms. Multilevel models demonstrated a significantly lower TSI in participants with depressive symptoms at both 60 and 90 seconds post-stand with coefficients of -0.43 (95% CI: -0.63 – -0.22) and -0.37 (95% CI: -0.57 – -0.16) respectively. Controlling for relevant covariates did not significantly attenuate these associations. After addition of systolic BP this association was no longer significant however, suggesting lower BP may modify this relationship.

### *Conclusions*

This study demonstrates that lower frontal lobe perfusion, related to lower values of baseline systolic BP, is associated with clinically significant depressive symptoms in a cohort of community-dwelling older people. Given the recognised longitudinal association between lower BP and depression in older people, this may represent a potential therapeutic target for prevention of incident depression.

### **6.3 Background**

Structural and functional changes in the frontal lobe have been implicated in LLD(33, 49).

Neuroimaging studies have demonstrated that older people with late onset depression have higher rates of frontal lobe atrophy than controls, as well as their older counterparts with earlier onset depression(105, 238). WMH, particularly those involving the frontal lobe, are closely associated with LLD and progression of WMH is associated with poorer response to treatment(44, 46).

It is proposed that these pathological changes in frontal lobe structure disrupt neural connections along frontostriatal circuits, which are particularly important in the regulation of mood and cognition(33, 49). This is supported by neuroimaging studies demonstrating loss of functional connectivity (239), and abnormal frontal lobe biochemistry (106), as well as neuropathological studies demonstrating a reduction in frontostriatal neuronal cell volume, in depressed older people (105, 107).

Clinically, depression in later life is associated with presentations such as executive dysfunction and apathy which are related to frontostriatal dysfunction(49, 213). Depressed older people have demonstrated poorer scores on formal frontal lobe-related cognitive tests compared to controls(49) and LLD is also closely associated with other clinical syndromes where frontostriatal connectivity has been implicated, including gait disorders, dementia and urinary incontinence(114).

The frontal lobe is particularly susceptible to damage by cerebral hypoperfusion(240)and conditions affecting CBF, such as systemic hypotension and OH, have been shown to increase the risk of incident depression in older people(241, 242).A hypothesised mechanism for this is via reduction in blood flow to the frontal lobe resulting in frontal WMHs and altered frontal lobe function(33).Cross-sectional SPECT and MRI studies have shown frontal lobe perfusion deficits in older depressed participants when compared to controls (243, 244)and prospectively, reduced global cerebral perfusion measured by TCD is a predictor of greater depressive symptomology in older people with heart failure at 1-year follow-up(71).

However, studies to date examining the association between frontal lobe cerebral perfusion and depression have involved relatively small numbers and did not control for important clinical conditions such as heart disease or stroke. Studies have also utilised imaging modalities such as MRI and SPECT rather than techniques such as NIRS.

NIRS provides a non-invasive index of cerebral perfusion, based on the finding that light in the near infra-red spectrum penetrates the skull and allows measurement of oxy- and deoxy-haemoglobin concentrations in the brain(245). It is used extensively in cardiac and other surgery to measure intra-operative cerebral perfusion on a continuous basis and is now available outside these setting as a validated, portable, non-invasive bedside test(246).

The aim of this study therefore is to examine the association between clinically significant depressive symptoms and frontal lobe cerebral perfusion, measured by NIRS, in a large cohort of community-dwelling older people, embedded within TILDA. Furthermore, we will determine how conditions such as OH and hypotension modify this relationship. The comprehensive TILDA dataset also allows us to control for important competing covariates such as heart disease, stroke and antidepressant use.

## **6.4 Methods**

### *Ethics*

The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki. All assessments were carried out by trained research nurses.

### *Study Design*

This is a cross-sectional study examining the association between clinically significant depressive symptoms and frontal lobe cerebral perfusion, measured by NIRS.

This study is embedded within TILDA, a large population-based study of a nationally representative sample of community dwelling older adults aged 50 years and over, with an initial study population of over 8,000 participants.

The TILDA study design has been outlined previously(117).We analysed data from the third wave of TILDA collected between 2014 and 2015. Participants were included in this study if they were aged 50 years or more, and underwent a complete health assessment at wave 3 including measurement of orthostatic BP, frontal lobe perfusion by NIRS and screening for depressive symptoms.

### *Cerebral Perfusion and Orthostatic Blood Pressure*

Real-time Frontal lobe cerebral oxygenation was measured by the Artinis Portalite System, a portable continuous wave NIRS system, which uses spatially resolved spectroscopy, reporting absolute values, developed to measure cerebral perfusion(128). The NIRS technique, first described by Jobsis (129) is based on the property of human tissue being relatively transparent to light in the near infra-red spectrum; by measuring changes in light absorption at different wavelengths, the oxygenation of tissue can be monitored continuously (130).

An optical sensor is placed on the participant's forehead, on the equivalent of the FP1 position in the international 10-20 electrode system, to measure changes in frontal lobe oxyhemoglobin and deoxyhemoglobin continuously. Tissue Saturation Index (TSI) was the primary measure used in this study, and is defined as  $(\text{oxyhemoglobin}) / (\text{oxyhemoglobin} + \text{deoxyhemoglobin}) \times 100$  and expressed as a percentage(131).

Continuous orthostatic BP was measured in parallel with this by active stand using a Finometer® Midi as described previously(126). Briefly, participants lay in the supine position for 10 minutes in a quiet room, before standing in a timely manner (<5 seconds), and were aided by a research nurse to mobilize as necessary. Baseline values for TSI and BP were an average of the readings between 30-60 seconds prior to standing. After standing, sBP, dBP, heart rate and oxy- and deoxyhemoglobin and TSI were monitored for a further 180 seconds. Throughout the recording, subjects stood quietly.

OH at was defined as a drop in systolic BP  $\geq 20$  mmHg or drop in diastolic BP  $\geq 10$  mmHg at 30 seconds compared to baseline BP(78). Signal processing included a median average filter and 10 second moving average filter applied to both BP and NIRS data. The sampling rate of the output data was 1 Hz. TSI was recorded continuously during the active stand but as OH is typically measured at 30, 60 and 90 seconds, we focused primarily on TSI at these time points in this study.

### *Depression*

Depressive symptoms were assessed using the CES-D-8. A score  $\geq 9$  was used to define those with clinically significant depressive symptoms (125). This shortform version of the longer 20-item scale was utilised in the TILDA study in order to reduce the time taken to conduct participant assessments, as well as to reduce respondent burden and fatigue, and previous work has confirmed its reliability in comparison to the CES-D-20 in terms of internal consistency and factor structure within the TILDA cohort(124). This was performed generally within one month of measurement of cerebral perfusion and orthostatic BP.

### *Other Measures*

Detailed social and biological data were also collected. Seated systemic BP was measured using an OMRON™ digital automatic BP monitor. Chronic disease burden was defined as the number of chronic illnesses from the following list: liver disease, kidney disease, lung disease, cancer, arthritis and diabetes. Cardiac disease was defined as self-report of angina, prior myocardial infarct or cardiac failure. Self-report was also elicited for prior stroke. Cognitive impairment was defined as a MMSE Score  $\leq 24$ .

Medication records were examined using ATC codes, which are assigned to the active substances contained in medicines by the World Health Organisation based on the therapeutic indication for the medicine, e.g. all antidepressants are listed under the ATC code N06A. Medication records were examined specifically for antidepressant use (ATC codes N06AB

(selective serotonin reuptake inhibitors), N06AX16 (venlafaxine), N06AX21 (duloxetine), N06AX11 (mirtazapine), N06AX22 (agomelatine) and N06AX12 (bupropion)), as well as antihypertensive use (ATC codes C02 (antihypertensives), C03 (diuretics), C07 (beta blockers), C08 (calcium channel blockers) and C09 (Agents acting on the renin–angiotensin system)).

### *Statistical Analysis*

Data were analysed using Stata 14 (Statacorp).

Normally distributed continuous variables were described as means and standard deviations and compared using Student's t-test. Categorical variables were compared using the chi-square test.

Multilevel models with TSI as the dependent variable were used to compare TSI data across specific time points after standing, i.e. 30, 60 and 90 seconds, by depressive symptoms. These models assess the effect of the two-way interaction between depressive symptoms and time (Depressive Symptoms # Time) on TSI which accounts for the fact that TSI at 60 seconds is significantly influenced by TSI at 30 seconds and so on.

Models were adjusted for covariates, which were chosen a priori, based on their hypothesised role in modifying this relationship. Two models were tested initially: the first model was unadjusted; the second model adjusted for age, sex, height and weight and for clinical covariates such as cardiac disease, other chronic diseases, cognitive impairment, stroke and antidepressant use.

Further post-hoc analyses were undertaken by testing further models by adding OH and systolic BP separately to assess the role BP behaviour had in modifying the relationship between depression and TSI. This allows us to analyse the three-way interaction (e.g. Depressive Symptoms # Time # Sys. BP), which allows us to see whether the association between the two-way interaction of Depressive Symptoms # Time and TSI differs depending on systolic BP or OH.

In order to ensure findings were independent of antidepressant use, subgroups of participants taking these medications were excluded from the analysis and models were rerun in order to ensure that findings were not significantly different when these groups were omitted.

A p value  $\leq 0.05$  was considered statistically significant.

## 6.5 Results

Almost 8% (209/2,616) of participants had significant depressive symptoms. 11% of participants were aged 75 years or more, 34% were aged 65 to 74 years and 55% were aged 50-64 years.

Depressed participants were more likely to be female and taking antidepressant medication. Baseline characteristics by depression status are shown in table 6.1.

**Table 6.1: Baseline Characteristics of study sample by Depressive Symptoms**

|                                                   | Not depressed<br>n = 2,407 | Depressed<br>n = 209  | Statistical Test                  |
|---------------------------------------------------|----------------------------|-----------------------|-----------------------------------|
| <b>Age (years), Mean (95% CI)</b>                 | 64.5 (64.2 – 64.8)         | 63.5 (62.4 – 64.6)    | t = 1.75; p = 0.0796; d = 0.13    |
| <b>Females, % (n)</b>                             | 53 (1,282/2,407)           | 62 (129/209)          | X <sup>2</sup> =5.54; p = 0.019   |
| <b>Sys. BP, (Mean) mmHg (95% CI) <sup>A</sup></b> | 141.0 (140.2 – 141.9)      | 140.5 (140.2 – 141.9) | t = 0.33; p = 0.7429; d = 0.10    |
| <b>Cardiac Disease: <sup>B</sup></b>              |                            |                       |                                   |
| - Myocardial Infarct, % (n)                       | 4 (99/2,407)               | 4 (9/209)             | X <sup>2</sup> =0.02; p = 0.893   |
| - Cardiac Failure, % (n)                          | 1 (12/2,407)               | 1 (3/209)             | X <sup>2</sup> =2.96; p = 0.085   |
| - Angina, % (n)                                   | 3 (80/2,407)               | 6(12/209)             | X <sup>2</sup> =3.31; p = 0.069   |
| <b>Chronic Disease Number: <sup>C</sup></b>       |                            |                       |                                   |
| - 0, % (n)                                        | 63 (1,515/2,407)           | 46 (96/209)           | X <sup>2</sup> =24.13; p < 0.001  |
| - 1, % (n)                                        | 32 (770/2,407)             | 45 (95/209)           |                                   |
| - 2, % (n)                                        | 5 (114/2,407)              | 8 (17/209)            |                                   |
| - 3, % (n)                                        | 0 (33/2,407)               | 0 (1/209)             |                                   |
| <b>Prior stroke, % (n)<sup>D</sup></b>            | 1 (32/2,407)               | 1 (3/209)             | X <sup>2</sup> =0.02; p = 0.898   |
| <b>MMSE, Mean (95% CI)</b>                        | 29.0 (29.0 – 29.1)         | 28.9 (28.8 – 29.1)    | t = 0.87; p = 0.3793; d = 0.06    |
| <b>Cognitive Impairment, % (n) <sup>E</sup></b>   | 1 (32/2,407)               | 1 (3/209)             | X <sup>2</sup> =0.02; p = 0.898   |
| <b>Orthostatic Hypotension, % (n)<sup>F</sup></b> |                            |                       |                                   |
| - 30 sec.                                         | 14 (327/2,407)             | 12 (26/209)           | X <sup>2</sup> =0.22; p = 0.642   |
| - 30 & 60 sec.                                    | 7(163/2,407)               | 5 (10/209)            | X <sup>2</sup> =1.23; p = 0.267   |
| - 30, 60 & 90 sec.                                | 4 (100/2,407)              | 3 (7/209)             | X <sup>2</sup> =0.32; p = 0.573   |
| <b>Antidepressant Use, % (n) <sup>G</sup></b>     | 5 (117/2,407)              | 21 (43/209)           | X <sup>2</sup> = 82.69; p < 0.001 |
| <b>Antihypertensive Use, % (n) <sup>H</sup></b>   | 37 (883/2,407)             | 39 (81/209)           | X <sup>2</sup> =0.35; p = 0.552   |

Notes:

Categorical variables were compared using the chi-square test. Normally distributed continuous variables were analysed using the student t-test.

Abbreviations: CI = confidence interval; Sys. BP = systolic blood pressure. MMSE = Mini Mental State Examination; d denotes Cohen's d test for effect size.

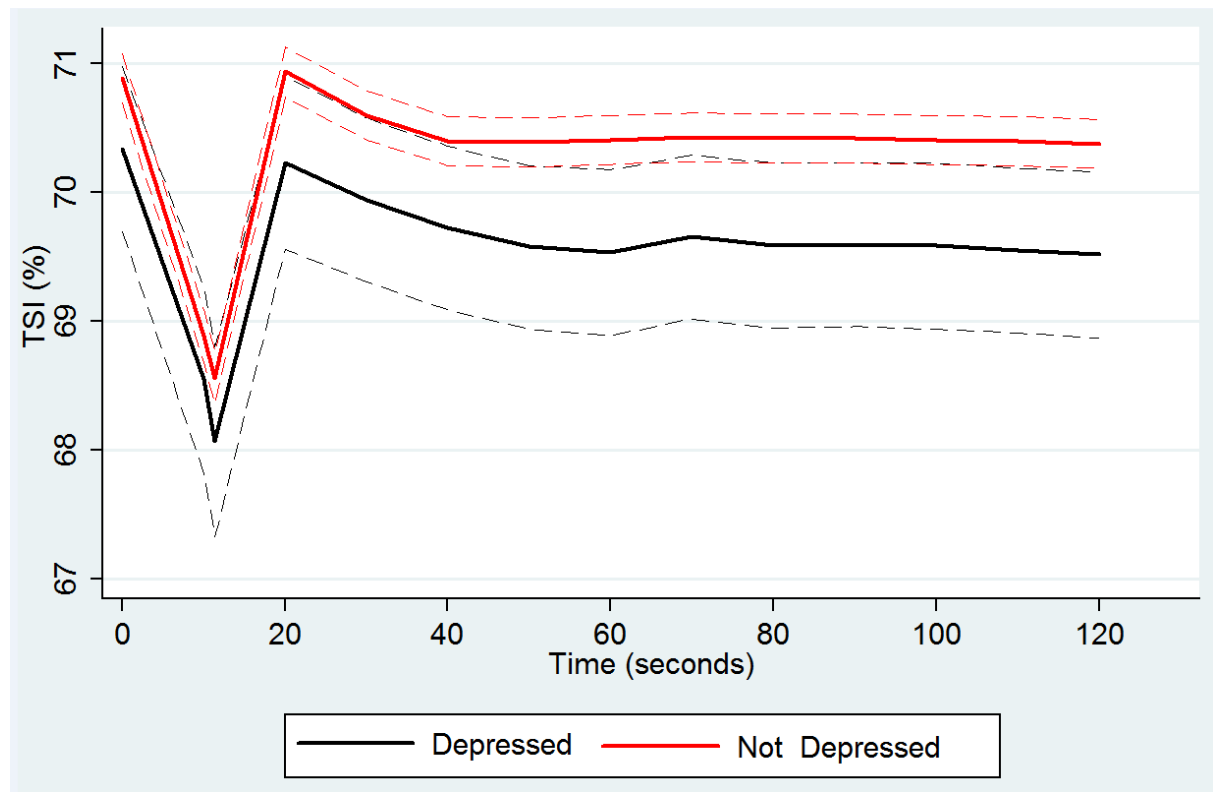
A Blood pressure measured in seated position using Omron digital automatic BP monitor; B Cardiac Disease defined as self-report of heart attack, heart failure or angina; C Number of chronic diseases from the following list: liver disease, kidney disease, lung disease, cancer, arthritis and diabetes; D Stroke defined as self-report of prior stroke; E Cognitive impairment defined as Mini Mental State Examination

Score  $\leq 24$ ; F Orthostatic Hypotension defined as drop in systolic blood pressure  $\geq 20$  mmHg or drop in diastolic blood pressure  $\geq 10$  mmHg at 30 seconds, 30 and 60 seconds and 30, 60 and 90 seconds respectively, compared to baseline BP; G Antidepressants are those with Anatomical therapeutic classification codes N06AB, N06AX16, N06AX21, N06AX11, N06AX22 and N06AX12; H Antihypertensives are those with Anatomical therapeutic classification codes C02, C03, C07, C08 and C09.

There were no significant differences between groups in terms of prevalence of cardiac disease, BP, history of stroke and current antihypertensive drug use.

Figure 6.1 demonstrates mean absolute TSI after standing by depressive symptoms, while figure 6.2 presents the mean TSI drop from baseline by depressive symptoms.

**Figure 6.1: Tissue Saturation Index (TSI) post standing stratified by depression status**



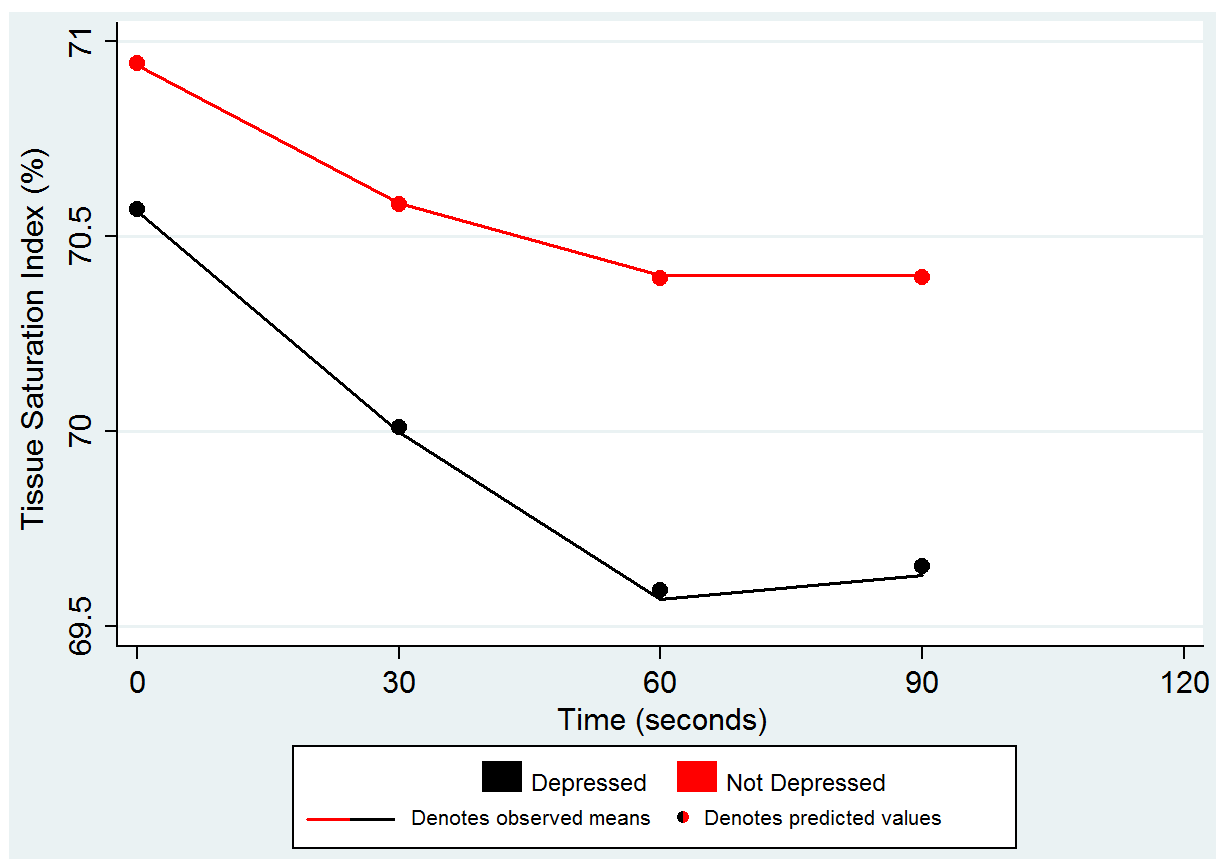
Notes:

N = 2,616 (Depressed = 209; Non-depressed = 2,407). TSI = Tissue Saturation Index, measured by Near-infrared spectroscopy.

Solid lines indicate mean TSI, while dashed lines indicate 95% confidence interval, for given time point post standing. TSI at 0 seconds = baseline TSI, i.e. the average of the readings between 30-60 seconds prior to standing. Depression status based on 8-item Centre for Epidemiological Studies Depression Scale.

As presented in table 6.2, the time x group interactions revealed significantly lower TSI in participants with depressive symptoms compared to the non-depressed group at both 60 and 90 seconds post-stand with coefficients of -0.43 (95% CI: -0.63 – -0.22),  $z=-4.11$ ,  $p<0.001$  and 0.37 (95% CI: -0.57 – -0.16),  $z=-3.54$ ,  $p<0.001$  respectively. Controlling for age, sex and clinical covariates such as cardiac disease, stroke and antidepressant use did not significantly attenuate these associations. Depressive symptoms were not associated with TSI at 30 seconds post stand in unadjusted models.

**Figure 6.2: Drop in Tissue Saturation Index from baseline after standing by Depression status**



Notes:

$N = 2,616$  (Depressed = 209; Non-depressed = 2,407).

Abbreviations: TSI = Tissue Saturation Index.

TSI measured by Near-infrared spectroscopy at baseline (lying down, denoted as 0 seconds, an average of the readings between 30-60 seconds prior to standing) and 30, 60 and 90 seconds post standing. Results from multilevel modelling with TSI as the dependent variable nested within participant.

Full outputs from regression models are shown in table 6.2.

**Table 6.2: Multilevel linear regression model with Tissue Saturation Index as dependent variable, Model 2**

| <b>TSI</b>                                  | <b>Coefficient (95% CI)</b> | <b>SE</b> | <b>z</b> | <b>p</b> |
|---------------------------------------------|-----------------------------|-----------|----------|----------|
| <b>Model 2:</b>                             |                             |           |          |          |
| <b>Depression <sup>A</sup></b>              | -0.21 (-0.91 – 0.48)        | 0.35      | -0.60    | 0.549    |
| <b>Time: <sup>B</sup></b>                   |                             |           |          |          |
| - 30 seconds                                | -0.35 (-0.41 - -0.30)       | 0.03      | -11.94   | <0.001   |
| - 60 seconds                                | -0.54 (-0.60 - -0.48)       | 0.03      | -18.21   | <0.001   |
| - 90 seconds                                | -0.54 (-0.60 - -0.48)       | 0.03      | -18.18   | <0.001   |
| <b>Depression # Time</b>                    |                             |           |          |          |
| - 30 seconds                                | -0.21 (-0.42 - -0.01)       | 0.11      | -2.01    | 0.044    |
| - 60 seconds                                | -0.46 (-0.66 - -0.25)       | 0.11      | -4.33    | <0.001   |
| - 90 seconds                                | -0.39 (-0.60 - -0.19)       | 0.11      | -3.75    | <0.001   |
| <b>Female Sex</b>                           | -0.03 (-0.57 – 0.52)        | 0.28      | -0.10    | 0.918    |
| <b>Age: <sup>C</sup></b>                    |                             |           |          |          |
| - 65 – 74 years                             | -0.14 (-0.56 – 0.27)        | 0.21      | -0.67    | 0.504    |
| - ≥ 75 years                                | -0.43 (-1.05 – 0.19)        | 0.32      | -1.35    | 0.176    |
| <b>Height (cm)</b>                          | 0.02 (-0.01 – 0.05)         | 0.02      | 1.21     | 0.185    |
| <b>Weight (kg)</b>                          | 0.02 (0.00 – 0.03)          | 0.01      | 2.53     | 0.011    |
| <b>Chronic Disease Number: <sup>D</sup></b> |                             |           |          |          |
| - 1                                         | -0.26 (0.66 – 0.15)         | 0.21      | -1.24    | 0.217    |
| -2                                          | -0.65 (-1.51 – 0.22)        | 0.44      | -1.46    | 0.145    |
| -3                                          | -2.18 (-5.25 – 0.90)        | 1.57      | -1.38    | 0.166    |
| <b>Cognitive Imp. <sup>E</sup></b>          | 0.69 (-0.95 – 2.33)         | 0.84      | 0.83     | 0.409    |
| <b>Cardiac Disease <sup>F</sup></b>         | -0.73 (-1.49 - -0.03)       | 0.39      | -1.87    | 0.061    |
| <b>Stroke <sup>G</sup></b>                  | 1.68 (-1.39 – 4.75)         | 1.57      | 1.07     | 0.285    |
| <b>Antidepressant <sup>H</sup></b>          | -0.30 (-1.08 – 0.47)        | 0.40      | -0.76    | 0.445    |
| <b>Antihypertensive <sup>I</sup></b>        | -0.29 (-0.71 – 0.12)        | 0.21      | -1.39    | 0.166    |
| <b>Random-effects Parameters:</b>           |                             |           |          |          |
|                                             | <b>Estimate (95% CI)</b>    | <b>SE</b> |          |          |
| <b>Variance of Constant</b>                 | 21.6 (20.4 – 22.8)          | 0.61      |          |          |
| <b>Variance of Residual</b>                 | 1.04 (1.00 – 1.07)          | 0.02      |          |          |

Notes: N = 2,616. Results from multilevel modelling with TSI as the dependent variable. Abbreviations: TSI = tissue saturation index measured by near-infrared spectroscopy; CI = confidence interval; SE = standard error; Cognitive Imp. = cognitive impairment.

A Depression defined as 8-item Centre for Epidemiological Studies Depression Scale ≥ 9; B Reference value for Time is baseline, i.e. an average of the readings between 30-60 seconds prior to standing; C reference value for age is 50-64 years; D Defined as number of self-reported chronic illnesses from the following list: lung disease, liver disease, chronic kidney disease, arthritis, cancer and diabetes mellitus. Reference value =0 chronic diseases; E Cognitive impairment defined as Mini Mental State Examination Score ≤ 24; F Cardiac Disease defined as self-report of angina, heart attack or heart failure; G Stroke defined as self-report of prior stroke; H Antidepressant denotes prescribed antidepressant treatment (Anatomical therapeutic classification codes N06AB, N06AX16, N06AX21, N06AX11, N06AX22,

*N06AX12*); *I* Antihypertensive denotes prescribed Antihypertensive medication (Anatomical therapeutic classification codes C02, C03, C07, C08 and C09).

The Depressive Symptoms # Time interaction was not modified by OH, suggesting that co-existing OH does not influence the relationship between depressive symptoms and TSI across these time points. See table 6.3, model 3.

After addition of systolic BP to Model 5 however, Depressive Symptoms # Time interaction was no longer significant, suggesting that systolic BP may modify the association between depressive symptoms and frontal lobe perfusion. At 30, 60 and 90 seconds post-stand, there is a significant drop in TSI in those who had depressive symptoms with systolic BP less than 120 mm Hg, compared to non-depressed participants with normal BP. This is also the case for those who have depressive symptoms with high systolic BP values ( $\geq 160$  mm Hg) at 30 seconds. See table 6.3, model 4.

Table 6.3 also demonstrates that findings remained robust after rerunning analyses with exclusion of all participants taking antidepressant medication.

**Table 6.3: Multilevel linear regression models with Tissue Saturation Index as dependent variable**

| TSI                                                        | Coefficient (95% CI)  | SE   | z     | p      |
|------------------------------------------------------------|-----------------------|------|-------|--------|
| <b>Model 1:</b>                                            |                       |      |       |        |
| <b>Depressive Symptoms # Time <sup>A</sup></b>             |                       |      |       |        |
| - 30 seconds                                               | -0.20 (-0.40 – 0.01)  | 0.10 | -1.89 | 0.058  |
| - 60 seconds                                               | -0.43 (-0.63 - -0.22) | 0.10 | -4.11 | <0.001 |
| - 90 seconds                                               | -0.37 (-0.57 - -0.16) | 0.10 | -3.54 | <0.001 |
| <b>Model 2:</b>                                            |                       |      |       |        |
| <b>Depressive Symptoms # Time <sup>A</sup></b>             |                       |      |       |        |
| - 30 seconds                                               | -0.21 (-0.42 - -0.01) | 0.11 | -2.01 | 0.044  |
| - 60 seconds                                               | -0.46 (-0.66 - -0.25) | 0.11 | -4.33 | <0.001 |
| - 90 seconds                                               | -0.39 (-0.60 - -0.19) | 0.11 | -3.75 | <0.001 |
| <b>Random-effects Parameters:</b>                          |                       |      |       |        |
|                                                            | Estimate (95% CI)     | SE   |       |        |
| Variance of Constant                                       | 21.6 (20.4 – 22.8)    | 0.61 |       |        |
| Variance of Residual                                       | 1.04 (1.00 – 1.07)    | 0.02 |       |        |
| <b>Model 3: Orthostatic Hypotension added to Model 2</b>   |                       |      |       |        |
| <b>Depressive Symptoms # Time # OH <sup>B</sup></b>        |                       |      |       |        |
| - 30 seconds                                               | 0.28 (-0.35 – 0.90)   | 0.32 | 0.88  | 0.381  |
| - 60 seconds                                               | -0.00 (-0.62 – 0.62)  | 0.32 | -0.00 | 0.998  |
| - 90 seconds                                               | -0.04 (-0.67 – 0.58)  | 0.32 | -0.14 | 0.889  |
| <b>Model 4: Systolic Blood Pressure added to Model 2</b>   |                       |      |       |        |
| <b>Depressive Symptoms # Time # Sys. BP <sup>C</sup></b>   |                       |      |       |        |
| - 30 sec, Sys. BP < 120 mm Hg                              | -0.68 (-1.17 - -0.18) | 0.25 | -2.67 | 0.008  |
| - 30 sec, Sys. BP 140 – 159 mm Hg                          | -0.30 (-0.83 – 0.24)  | 0.27 | -1.09 | 0.276  |
| - 30 sec, Sys. BP ≥ 160 mm Hg                              | -1.18 (-2.05 - -0.31) | 0.44 | -2.66 | 0.008  |
| - 60 sec, Sys. BP < 120 mm Hg                              | -0.53 (-1.03 - -0.03) | 0.25 | -2.09 | 0.036  |
| - 60 sec, Sys. BP 140 – 159 mm Hg                          | -0.09 (-0.62 – 0.45)  | 0.27 | -0.31 | 0.754  |
| - 60 sec, Sys. BP ≥ 160 mm Hg                              | -0.76 (-1.62 – 0.11)  | 0.44 | -1.70 | 0.088  |
| - 90 sec, Sys. BP < 120 mm Hg                              | -0.54 (-1.03 - -0.04) | 0.25 | -2.13 | 0.033  |
| - 90 sec, Sys. BP 140 – 159 mm Hg                          | -0.12 (-0.65 – 0.42)  | 0.27 | -0.42 | 0.671  |
| - 90 sec, Sys. BP ≥ 160 mm Hg                              | -0.45 (-1.32 – 0.41)  | 0.44 | -1.03 | 0.305  |
| <b>Model 5: Model 2 with Antidepressant Users excluded</b> |                       |      |       |        |
| <b>Depressive Symptoms # Time <sup>D</sup></b>             |                       |      |       |        |
| - 30 seconds                                               | -0.24 (-0.47 - -0.01) | 0.12 | -2.04 | 0.041  |
| - 60 seconds                                               | -0.45 (-0.68 - -0.22) | 0.12 | -3.88 | <0.001 |
| - 90 seconds                                               | -0.40 (-0.63 - -0.17) | 0.12 | -3.42 | 0.001  |

Notes: N = 2,616. Results from multilevel modelling with TSI as the dependent variable.

Model 1 is unadjusted; Model 2 controls for age, sex, height, weight, number of chronic diseases, cognitive impairment, cardiovascular disease, stroke, antidepressant and antihypertensive use.

A Depressive Symptoms # Time denotes the two-way interaction between depressive symptoms and time after standing, allowing us to account for the fact that TSI at 60 seconds after standing is significantly influenced by TSI at 30 seconds and so on.

*B Depressive Symptoms # Time # OH denotes the three-way interaction between depressive symptoms, time after standing and OH and shows that the effect of the two-way interaction between depressive symptoms and time on TSI is not modified by the presence or absence of OH.*

*C Depressive Symptoms # Time # Sys. BP denotes the three-way interaction between depressive symptoms, time and systolic BP and demonstrates that the effect of the two-way interaction between depression and time on TSI is significantly affected by systolic BP, i.e. it is only persistently significant (at 30, 60 and 90 seconds) in those with systolic BP < 120 mm Hg.*

*D Depressive Symptoms # Time demonstrates that results are not significantly changed when antidepressant users are excluded from analyses.*

*Abbreviations: TSI = Tissue Saturation Index; CI = confidence interval; OH = orthostatic hypotension; Sys. BP = systolic blood pressure. Orthostatic Hypotension defined as drop in systolic blood pressure  $\geq 20$  mmHg or drop in diastolic blood pressure  $\geq 10$  mmHg at either 30, 60 or 90 seconds post stand, compared to baseline BP; Systolic blood pressure measured twice in seated position using Omron digital cuff with average of values then taken. Reference value is systolic blood pressure 120-139 mm Hg.*

## **6.6 Discussion**

This study shows that, in a cohort of community-dwelling older people, participants with depressive symptoms had lower frontal lobe perfusion measured by NIRS after standing, and that depressive symptoms were associated with a more significant drop in frontal lobe perfusion at both 30, 60 and 90 seconds, when controlling for important covariates including prior stroke, heart disease and cognitive impairment.

Further analyses found that this association was not modified significantly by OH and was also independent of antidepressant use. However, addition of systolic BP to the analysis demonstrated that the association between depressive symptoms and TSI was only persistent across time points in those with systolic BP < 120 mm Hg, suggesting that lower systolic BP in depressed individuals may be the predominant driver of this association.

While the degree of drop in TSI we demonstrate in this study is relatively small (0.5 – 1%), it is likely to be significant, given that prior work has shown that patients with spontaneous vasovagal syncope while undergoing tilt table testing had a change in TSI of 4.5% (+/- 3.0%)(247), and that the changes observed in this study are provoked only by changing from a supine to standing position, which is likely to occur multiple times per day / week.

These findings are supported by prior neuroimaging studies showing a similar association between LLD and both global and frontal cerebral perfusion(241, 242). Smaller studies utilizing NIRS have also demonstrated similar disparities between depressed and non-depressed participants when undertaking cognitive tasks(248, 249). Our findings are cross-sectional however and the direction of the relationship between frontal lobe cerebral perfusion and depressive symptoms remains uncertain, with limited longitudinal analyses to date.

There is also some evidence that remission of depression leads to subsequent improvements in CBF in specific brain regions, including the frontal lobe, suggesting that frontal lobe perfusion deficits may form part of the clinical syndrome of depression in later life(250). Rather than representing a factor in the aetiology of depression, it may be that these deficits are related to reduced demand in the context of frontal hypoactivity, and that they may respond to appropriate therapy, such as antidepressants or electroconvulsive therapy(251, 252). Furthermore, the disparity in frontal lobe perfusion between depressed and non-depressed participants that we have demonstrated is significant only when standing, and not at rest. This may be related to the fact that when we stand, BP and therefore cerebral perfusion generally drop, and while baroreflexes act to return these to baseline, blood flow is

preferentially directed towards the most metabolically active brain regions and given the reduced frontal lobe activity seen in depression, blood flow may be compromised there temporarily.

Conversely, there is also some evidence that cerebral perfusion deficits may have a role in the aetiology of depression in later life. WMH have been implicated in LLD and it has been shown that these lesions can be caused by strategic deficits in cerebral perfusion(253). Depression has been identified as a potential prodromal feature of dementia and pathological changes in brain perfusion have also been identified during this prodrome(254). Depression in later life has also been independently associated with other conditions where global cerebral hypoperfusion occurs, including unexplained falls and syncope(75, 76). Additionally, conditions causing global cerebral hypoperfusion, such as OH or chronically low BP, have been shown to increase the risk of incident depression in older people(102).

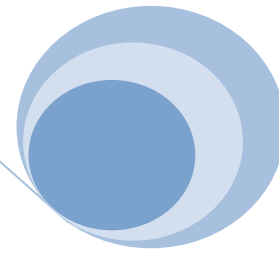
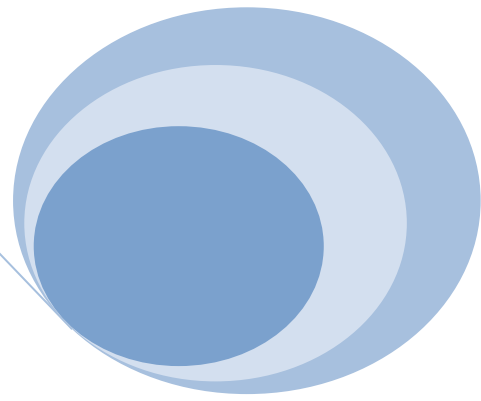
Understanding the nature of the link between incident depression and cerebral perfusion is important because CBF is potentially modifiable. Factors such as alcohol intake, BP, and cognitive training may influence CBF(255-257). Exercise has also been shown to enhance CBF in older people, as well as improving remission rates in LLD when added to standard therapy(258). Other factors we have shown in this study that are independently associated with frontal lobe perfusion include heart disease and higher weight. Lower BP, as well as OH, is significantly associated with lower frontal lobe TSI, while higher values of systolic BP are also associated with higher TSI values at 90 seconds after standing.

There are some limitations of this study which should be noted. Depressive symptoms were assessed with the CES-D-8 rather than the gold standard structured psychiatric interview. The 8-item CES-D has been well validated in the TILDA population however(125). Furthermore, data is cross-sectional with no prospective follow-up to determine a longitudinal relationship between cerebral perfusion and depressive symptoms. Information regarding chronic illnesses such as diabetes or stroke are based on self-report and may therefore be subject to self-report bias and under-reporting. Importantly, while we consider that cerebral hypoperfusion may cause frontal white matter disease we do not have access to structural neuroimaging, such as MRI which would help confirm this association. Prior studies have demonstrated a significant association between cerebral perfusion and WMH burden however(253).

The strengths of this study include the well-described large population-based cohort of older people involved. This is the largest study to date examining the association between NIRS and

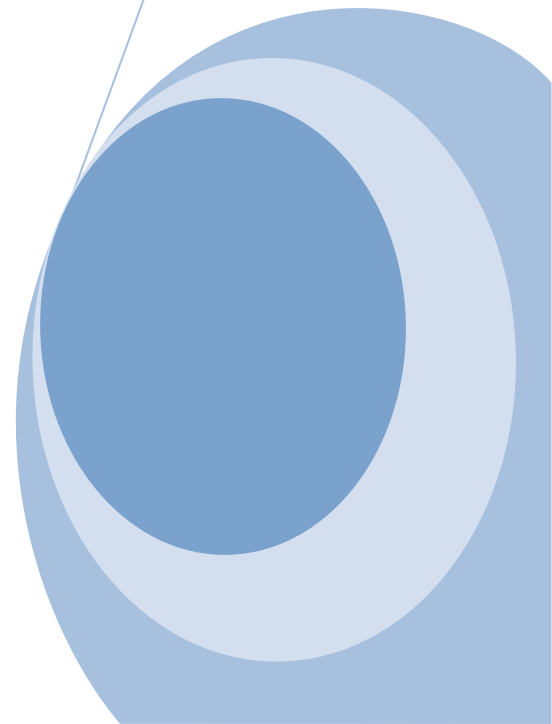
depressive symptoms in older people and controls for important covariates such as cardiovascular disease and antidepressant use, which has not been a feature of studies, including those using neuroimaging techniques, up to now. This study also shows that it is feasible for a large population of older people to undergo bedside testing with NIRS for cerebral perfusion analysis. NIRS is non-invasive, portable and given the results we have demonstrated, could therefore potentially be used as a biomarker of either risk or response to treatment in LLD.

In conclusion, we have demonstrated that lower frontal lobe perfusion, related to lower baseline systolic BP, is associated with clinically significant depressive symptoms in a cohort of community-dwelling older people. Given the recognised longitudinal association between lower BP and depression in older people, this may represent a potential therapeutic target for prevention of incident depression.



## **CHAPTER 7:**

Study 4: How does Blood Pressure  
affect Cerebral White Matter  
Hyperintensity Burden in Depressed  
Older People?



### **7.1 Key Findings**

- In line with prior studies, older people with depressive symptoms had a significantly higher burden of cerebral WMH, measured by Scheltens Score.
- This association is independent of age, sex, heart disease, stroke, cognition and antidepressant use.
- However, when assessed alongside orthostatic BP and systemic BP, this association only remained robust in those where depressive symptoms co-existed with lower systolic BP (< 130 mm Hg) or with OH during an active stand.
- These findings support the hypothesis that lower BP, either systemic or orthostatic, may increase the risk of depression by causing strategic WMH due to cerebral hypoperfusion.
- These findings are important as WMH burden is strongly associated with both incidence and prognosis of LLD and identifying the processes that lead to WMH accumulation and progression in depression is crucial in order to inform strategies aimed at preventing and ameliorating LLD.

## **7.2 Abstract**

### *Background*

Cerebral WMH burden is a key biological risk factor underpinning LLD and cerebral hypoperfusion has been identified as an important cause of WMH.

The aim of this study therefore is to clarify if OH and lower systemic BP, both of which cause reduced CBF, modify the relationship between depressive symptoms and cerebral white matter disease in a cohort of community-dwelling older people aged  $\geq 70$  years.

### *Methods*

This study uses data from wave 3 of TILDA collected between 2014 and 2015. Participants were included if they were aged  $\geq 70$  years and had undergone assessment for depressive symptoms, brain MRI, as well as other cardiovascular assessments.

Depressive symptoms were measured using the CES-D-8.

MRI was performed using a 3T scanner. Scheltens Score was used by a trained radiologist in order to calculate overall WMH burden.

Orthostatic BP was measured by active stand using a Finometer and OH was defined as a drop in sBP  $\geq 20$  mmHg or drop in diastolic BP  $\geq 10$  mmHg at 30, 60 or 90 seconds post standing. Systemic BP was measured in seated position using Omron digital cuff.

### *Results*

Participants with depressive symptoms (8%, 16/202) had a significantly higher burden of WMH, as measured by Scheltens Score (14.6 (95% CI: 11.0 – 18.2) vs. 11.0 (95% CI: 10.1 – 11.8);  $p = 0.0211$ ).

Two-way interaction models demonstrated that the association between depressive symptoms and WMH burden is significant only in those with co-existing OH. Similarly, the two-way interaction between depressive symptoms and sBP shows that this association remains statistically significant only in those with both depressive symptoms and lower sBP, i.e.  $< 130$  mm Hg.

### *Conclusion*

This study demonstrates that depressive symptoms are associated with cerebral WMH in a cohort of community-dwelling people aged  $\geq 70$  years but that this relationship is modified by co-existing OH or lower sBP.

Identifying the processes that lead to WMH accumulation and progression in depression is crucial in order to inform strategies aimed at preventing and ameliorating LLD.

### **7.3 Background**

LLD is a potent risk factor for functional decline, admission to residential care and early death(155). Given the challenges involved in treating LLD, including the fact that the majority of older adults living with LLD are undiagnosed (11), prevention is a priority and the identification of important risk factors is therefore crucial.

Cerebral white matter disease, reflected by WMH burden on brain MRI, is a key biological risk factor underpinning LLD(41, 42).

WMH burden independently predicts incident late life depressive symptoms(39), while older people with late onset depression have WMH burden scores 0.7-0.8 standard deviations higher than their peers with earlier-onset depression (44). Greater progression of WMH is associated with poorer treatment response during both short (12 weeks) and longer term (2 years) interval follow-up (37, 45).

WMH may interfere with and disrupt important frontal–subcortical–limbic networks involved in mood regulation(33). Strategically located WMH may therefore explain differences in clinical presentation in LLD. For example, WMH burden in specific brain regions correlates with executive dysfunction and processing speed in depressed older people (52), while further studies have demonstrated an association between depression and other conditions associated with WMH in later life, including urinary incontinence (259)and gait disorders(260).

Several pathophysiological causes of WMH have been suggested (58)including reduced CBF(59). Cerebral hypoperfusion is of particular interest in LLD as neuroradiological studies have consistently demonstrated associations with both global and frontal cerebral perfusion (69).

OH is defined as a sustained drop in sBP by at least 20 mmHg or dBP by at least 10 mmHg within 3 minutes of standing(78). Systemic hypotension is less well defined as BP treatment targets are becoming increasingly individualised (261) but both OH and lower systemic BP cause cerebral hypoperfusion(99, 262) and have been linked with LLD (241, 242). There is accumulating evidence that there is a paradoxical inverse relationship between BP and adverse outcomes in the ‘oldest old’ (263)and this may be partly due to increased susceptibility to cerebral hypoperfusion and OH in this cohort(93).

The aim of this study therefore is to clarify if lower systemic BP and OH modify the relationship between depressive symptoms and cerebral white matter disease in a cohort of community-dwelling older people aged  $\geq 70$  years.

## **7.4 Methods**

This is a cross-sectional study examining the association of depressive symptoms with WMH burden in a cohort of community-dwelling people aged  $\geq 70$  years, and whether this relationship is modified by conditions that cause cerebral hypoperfusion, specifically lower systemic BP and OH.

### *Study Design*

This study is embedded within TILDA, a large population-based study of a nationally representative sample of community dwelling older adults (120). Data from wave 3, collected between 2014 and 2015, were used for this analysis.

At wave 3, a subset of participants underwent brain MRI. Participants were sampled on a random basis. Participants meeting exclusion criteria, e.g. pacemakers, cerebral aneurysm clips or other MRI contraindications, were excluded prior to selection. In total, 501 MRI scans were completed with a mean delay between the health assessment and MRI of 62 days.

Participants were included in this study if they were aged  $\geq 70$  years and had undergone assessment for depressive symptoms, brain MRI, as well as other cardiovascular assessments including active stand and BP measurement.

This study focuses on this older group specifically because studies examining the adverse impact of lower BP and resultant cerebral hypoperfusion have done so in similarly older cohorts. For example, in a cohort of older adults aged  $\geq 85$  years, Boshuizen et al demonstrated higher mortality in those with lower BP(264), while both lower systolic and diastolic BP in hospitalised patients aged  $\geq 70$  years is a poor prognostic factor (95, 265).

### *Depression*

Depressive symptoms were measured using the CES-D-8. A score  $\geq 9$  was used to define cases of depression(125). The short-form CES-D-8 was introduced in the TILDA study from wave 2 in order to reduce the time taken to conduct participant assessments, as well as to reduce respondent burden and fatigue, and previous work has confirmed its reliability in comparison to the CES-D-20 in terms of internal consistency and factor structure within the TILDA cohort (124).

### *Brain MRI*

All imaging was performed using a 3T MRI scanner (Achieva, Philips, Netherlands) equipped with 32-channel head coil.

High-resolution anatomical images were acquired using a three-dimensional magnetization-prepared rapid gradient echo T1-weighted sequence with the following parameters: TR = 6.7ms, TE = 3.1ms,  $\alpha = 8^\circ$ , voxel size =  $0.9 \times 0.9 \times 0.9 \text{ mm}^3$ , FOV =  $240 \times 218 \times 162 \text{ mm}^3$ , a parallel imaging factor (SENSE) = 2, and total scan duration = 5:24.

Heavily T2-weighted fluid attenuated inversion recovery (FLAIR) images were also acquired using a two-dimensional turbo spin-echo sequence with the following parameters: TR =

11000ms, TE = 125ms, TI = 2800ms,  $\alpha = 90^\circ$ , number of slices = 30, slice thickness = 4mm, slice gap = 1 mm, voxel size =  $0.65 \times 0.87 \times 4 \text{ mm}^3$ , FOV =  $230 \times 183 \times 149 \text{ mm}^3$ , and total scan duration = 2:34.

A visual rating scale was used by a trained radiologist in order to calculate overall WMH burden. Scheltens Score is a semi-quantitative scoring method, applied separately in the periventricular region and in the lobar white matter, as well as in the basal ganglia and in the infratentorial region(266).

For the periventricular regions, three areas (frontal, occipital and lateral ventricles) were assessed separately. Scores for WMH were applied as follows: 0=absent, 1= $\leq 5\text{mm}$ , 2=  $>5\text{mm}$  and  $< 10\text{mm}$ ,  $>10\text{mm}$  included in lobar score. For the lobar white matter, 4 areas (frontal, parietal, occipital and temporal) were assessed with scoring as follows: 0=absent, 1= $<3\text{mm}$ ;  $n \leq 5$ , 2= $<3\text{mm}$ ;  $n > 6$ , 3= $4-10\text{mm}$ ;  $n \leq 5$ , 4 =  $4-10\text{mm}$ ;  $n > 6$ , 5 =  $>11\text{mm}$ ;  $n > 1$ , 6 = confluent. For the basal ganglia scores were applied as follows: 0 = none, 1 =  $<3\text{mm}$ ;  $n \leq 5$ , 2 =  $<3\text{mm}$ ;  $n > 6$ , 3 =  $4-10\text{mm}$ ;  $n \leq 5$ , 4 =  $4-10\text{mm}$ ;  $n > 6$ , 5 =  $>11\text{mm}$ ;  $n > 1$ , 6 = confluent. For the infratentorial region scores were applied as follows: 0 = none, 1 =  $<3\text{mm}$ ;  $n \leq 5$ , 2 =  $<3\text{mm}$ ;  $n > 6$ , 3 =  $4-10\text{mm}$ ;  $n \leq 5$ , 4 =  $4-10\text{mm}$ ;  $n > 6$ , 5 =  $>11\text{mm}$ ;  $n > 1$ , 6 = confluent(266). An overall score was then calculated by adding individual scores for each of the four regions assessed.

### *Orthostatic Hypotension*

Orthostatic BP was measured by active stand using a Finometer® Midi as described previously(126). Briefly, participants lay in the supine position for 10 minutes in a quiet room, before standing in a timely manner ( $<5$  seconds), and were aided by a research nurse to mobilize as necessary. After standing, sBP, diastolic BP, and heart rate were monitored for a further 120 seconds.

OH was defined as a drop in sBP  $\geq 20 \text{ mmHg}$  or drop in diastolic BP  $\geq 10 \text{ mmHg}$  at 30, 60 or 90 seconds post standing compared to baseline BP(78). Time-point values were 5-second moving averages, i.e. the 30 second time point was the average of 27.5 to 32.5 seconds.

### *Other Measures*

Cardiovascular disease was defined as self-report of angina, congestive cardiac failure or prior myocardial infarction, while self-report was also elicited for a prior history of stroke. The MMSE was used to assess cognition. Antidepressant use was determined by examining medication records for medicines with ATC code N06A. BP was measured twice in seated position using Omron digital cuff by trained research nurse and mean of two values use.

### *Statistical Analysis*

Data were analysed using Stata (Statacorp). Normally distributed continuous variables were compared using Student's t-test. Chi-square test was used for categorical variables.

Linear regression models with Scheltens score as the dependent variable were used to analyse the association of depressive symptoms with WMH burden. Variables added to the model

were chosen a priori based on their likelihood of impacting on WMH burden. Two-way interactions between depressive symptoms and OH and depressive symptoms and sBP were used to assess whether OH or sBP modified the relationship between depressive symptoms and WMH.

A p value  $\leq 0.05$  was considered statistically significant.

### *Ethics*

The TILDA study was approved by the Faculty of Health Sciences research ethics committee at Trinity College Dublin and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki.

## 7.5 Results

Just fewer than 8% (16/202) of the study sample had significant depressive symptoms. As shown in table 7.1, there were no significant differences between groups in terms of age, sex, history of cardiovascular disease, stroke or OH, and scores on MMSE. As one would expect, the group with depressive symptoms were significantly more likely to be prescribed antidepressant medication.

**Table 7.1: Baseline Characteristics by Depressive Symptoms**

| Variable                                    | Depressed (n=16)      | Non-depressed (n=186) | Statistical Test           |
|---------------------------------------------|-----------------------|-----------------------|----------------------------|
| Age (Years), Mean (95% CI)                  | 76.6 (74.5 – 78.7)    | 76.4 (75.7 – 77.1)    | t = -0.19; p = 0.847       |
| Female: % (n)                               | 56 (9/16)             | 46 (86/186)           | $\chi^2=0.59$ ; p = 0.441  |
| Cardiovascular Disease: % (n) <sup>A</sup>  | 13 (2/16)             | 8 (14/186)            | $\chi^2=0.50$ ; p = 0.480  |
| Stroke: % (n)                               | 6 (1/16)              | 2 (3/186)             | $\chi^2=1.63$ ; p = 0.201  |
| MMSE, Mean (95% CI)                         | 28.6 (27.5 – 29.7)    | 28.4 (28.2 – 28.7)    | t = -0.47; p = 0.640       |
| Antidepressant Use: % (n) <sup>B</sup>      | 31 (5/16)             | 6 (12/186)            | $\chi^2=11.75$ ; p = 0.001 |
| Orthostatic Hypotension: % (n) <sup>C</sup> | 31 (5/16)             | 21 (39/186)           | $\chi^2=0.914$ ; p = 0.339 |
| sBP (mm Hg), Mean (95% CI) <sup>D</sup>     | 133.1 (125.4 – 140.7) | 140.0 (137.3 – 142.8) | t = 1.43; p = 0.156        |
| sBP < 130 mm Hg: % (n) <sup>D</sup>         | 44 (7/16)             | 28 (52/186)           | $\chi^2=1.78$ ; p = 0.182  |

Notes:

*Depression defined as 8-item Centre for Epidemiological Studies Depression Scale  $\geq 9$ .*

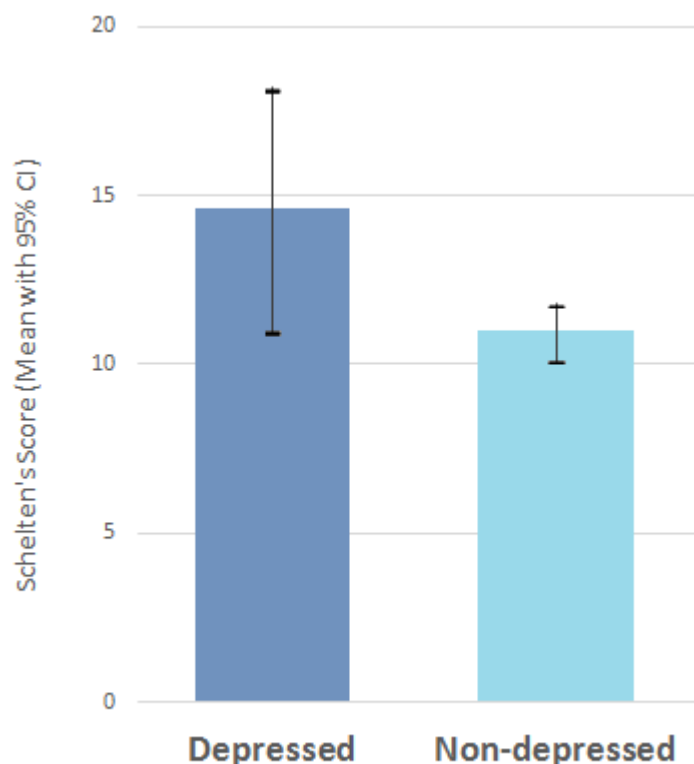
*Student's t-test used for continuous variables; Chi-square test used for categorical variables.*

*Abbreviations: CI = confidence interval; MMSE = Mini Mental State Examination Score; BP = blood pressure; sBP = systolic blood pressure.*

*A Self-report of either myocardial infarction, cardiac failure or angina; B Medication records examined for medicines with anatomical therapeutic classification code N06A; C defined as a drop in systolic blood pressure  $\geq 20$  mm Hg or diastolic blood pressure  $\geq 10$  mm Hg at either 30, 60 or 90 seconds after standing, measured continuously using a finometer; D blood pressure measured twice in seated position using Omron digital cuff by trained research nurse and mean of two values used.*

As shown in figure 7.1, the depressed group had a significantly higher burden of WMH, as measured by Scheltens Score (14.6 (95% CI: 11.0 – 18.2) vs. 11.0 (95% CI: 10.1 – 11.8);  $p = 0.0211$ ;  $t = -2.33$ ).

**Figure 7.1: White Matter Hyperintensity Burden (Scheltens Score) by Depression Status**



**Notes:**

Depression defined as 8-item Centre for Epidemiological Studies Depression Scale  $\geq 9$ . Depressed,  $n = 16$ ; Non-depressed,  $n = 186$ .

Student's  $t$ -test used to test difference in mean Scheltens Score between groups.

Abbreviations: CI = confidence interval.

Linear regression models demonstrate that depressive symptoms were associated with WMH burden with an unadjusted  $\beta$ -coefficient of 3.49 (0.54 – 6.44),  $P < 0.021$ . Findings remained robust after relevant covariates were added to the model. See table 2.

Addition of the two-way interaction between depressive symptoms and OH to the model shows that the association between depressive symptoms and WMH burden is significant only in those with co-existing OH. Similarly, the two-way interaction between depressive symptoms and sBP shows that this association remains statistically significant only in those with both depressive symptoms and lower sBP, i.e.  $<130$  mm Hg.

**Table 7.2: Linear regression models with WMH burden as dependent variable**

|                                                                    | Coefficient (95% CI) | SE   | t     | p     |
|--------------------------------------------------------------------|----------------------|------|-------|-------|
| Model 1: Unadjusted                                                |                      |      |       |       |
| <b>Depressive Symptoms <sup>A</sup></b>                            | 3.49 (0.54 – 6.44)   | 1.50 | 2.33  | 0.021 |
| Model 2                                                            |                      |      |       |       |
| <b>Depressive Symptoms <sup>A</sup></b>                            | 3.23 (0.17 – 6.29)   | 1.55 | 2.08  | 0.039 |
| <b>Age (Years)</b>                                                 | 0.23 (0.05 – 0.41)   | 0.09 | 2.54  | 0.012 |
| <b>Female sex</b>                                                  | 2.12 (0.48 – 3.76)   | 0.83 | 2.55  | 0.012 |
| <b>Cardiovascular Disease <sup>B</sup></b>                         | 1.22 (-1.74 – 4.17)  | 1.51 | 0.81  | 0.417 |
| <b>Stroke</b>                                                      | 5.28 (-0.51 – 11.08) | 2.94 | 1.80  | 0.074 |
| <b>MMSE</b>                                                        | -0.42 (-0.95 – 0.11) | 0.27 | -1.56 | 0.120 |
| <b>Antidepressant Use <sup>C</sup></b>                             | -0.53 (-3.51 – 2.44) | 1.51 | -0.35 | 0.724 |
| Model 3: Addition of Depression-OH two-way interaction to Model 2  |                      |      |       |       |
| <b>Depressive Symptoms # OH <sup>D</sup></b>                       |                      |      |       |       |
| - Non-depressed, OH                                                | 1.63 (-0.44 – 3.70)  | 1.04 | 1.56  | 0.121 |
| - Depressed, no OH                                                 | 2.75 (-0.89 – 6.39)  | 1.84 | 1.49  | 0.138 |
| - Depressed, OH                                                    | 5.52 (0.24 – 10.79)  | 2.67 | 2.06  | 0.040 |
| Model 4: Addition of Depression-sBP two-way interaction to Model 2 |                      |      |       |       |
| <b>Depressive Symptoms # sBP &lt; 130 mm Hg <sup>E</sup></b>       |                      |      |       |       |
| - Non-depressed, sBP < 130                                         | -0.79 (-2.64 – 1.06) | 0.94 | -0.84 | 0.401 |
| - Depressed, sBP > 130                                             | 1.65 (-2.37 – 5.67)  | 2.04 | 0.81  | 0.420 |
| - Depressed, sBP < 130                                             | 4.81 (0.23 – 9.40)   | 2.33 | 2.07  | 0.040 |

Notes: n =202

Abbreviations: WMH = white matter hyperintensity; CI = confidence interval; SE = standard error; OH = orthostatic hypotension; sBP = systolic blood pressure.

Depressive Symptoms # OH denotes the two-way interaction between depressive symptoms and OH regressing on WMH burden (Reference group is Non-depressed, no OH); Depressive symptoms # sBP < 130 denotes two-way interaction between depressive symptoms and systolic blood pressure less than 130 mm Hg regressing on WMH burden (Reference group is Non-depressed, sBP > 130 mm Hg mm Hg).

A Defined as a score of  $\geq 9$  on 8-item Centre for Epidemiological Studies Depression Scale (CES-D); B Self-report of either myocardial infarction, cardiac failure or angina; C Medication records examined for medicines with anatomical therapeutic classification code N06A; D defined as a drop in systolic blood pressure  $\geq 20$  mm Hg or diastolic blood pressure  $\geq 10$  mm Hg at either 30, 60 or 90 seconds after standing, measured continuously using a finometer; E blood pressure measured twice in seated position using Omron digital cuff by trained research nurse and mean of two values used.

## **7.6 Discussion**

This study demonstrates that depressive symptoms are strongly associated with WMH burden in a cohort of community-dwelling older people. This association is independent of age, sex, heart disease, stroke, cognition and antidepressant use. After addition of both OH and sBP to regression models however, the association between depressive symptoms and WMH burden remains significant only in those with OH or sBP<130 mm Hg respectively.

Colloby et al have previously shown that the drop in orthostatic BP measured continuously during active stand is associated with WMH volumes in temporal and parietal regions in a cohort of depressed older people (189). This study adds to the current evidence base by controlling for important covariates such as cardiovascular disease and stroke, and by defining OH based on international consensus criteria.

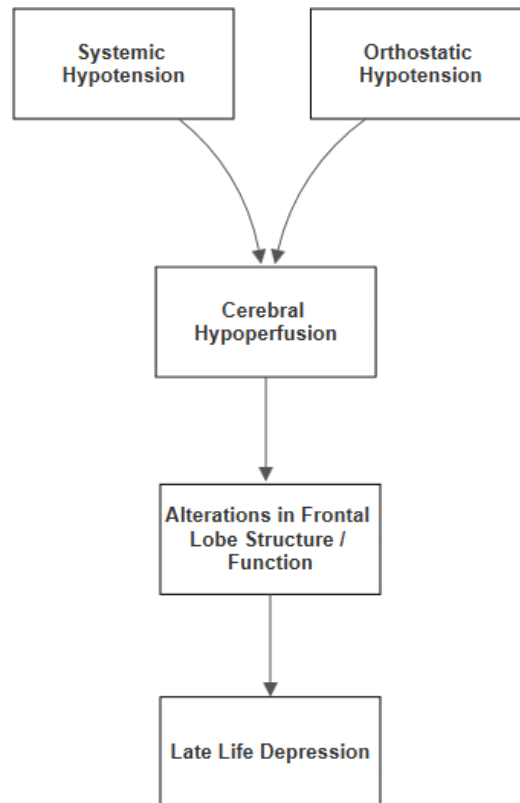
These findings are important as WMH burden has been strongly implicated in LLD(44), and the vascular basis of depression in later life is well recognised (33), yet studies have found no clear association between hypertension and depression in older people (267).

There is growing evidence that systemic hypotension and OH are both important risk factors for depression in later life however. For example, older people with symptomatic OH have a two-fold increased risk of depression during 4-year follow-up, independent of other risk factors including subthreshold depressive symptoms (242) while sBP<130 mm Hg is associated with a 40% increased risk of incident depression at 2 years (241).

It must also be noted however that we did not demonstrate a significant cross-sectional association between depression and either OH or lower systemic BP in this study. This is unexpected given the findings from our systematic review and the thesis hypothesis, however it could be explained by the fact that there were relatively lower numbers of depressed participants in this study and it involved an exclusively older cohort of participants with a mean age of over 76 years.

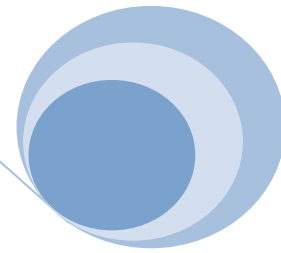
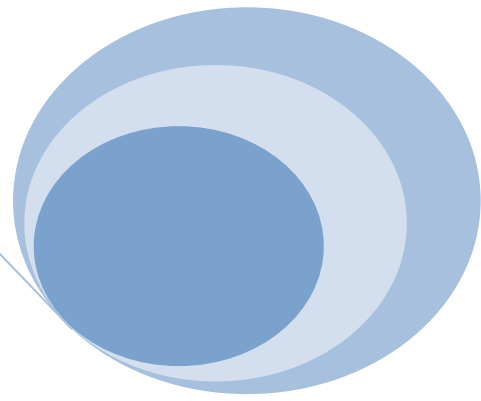
Hypotension, either orthostatic or systemic, causes cerebral hypoperfusion, which can in turn lead to white matter ischaemia (59). Several studies have shown reduced cerebral blood flow in older people with depression, using techniques such as TCD(70), SPECT(243) and perfusion MRI (268). We have previously shown that older people with depressive symptoms had significantly lower frontal lobe perfusion after standing when compared to non-depressed peers using NIRS (269). Depression in later life is also associated with other conditions related to cerebral perfusion deficits, including syncope and unexplained falls (13, 76). The proposed schema for this relationship is therefore shown in figure 7.2.

**Figure 7.2: Proposed relationship between blood pressure, cerebral perfusion and depression in later life**



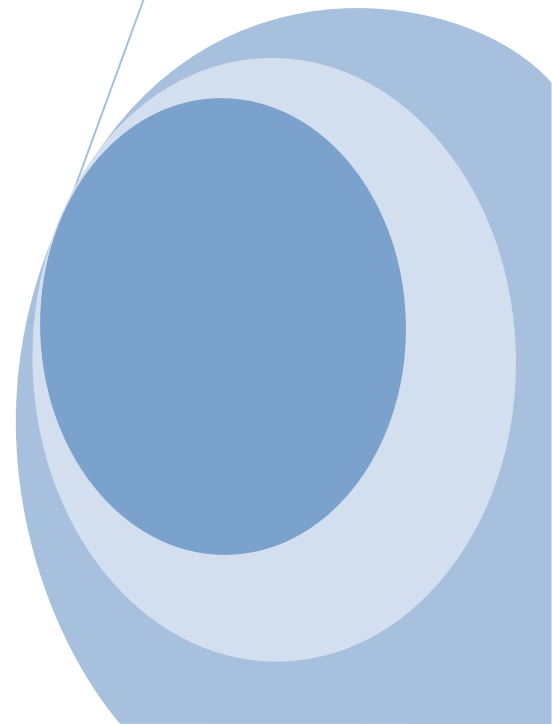
A limitation of this study is that, as for many studies involving MRI brain scans alongside detailed health assessments, the sample size is relatively small, especially when subdivided for two-way interactions. For example, there are only 7 participants in the 'depressed, sBP<130 mm Hg' group. Validation of these findings using a larger sample size is therefore important. Furthermore, assessment of depression is based on a diagnostic tool rather than the gold standard clinical assessment, although the CES-D is well validated in an older population against depression diagnosis (123).

WMH burden appears to be a key factor in incidence and trajectory of depressive symptoms in older people. This study demonstrates that depressive symptoms are associated with cerebral white matter disease in a cohort of community-dwelling people aged  $\geq 70$  years but that this relationship is modified by co-existing OH or lower sBP. Identifying the processes that lead to WMH accumulation and progression in depression is crucial in order to inform strategies aimed at preventing and ameliorating depression in later life, especially given the impact depression has on functional status and life expectancy. Further studies confirming these findings prospectively and in a larger cohort would therefore be welcome.



## **CHAPTER 8:**

Study 5: What is the Relationship  
between Timed Up and Go and  
Depressive Symptoms in Later Life?



### **8.1 Key Findings**

- This study demonstrates that almost one fifth of older people with depressive symptoms had a co-existing gait problem, measured using TUG ( $\geq 12$  seconds).
- Older people with a gait problem at initial assessment were 84% more likely to have co-existing depressive symptoms in fully adjusted models.
- Longitudinally, non-depressed older people with a TUG  $\geq 12$  seconds had a two-fold increased likelihood of developing incident depressive symptoms at 2-year follow-up.
- While baseline depressive symptoms predicted incident gait disturbance in unadjusted models, statistical significance was lost when adjusted for clinical covariates, particularly loneliness, arthritis and cognitive impairment.
- The modest results for average marginal effects we have shown do not support the use of gait analysis in isolation as an objective marker of depression risk in later life however.
- Prior studies have shown that a combination of gait impairment and depression has an additive effect on the incidence of significant disability in later life and older people with co-existing gait problems and depression may therefore be an appropriate target for multimodal interventions aimed at reducing functional decline.
- This study was published in the American Journal of Geriatric Psychiatry: DOI 10.1016/j.jagp.2017.08.012.

## **8.2 Abstract**

### *Background*

Both LLD and gait disturbance are common in later life and can have significant implications for functional status and quality of life. Furthermore, they are both closely associated with cerebral WMH.

The aim of this study is to clarify the longitudinal association between gait problems and depression in later life.

### *Methods*

This is a longitudinal study embedded within TILDA, examining the association between depressive symptoms, measured by CES-D, and gait abnormalities, measured by TUG. Assessments were carried out at baseline (wave 1) and at 2 year follow-up (wave 2).

### *Results*

At wave 1, 7% (179/2,638) had baseline depressive symptoms and 11% (296/2,638) had a gait abnormality. The incidence of new-onset depressive symptoms and gait abnormality at wave 2 was 4% (95/2,364) and 13% (308/2,342) respectively.

Logistic regression models demonstrated that baseline gait disturbance was a significant predictor of incident depressive symptoms at wave 2 with an Incidence Rate Ratio (IRR) of 2.00 (95% CI: 1.18 – 3.40,  $p = 0.010$ ,  $t=2.57$ ,  $df=625$ ). This was not attenuated after controlling for covariates. Baseline depressive symptoms were a predictor of incident gait abnormality at wave 2 with an IRR of 1.68 (95% CI: 1.16 – 2.43,  $p = 0.006$ ,  $t=2.75$ ,  $df=625$ ) but this association was no longer statistically significant when analysis was adjusted for clinical variables.

### *Conclusions*

This study demonstrates that baseline gait disturbance, measured by TUG, predicted incident depressive symptoms in a population-representative cohort of community-dwelling older people.

Possible biological mechanisms for this relationship include white matter disease and executive dysfunction.

### **8.3 Background**

While later life is generally a time of emotional well-being, depression affects 1 in 8 older people and causes significant morbidity in later life (153, 270). Depressive symptoms increase the risk of falls in older people by almost 50% (271). Furthermore, older fallers are twice as likely to have significant depressive symptoms compared to non-fallers (272) and depression is also a strong predictor of falls in nursing home residents (273). The association between depression and falls is complex but gait abnormalities may represent one of the underlying mechanisms. Similarly, gait disorders also represent an often unrecognised 'Geriatric Giant', affecting over one third of community-dwelling people aged over 70 years (109). They are independent predictors of adverse outcomes, such as admission to hospital (110), cognitive decline (111), nursing home admission and death (112).

Gait disorders are generally classified based on the level of sensorimotor deficit involved (113). Lower level gait disorders are due to deficits distal to the central nervous system, e.g. osteoarthritis, while middle level gait disorders are due to focal deficits caused by neurological disease, such as in Parkinson's disease or stroke (113). Higher level gait disorders cannot be explained by demonstrable deficits in the pyramidal, extrapyramidal, sensory or cerebellar systems and are strongly associated with cerebral white matter disease, particularly frontal lobe disease (114).

There is an established cross-sectional relationship between LLD and gait disturbance, with higher burden of depressive symptoms associated with poorer performance in specific components of gait such as velocity, stride, and swing time variability (115, 274). However, studies examining the longitudinal relationship between gait and LLD are less consistent. The English Longitudinal Study of Ageing demonstrated a bidirectional relationship between gait speed and depressive symptoms in both sexes at 2 year follow-up but did not control for antidepressant use (275). The Amsterdam Longitudinal Ageing Study found that slower gait speed predicted incident depressive symptoms but this finding was significant in males alone and analysis was controlled for CES-D and height only (276). Furthermore, longitudinal studies to date have used gait speed rather than TUG (132).

The aim of this study therefore is to clarify if baseline gait problems measured with the TUG predict incident depressive symptoms in community-dwelling older people. We aim to enhance the current evidence base by controlling for multiple chronic medical conditions that can contribute to gait disturbance, as well as falls burden.

## **8.4 Methods**

This is a longitudinal study in a cohort of community-dwelling participants aged 60 years and over, examining the relationship between gait disturbance and depression. We specifically examined the association between baseline depression and incident gait abnormalities at 2 year follow-up, as well as baseline gait abnormalities and incident depression at 2 year follow-up.

### *Study design*

We analysed data from the first and second wave of TILDA collected between 2009 and 2012. TILDA is a study of a nationally representative sample of community dwelling older adults aged 50 years and over. The TILDA study design has been outlined previously (117).

At baseline, participants completed a CAPI in their own homes which included detailed questions on health, social and economic circumstances. Each participant was then invited to a health centre for a comprehensive health assessment. Participants who were unable or unwilling to attend a health centre were offered a modified assessment in their own home.

The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki.

### *Inclusion / Exclusion Criteria*

People with known or suspected dementias were ineligible at baseline for participation. Participants were included if they were aged 60 years and over at baseline, and completed the initial baseline assessment, as well as a follow-up assessment at 2 years.

### *Depression*

The CES-D was used to measure depressive symptoms. The CES-D is a 20-item scale, with response values are 4-point Likert scales, with range 0 to 3, yielding a total possible score of 60 (121). The CES-D has been validated in an older population, and a value of 16 or more has been shown to have a sensitivity of 92% and a specificity of 87% for diagnosis of depression (122).

The CES-D was administered at baseline and at wave 2 follow-up 2 years later. Participants with a score of 16 or more on the CES-D at baseline were considered to have baseline clinically

significant depressive symptoms (123). A score of 16 or more at follow-up in the baseline non-depressed cohort was used to define incident depressive symptoms.

### *Gait*

The TUG was used to assess gait(132). This involves measuring the time taken for a participant to rise from a chair, walk 3 metres, turn around and then walk back to the chair and sit down. The TUG is a reliable screening assessment for gait disturbance all levels, as well as a predictor of falls risk (133), correlating well with both gait speed and the Berg Balance Scale (134).

The TUG was administered at baseline and at wave 2 follow-up 2 years later. Participants with a score of 12 seconds or more at baseline were considered to have gait disturbance (135). A score of 12 or more seconds at follow-up in those with no gait abnormalities at baseline was used to define incident gait disturbance.

### *Other measures*

We controlled for several important covariates that may impact on the relationship between depression and gait abnormalities. Alcohol excess was measured using the CAGE scale (277). Functional impairment was defined as having one or more impairment in instrumental ADL, including shopping, housekeeping, accounting, food preparation, and telephone/transportation. Participants were asked if they had fallen in the last 12 months. Cardiac disease was defined as self-report of prior myocardial infarction, current cardiac failure, cardiac arrhythmia, hypertension or angina. Participants were also asked if they had a history of Diabetes, Parkinson's disease, arthritis, or stroke. Loneliness was defined as answering either a 'moderate amount of time' or 'all of the time' when participants were asked 'How often are you lonely?' Cognitive impairment was defined as a score of 24 or less on the MMSE. Additionally, medication lists were examined for antidepressant medication use.

### *Statistical analysis*

Data were analysed using Stata (Statacorp).

Cross-sectional analysis was weighted. Weights were estimated by comparing the proportion of individuals in the sample across age, sex and highest level of educational attainment, marital status and urban or rural dwelling, with the proportion of the population with the same characteristics using information from the Central Statistics Office of Ireland. Differences in baseline binary demographic and clinical variables between study groups were therefore

presented as weighted prevalence estimates using proportional estimation. Continuous variables were analysed by linear regression with study group as a predictor. Marginal mean values calculated post-estimation and data was presented by recalculating as  $1/(\text{marginal mean})$ .

Additionally, attrition weights were applied to the longitudinal analysis. These weights corrected for the difference in attrition rates over subgroups and reduced the bias caused by this difference in attrition rates. These weights are calculated based on the reciprocal probability of a wave 1 respondent taking part in wave 2. This probability was calculated using a logistic regression model. Factors which were shown to affect attrition included measures of cognitive and behavioural health, marital status and several health measures.

Logistic regression models were used to predict binary outcomes, with IRR; models were adjusted for relevant covariates. In order to report IRRs, a generalised linear model with poisson distribution was used. As it is not possible to specify robust standard errors with the survey weights used in this study we ran the analysis with and without weights and reported both the weighted and unweighted IRRs.

Three models were tested, with the first model examining the unadjusted IRR of the variable for the outcome of interest; the second model adjusted for age, sex and baseline depression/gait symptoms and the third model adjusted for additional clinical factors such as co-existing chronic medical illnesses, antidepressant use and cognitive impairment. In the third model, we controlled for clinical conditions which may cause middle and lower level gait disturbance, such as alcohol, stroke, Parkinson's disease, diabetes and arthritis. For logistic regression involving incident depression, participants with baseline depression were excluded from the analysis. Participants with baseline gait disturbance were excluded from the logistic regression models for incident gait disturbance.

Average marginal effects were calculated for relevant predictor variables post-estimation. The marginal effect is a measure of the effect that a change in an explanatory variable has on the predicted probability when other covariates are kept constant. Average marginal effects were utilised in preference to directly computing conditional predicted probabilities as several covariates were observed to impact depression/gait abnormality incidence. Average marginal effects models allow us to control for these covariates at the individual level and clarify what the average difference in probability of outcome was across individuals, whereas probability difference estimates are calculated on a case-wise basis to begin with.

In order to correct for non-normality of the distribution, reciprocal transformation was applied to the TUG variables as they demonstrated a highly positive skew.

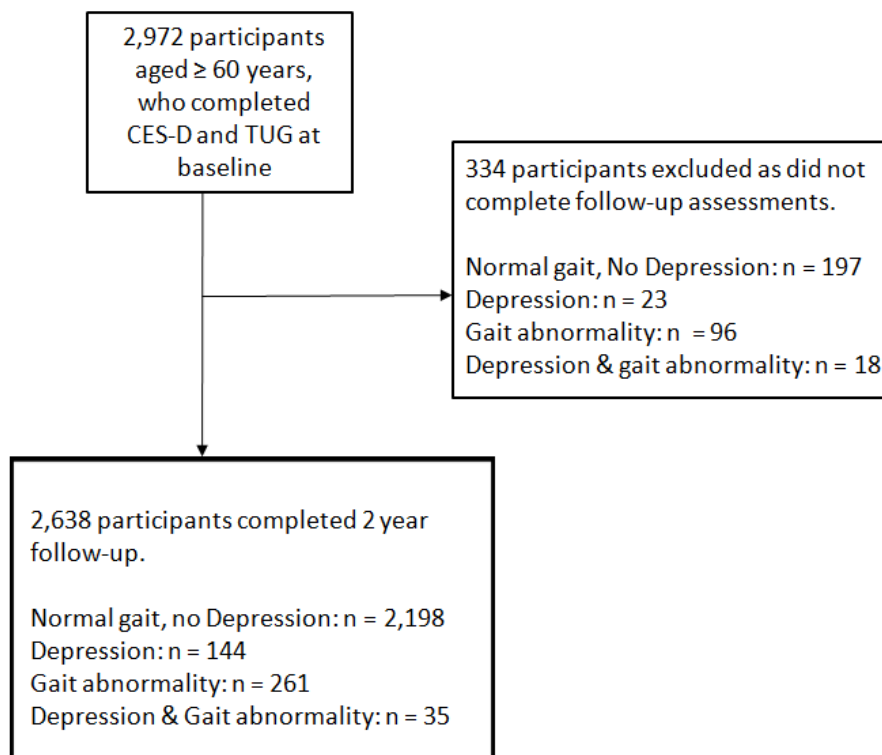
Tetrachoric correlations were used to assess collinearity amongst binary variables used in the regression models; variables that were highly correlated were excluded from the analyses. A tetrachoric correlation matrix demonstrated significant correlations between ADL impairment and other predictor variables. The variable defining ADL impairment was therefore excluded from the regression analyses. See appendix 1 for correlation matrix.

A p value  $\leq 0.05$  was considered statistically significant.

## 8.5 Results

2,972 participants were eligible for inclusion in the study. 11% (334/2,972) of this initial group did not complete 2 year follow-up and were excluded from the final study sample. See figure 8.1 for flow diagram. 2,638 participants were therefore included in the full longitudinal analyses. One fifth of those included in the study were aged 75 years or more at initial assessment, while 47% were aged 65 to 74 years and one third were aged 50-64 years. Of this sample, 7% (179/2,638) had baseline significant depressive symptoms at wave 1 and 11% (296/2,638) had a gait abnormality at wave 1.

**Figure 8.1: Flow Diagram of Study Recruitment**



Key: CES-D = Centre for Epidemiological Studies Depression Scale; TUG = Timed Up and Go.

### 8.5.1 Cross-sectional analysis

Table 8.1 shows the baseline characteristics as weighted prevalence estimates for the study sample, based on their diagnoses at wave 1.

**Table 8.1: Baseline Characteristics of study sample by diagnosis at Wave 1**

|                                     | Non-depressed,<br>normal gait<br>n = 2,198 | Depressed<br>n = 144 | Gait disturbance<br>n = 261 | Depressed &<br>gait disturbance<br>n = 35 |
|-------------------------------------|--------------------------------------------|----------------------|-----------------------------|-------------------------------------------|
| Age, years~                         | 67.9 (67.5 – 68.2)                         | 66.3 (65.4 – 67.3)   | 76.8 (75.9 – 77.8)          | 73.2 (70.6 – 75.8)                        |
| Females*                            | 0.51 (0.50 – 0.53)                         | 0.67 (0.59 – 0.75)   | 0.56 (0.51 – 0.62)          | 0.59 (0.43 – 0.75)                        |
| TUG, seconds~                       | 8.6 (8.5 – 8.6)                            | 8.8 (8.6 – 9.1)      | 14.2 (14.0 – 14.5)          | 16.1 (14.8 – 17.6)                        |
| ≥1 IADL Impairment*                 | 0.03 (0.25 – 0.04)                         | 0.15 (0.09 – 0.21)   | 0.22 (0.16 – 0.27)          | 0.33 (0.18 – 0.49)                        |
| CAGE score ≥ 2*                     | 0.09 (0.78 – 0.10)                         | 0.16 (0.10 – 0.22)   | 0.04 (0.02 – 0.06)          | 0.11 (0.00 – 0.23)                        |
| Fall in last year*                  | 0.20 (0.18 – 0.22)                         | 0.32 (0.25 – 0.40)   | 0.26 (0.21 – 0.32)          | 0.38 (0.22 – 0.57)                        |
| Lonely* <sup>A</sup>                | 0.04 (0.03 – 0.05)                         | 0.38 (0.30 – 0.46)   | 0.08 (0.04 – 0.11)          | 0.39 (0.23 – 0.56)                        |
| <b>Cardiac Disease*:</b>            |                                            |                      |                             |                                           |
| - Hypertension                      | 0.40 (0.38 – 0.42)                         | 0.53 (0.45 – 0.62)   | 0.58 (0.51 – 0.64)          | 0.63 (0.48 – 0.78)                        |
| - Myocardial Infarct                | 0.05 (0.04 – 0.06)                         | 0.07 (0.03 – 0.11)   | 0.09 (0.05 – 0.12)          | 0.12 (0.01 – 0.23)                        |
| - Cardiac Failure                   | 0.01 (0.00 – 0.01)                         | 0.01 (0.00 – 0.02)   | 0.01 (0.00 – 0.02)          | 0.07 (0.00 – 0.16)                        |
| - Cardiac Arrhythmia                | 0.09 (0.08 – 0.10)                         | 0.12 (0.07 – 0.18)   | 0.15 (0.10 – 0.19)          | 0.20 (0.06 – 0.35)                        |
| Prior stroke*                       | 0.01 (0.01 – 0.02)                         | 0.02 (0.00 – 0.04)   | 0.04 (0.02 – 0.07)          | 0.08 (0.00 – 0.17)                        |
| Diabetes*                           | 0.08 (0.07 – 0.10)                         | 0.09 (0.04 – 0.14)   | 0.14 (0.10 – 0.19)          | 0.13 (0.02 – 0.25)                        |
| Arthritis*                          | 0.32 (0.30 – 0.34)                         | 0.50 (0.41 – 0.59)   | 0.50 (0.44 – 0.57)          | 0.66 (0.48 – 0.83)                        |
| Parkinson's Disease*                | 0.00 (0.00 – 0.01)                         | 0.01 (0.00 – 0.02)   | 0.01 (0.00 – 0.03)          | 0.03 (0.00 – 0.08)                        |
| Antidepressant Use*                 | 0.05 (0.04 – 0.06)                         | 0.22 (0.15 – 0.29)   | 0.10 (0.06 – 0.14)          | 0.19 (0.04 – 0.35)                        |
| Cognitive Impairment * <sup>B</sup> | 0.03 (0.02 – 0.04)                         | 0.06 (0.02 – 0.11)   | 0.13 (0.08 – 0.17)          | 0.11 (0.00 – 0.22)                        |

Notes:

Abbreviations: TUG = Timed Up and Go Test; IADL = instrumental activities of daily living; CES-D = Centre for Epidemiological Studies Depression Scale; MMSE = Mini Mental State Examination.

Group who were non-depressed with normal gait did not meet criteria for depression or gait abnormality at wave 1.

\* denotes weighted prevalence estimates using proportional estimation, presented with 95% confidence intervals.

~ denotes analysis by linear regression with subgroup as predictor. Marginal mean values calculated post-estimation and data presented by recalculating as 1/ (marginal mean).

<sup>a</sup>Lonely defined as answering either a 'moderate amount of time' or 'all of the time' when asked 'How often are you lonely?'. <sup>b</sup> Cognitive impairment defined as Mini Mental State Examination score ≤ 24.

There was a significant baseline association between depressive symptoms and gait disturbance. See table 8.2.

**Table 8.2: Baseline association between depression and gait disturbance, Chi-Square Table**

|                      | Gait abnormality | Normal Gait       | Total            |
|----------------------|------------------|-------------------|------------------|
| <b>Depressed</b>     | n = 35 (19.6%)   | n = 144 (80.4%)   | n = 179 (100%)   |
| <b>Not Depressed</b> | n = 261 (10.6%)  | n = 2,198 (89.4%) | n = 2,459 (100%) |
| <b>Total</b>         | n = 297 (11.1%)  | n = 2,345 (88.8%) | n = 2,638 (100%) |

*Notes:*

*Depressed= CES--20  $\geq 16$ ; Gait abnormality = TUG  $\geq 12$  seconds.*

$\chi^2 = 13.384, p < 0.001$

Multiple logistic regression models confirmed this association with an unadjusted IRR of 1.84 (95% CI: 1.28 – 2.66)  $p < 0.001$ ;  $df=625$ , which was not attenuated after controlling for covariates. See table 8.3.

**Table 8.3: Logistic Regression for cross-sectional association between baseline Depressive Symptoms and Gait Abnormality at Wave 1**

| Depressive Symptoms Wave 1        | IRR (Weighted) | p Value | t     | 95% CI      | IRR (Non-weighted) with 95% CI |
|-----------------------------------|----------------|---------|-------|-------------|--------------------------------|
| <b>Model 1:</b>                   |                |         |       |             |                                |
| TUG $\geq$ 12 seconds Wave 1      | 1.84           | 0.001   | 3.29  | 1.28 – 2.66 | 1.92 (1.36 – 2.73)             |
| <b>Model 2:</b>                   |                |         |       |             |                                |
| TUG $\geq$ 12 seconds Wave 1      | 2.61           | <0.001  | 4.48  | 1.72 – 3.99 | 2.73 (1.88– 3.98)              |
| <b>Age:</b>                       |                |         |       |             |                                |
| - Age 65 – 74 years               | 0.81           | 0.192   | -1.31 | 0.59 – 1.11 | 0.80 (0.59 – 1.10)             |
| - Age $\geq$ 75 years             | 0.41           | 0.001   | -3.23 | 0.24 – 0.71 | 0.39 (0.24 – 0.63)             |
| Female gender                     | 1.65           | 0.001   | 3.20  | 1.21 – 2.24 | 1.71 (1.26 – 2.31)             |
| <b>Model 3:</b>                   |                |         |       |             |                                |
| TUG $\geq$ 12 seconds Wave 1      | 1.77           | 0.004   | 2.90  | 1.20 – 2.60 | 1.84 (1.27 – 2.67)             |
| <b>Age:</b>                       |                |         |       |             |                                |
| - Age 65 – 74 years               | 0.69           | 0.013   | -2.48 | 0.51 – 0.92 | 0.70 (0.52 – 0.95)             |
| - Age $\geq$ 75 years             | 0.37           | <0.001  | -4.10 | 0.23 – 0.60 | 0.36 (0.23 – 0.57)             |
| Female gender                     | 1.25           | 0.203   | 1.27  | 0.89 – 1.75 | 1.27 (0.93 – 1.74)             |
| <b>CAGE Score:</b>                |                |         |       |             |                                |
| - CAGE=1                          | 1.14           | 0.562   | 0.58  | 0.73 – 1.78 | 1.14 (0.74 – 1.76)             |
| - CAGE=2                          | 1.07           | 0.790   | 0.27  | 0.65 – 1.76 | 0.93 (0.55 – 1.57)             |
| - CAGE=3                          | 2.11           | 0.002   | 3.12  | 1.32 – 3.37 | 2.03 (1.27 – 3.25)             |
| - CAGE=4                          | 1.48           | 0.478   | 0.71  | 0.50 – 4.33 | 1.07 (0.44 – 2.60)             |
| Falls in last year                | 1.38           | 0.031   | 2.16  | 1.03 – 1.86 | 1.33 (0.99 – 1.79)             |
| Lonely <sup>A</sup>               | 6.88           | <0.001  | 12.91 | 5.13 – 9.23 | 6.96 (5.28 – 9.17)             |
| Cardiac Disease <sup>B</sup>      | 1.49           | 0.006   | 2.79  | 1.13 – 1.98 | 1.35 (1.04 – 1.77)             |
| Stroke                            | 1.55           | 0.192   | 1.31  | 0.80 – 3.00 | 1.49 (0.74 – 3.00)             |
| Diabetes                          | 0.89           | 0.612   | -0.51 | 0.55 – 1.42 | 0.87 (0.55 – 1.38)             |
| Arthritis                         | 1.61           | 0.001   | 3.22  | 1.21 – 2.16 | 1.55 (1.17 – 2.06)             |
| Parkinson's Disease               | 1.53           | 0.620   | 0.50  | 0.29 – 8.15 | 1.18 (0.19 – 7.51)             |
| Antidepressant Use                | 2.38           | <0.001  | 5.61  | 1.76 – 3.22 | 2.55 (1.89 – 3.45)             |
| Cognitive Impairment <sup>C</sup> | 1.41           | 0.308   | 1.02  | 0.73 – 2.71 | 1.37 (0.72 – 2.59)             |

Notes:

$N = 2,638$ ; Design  $DF=625$ .

Abbreviations: IRR = Incident Rate Ratio; CI = Confidence Interval; TUG = Timed Up and Go Test.

<sup>A</sup> Lonely defined as answering either a 'moderate amount of time' or 'all of the time' when asked 'How often are you lonely?' <sup>B</sup> Cardiac disease defined as self-report of prior myocardial infarction, current cardiac failure, cardiac arrhythmia, hypertension or angina. <sup>C</sup> Cognitive impairment defined as Mini Mental State Examination score  $\leq 24$ .

### 8.5.2 Longitudinal analysis

#### Does gait abnormality predict incident depression?

The incidence of new-onset depressive symptoms at wave 2 was 4% (95/2,364).

Participants with incident depressive symptoms were more likely to have a baseline gait abnormality (Linear regression / Weighted proportion estimation: 0.23 (95% CI: 0.13 – 0.33) vs. 0.13 (95% CI: 0.11 – 0.14); DF=625).

Participants with incident depressive symptoms also had a longer TUG at wave 1 compared to those with no incident depressive symptoms at wave 2 (Linear regression with post-estimation marginal mean values: 9.86 seconds (95% CI: 9.38 – 10.40) vs. 9.04 seconds (95% CI: 8.94 – 9.14)).

Logistic regression models demonstrated that baseline gait disturbance (TUG  $\geq$  12 seconds at wave 1) was a significant predictor of incident depressive symptoms at wave 2 with an IRR of 2.00 (95% CI: 1.18 – 3.41,  $p = 0.010$ ,  $t=2.57$ ,  $df=625$ ), which was not attenuated after controlling for covariates. See table 8.4 and figure 8.2.

Average marginal effects estimated post-analysis showed the effects of abnormal TUG at wave 1 on incident depression at wave 2 was not statistically significant however (0.035 (95% CI: - 0.00 – 0.07,  $z=1.84$ ;  $p = 0.066$ )), suggesting that TUG abnormalities alone do not have a significant effect on the likelihood of developing incident depression when other covariates are kept constant.

**Table 8.4: Logistic Regression for association between Gait Abnormality at Wave 1 and incident Depressive Symptoms at Wave 2**

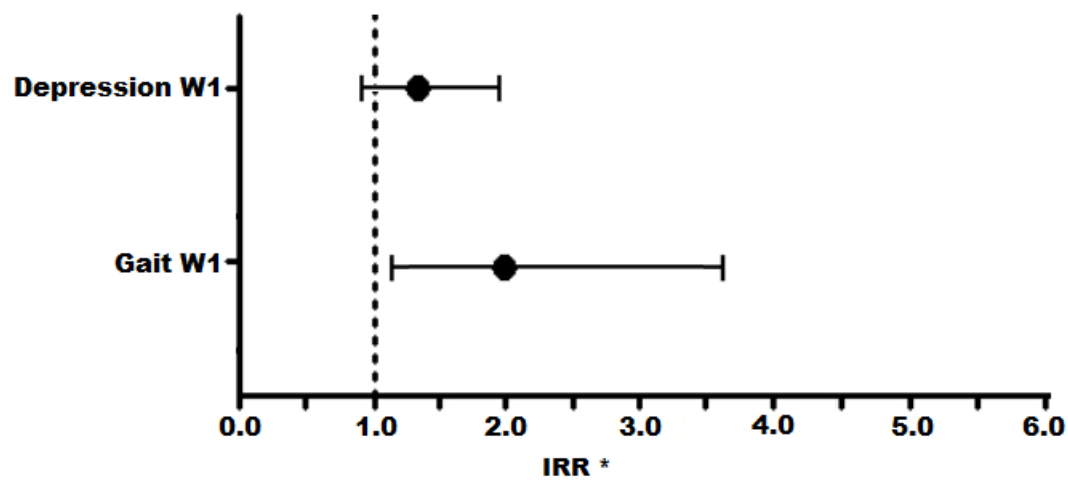
| <u>Incident Depressive Symptoms</u>           | <u>IRR (Weighted)</u> | <u>p Value</u> | <u>t</u> | <u>95% CI</u> | <u>IRR (Non-weighted) with 95% CI</u> |
|-----------------------------------------------|-----------------------|----------------|----------|---------------|---------------------------------------|
| <b>Model 1:</b>                               |                       |                |          |               |                                       |
| <b>TUG≥12 seconds Wave 1</b>                  | 2.00                  | 0.010          | 2.57     | 1.18 – 3.41   | 2.11 (1.29 – 3.42)                    |
| <b>Model 2:</b>                               |                       |                |          |               |                                       |
| <b>TUG≥12 seconds Wave 1</b>                  | 2.40                  | 0.003          | 2.93     | 1.34 – 4.33   | 2.25 (1.32 – 3.83)                    |
| <b>Age:</b>                                   |                       |                |          |               |                                       |
| - Age 65 – 74 years                           | 0.97                  | 0.896          | -0.13    | 0.60 – 1.56   | 1.14 (0.73 – 1.79)                    |
| - Age ≥ 75 years                              | 0.39                  | 0.022          | -2.30    | 0.17 – 0.87   | 0.45 (0.22 – 0.90)                    |
| <b>Female gender</b>                          | 1.17                  | 0.494          | 0.69     | 0.74 – 1.85   | 1.33 (0.87 – 2.02)                    |
| <b>Subsyndromal Depressive Sx<sup>A</sup></b> | 5.71                  | <0.001         | 7.73     | 3.67 – 8.89   | 5.40 (3.59 – 8.15)                    |
| <b>Model 3:</b>                               |                       |                |          |               |                                       |
| <b>TUG≥12 seconds Wave 1</b>                  | 2.01                  | 0.021          | 2.32     | 1.11 – 3.65   | 2.00 (1.18 – 3.39)                    |
| <b>Age:</b>                                   |                       |                |          |               |                                       |
| - Age 65 – 74 years                           | 0.87                  | 0.562          | -0.58    | 0.55 – 1.38   | 1.07 (0.69 – 1.67)                    |
| - Age ≥ 75 years                              | 0.35                  | 0.005          | -2.82    | 0.17 – 0.73   | 0.41 (0.21 – 0.81)                    |
| <b>Female gender</b>                          | 1.11                  | 0.663          | 0.44     | 0.69 – 1.78   | 1.26 (0.81 – 1.96)                    |
| <b>Subsyndromal Depressive Sx<sup>A</sup></b> | 5.38                  | <0.001         | 7.63     | 3.49 – 8.29   | 4.95 (3.24 – 7.57)                    |
| <b>CAGE Score:</b>                            |                       |                |          |               |                                       |
| - CAGE=1                                      | 1.28                  | 0.419          | 0.81     | 0.70 – 2.34   | 1.34 (0.71 – 2.51)                    |
| - CAGE=2                                      | 1.49                  | 0.332          | 0.97     | 0.66 – 3.37   | 1.54 (0.79 – 3.00)                    |
| - CAGE=3                                      | 0.70                  | 0.642          | -0.47    | 0.15 – 3.21   | 1.03 (0.25 – 4.18)                    |
| - CAGE=4                                      | 1.61                  | 0.515          | 0.65     | 0.38 – 6.71   | 1.88 (0.46 – 7.77)                    |
| <b>Falls in last year</b>                     | 0.76                  | 0.278          | -1.09    | 0.47 – 1.25   | 0.86 (0.54 – 1.35)                    |
| <b>Lonely<sup>B</sup></b>                     | 1.03                  | 0.938          | 0.08     | 0.48 – 2.19   | 0.91 (0.44 – 1.89)                    |
| <b>Cardiac Disease<sup>C</sup></b>            | 1.08                  | 0.739          | 0.33     | 0.68 – 1.71   | 1.03 (0.69 – 1.53)                    |
| <b>Stroke</b>                                 | 0.72                  | 0.735          | -0.34    | 0.11 – 4.74   | 0.60 (0.09 – 4.08)                    |
| <b>Diabetes</b>                               | 1.63                  | 0.164          | 1.39     | 0.82 – 3.26   | 1.40 (0.79 – 2.50)                    |
| <b>Arthritis</b>                              | 2.03                  | 0.001          | 3.26     | 1.32 – 3.10   | 1.85 (1.23 – 2.78)                    |
| <b>Parkinson's Disease</b>                    | 7.02                  | 0.052          | 1.95     | 0.99 – 49.97  | 4.43 (0.99 – 19.84)                   |
| <b>Antidepressant Use</b>                     | 2.69                  | <0.001         | 4.07     | 1.67 – 4.33   | 2.79 (1.72 – 4.52)                    |
| <b>Cognitive Impairment<sup>D</sup></b>       | 0.52                  | 0.301          | -1.04    | 0.15 – 1.80   | 0.67(0.22 – 2.03)                     |

Notes: N = 2,459; Design DF=625

Abbreviations: IRR = Incidence Rate Ratio; CI = confidence interval; Sx = symptoms; TUG = Timed Up and Go Test; CES-D = Centre for Epidemiological Studies Depression Scale.

<sup>a</sup>Subsyndromal depression defined as CES-D score 8-15. <sup>b</sup>Lonely defined as answering either a 'moderate amount of time' or 'all of the time' when asked 'How often are you lonely?' <sup>c</sup>Cardiac disease defined as self-report of prior myocardial infarction, current cardiac failure, cardiac arrhythmia, hypertension or angina. <sup>d</sup>Cognitive impairment defined as Mini Mental State Examination score ≤ 24.

**Figure 8.2: Incidence Rate Ratios (IRR) of baseline Depression /Gait Abnormality as predictor of Incident Gait Abnormality / Depression respectively**



**Notes:**

*Depression W1 demonstrates the odds ratio for depression at wave 1 predicting incident gait abnormality at wave2.*

*Gait W1 demonstrates the odds ratio for gait abnormality at wave 1 predicting incident depression at wave 2.*

*\* IRR presented with 95% confidence interval, after controlling for age, gender, baseline mood/gait problems, alcohol, prior falls, loneliness, heart disease, stroke, diabetes, arthritis, Parkinson's disease, antidepressant use, cognitive impairment.*

Analysis was repeated with participants taking antidepressants excluded. Baseline gait disturbance remained a significant predictor of incident depression after full adjustment. See table 8.5.

**Table 8.5: Logistic Regression for association between Gait Abnormality at Wave 1 and**

| <b>Incident Depressive Sx</b>                 | <b>IRR<br/>(Unweighted)</b> | <b>p Value</b> | <b>z</b> | <b>95% CI</b>    |
|-----------------------------------------------|-----------------------------|----------------|----------|------------------|
| <b>TUG≥12 seconds Wave 1</b>                  | 1.98                        | 0.041          | 2.04     | 1.03 – 3.83      |
| <b>Age:</b>                                   |                             |                |          |                  |
| - Age 65 – 74 years                           | 0.95                        | 0.829          | -0.22    | 0.58 – 1.54      |
| - Age ≥ 75 years                              | 0.48                        | 0.043          | -2.02    | 0.23 – 0.98      |
| <b>Female gender</b>                          | 1.43                        | 0.150          | 1.44     | 0.88 – 2.32      |
| <b>Subsyndromal Depressive Sx<sup>A</sup></b> | 5.10                        | <0.001         | 6.73     | 3.17 – 8.19      |
| <b>CAGE Score:</b>                            |                             |                |          |                  |
| - CAGE=1                                      | 1.58                        | 0.156          | 1.42     | 0.84 – 2.97      |
| - CAGE=2                                      | 1.69                        | 0.188          | 1.32     | 0.77 – 3.70      |
| - CAGE=3                                      | 1.17                        | 0.830          | 0.21     | 0.29 – 4.76      |
| - CAGE=4                                      | 3.17                        | 0.077          | 1.77     | 0.88 – 11.40     |
| <b>Falls in last year</b>                     | 0.79                        | 0.403          | -0.84    | 0.46 – 1.37      |
| <b>Lonely<sup>B</sup></b>                     | 0.68                        | 0.405          | -0.83    | 0.27 – 1.69      |
| <b>Cardiac Disease<sup>C</sup></b>            | 1.01                        | 0.971          | 0.04     | 0.65 – 1.57      |
| <b>Stroke</b>                                 | 6.11 e-06                   | <0.001         | -34.14   | 3.07 e-06 – 0.00 |
| <b>Diabetes</b>                               | 1.17                        | 0.671          | 0.42     | 0.56 – 2.46      |
| <b>Arthritis</b>                              | 1.98                        | 0.003          | 2.96     | 1.26 – 3.12      |
| <b>Parkinson's Disease</b>                    | 3.44                        | 0.273          | 1.10     | 0.38 – 31.19     |
| <b>Antidepressant Use</b>                     | Omitted                     |                |          |                  |
| <b>Cognitive Impairment<sup>D</sup></b>       | 0.46                        | 0.459          | -0.74    | 0.06 – 3.63      |

**incident Depressive Symptoms at Wave 2, excluding Antidepressant Users**

Notes:

Abbreviations: IRR = Incidence Rate Ratio; Sx = symptoms; TUG = Timed Up and Go Test; CES-D = Centre for Epidemiological Studies Depression Scale.

<sup>A</sup> Subsyndromal depression defined as CES-D score 8-15. <sup>B</sup> Lonely defined as answering either a 'moderate amount of time' or 'all of the time' when asked 'How often are you lonely?' <sup>C</sup> Cardiac disease defined as self-report of prior myocardial infarction, current cardiac failure, cardiac arrhythmia, hypertension or angina. <sup>D</sup> Cognitive impairment defined as Mini Mental State Examination score ≤ 24.

Does depression predict incident gait abnormality?

The incidence of new-onset gait abnormality at wave 2 was 13% (308/2,342).

Participants with incident gait abnormalities were more likely to be depressed at wave 1 compared to those with no incident gait problems at wave 2 (Linear regression / Weighted proportion estimation: 0.10 (0.06 – 0.14) vs. 0.06 (0.05 – 0.07); df=613).

Baseline depression (CES-D  $\geq$  16 at wave 1) was a predictor of incident gait abnormality at wave 2 with an IRR of 1.68 (95% CI: 1.16 – 2.43,  $p = 0.006$ ,  $t=2.75$ ,  $df=625$ ) but this association was no longer statistically significant when analysis was adjusted for clinical variables. See table 8.6 and figure 8.2.

**Table 8.6: Logistic Regression for association between Depressive Symptoms at Wave 1 and incident Gait Abnormality at Wave 2**

| Incident Gait Abnormality         | IRR (Weighted) | p Value | t     | 95% CI       | IRR (Non-weighted) with 95% CI |
|-----------------------------------|----------------|---------|-------|--------------|--------------------------------|
| <b>Model 1:</b>                   |                |         |       |              |                                |
| Depressive Sx Wave 1              | 1.68           | 0.006   | 2.75  | 1.16 – 2.43  | 1.47 (1.03 – 2.10)             |
| <b>Model 2:</b>                   |                |         |       |              |                                |
| Depressive SxWave 1               | 1.75           | 0.001   | 3.28  | 1.25 – 2.44  | 1.50 (1.07 – 2.11)             |
| <b>Age:</b>                       |                |         |       |              |                                |
| - Age 65 – 74 years               | 1.45           | 0.019   | 2.35  | 1.06 – 1.99  | 1.55 (1.15 – 2.09)             |
| - Age ≥ 75 years                  | 2.67           | <0.001  | 6.02  | 1.94 – 3.68  | 2.78 (2.03 – 3.80)             |
| Female gender                     | 1.12           | 0.258   | 1.13  | 0.92 – 1.36  | 1.18 (0.97 – 1.43)             |
| <b>TUG at Wave 1<sup>A</sup></b>  |                |         |       |              |                                |
| - TUG 2 <sup>nd</sup> Quartile    | 4.15           | <0.001  | 4.23  | 2.14 – 8.03  | 4.37 (2.30 – 8.30)             |
| - TUG 3 <sup>rd</sup> Quartile    | 9.40           | <0.001  | 6.93  | 4.98 – 17.73 | 9.32 (5.05 – 17.22)            |
| - TUG 4 <sup>th</sup> Quartile    | 14.14          | <0.001  | 8.26  | 7.53 – 26.54 | 14.62 (7.91 – 27.05)           |
| <b>Model 3:</b>                   |                |         |       |              |                                |
| Depressive Sx Wave 1              | 1.35           | 0.115   | 1.58  | 0.93 – 1.98  | 1.19 (0.82 – 1.73)             |
| <b>Age:</b>                       |                |         |       |              |                                |
| - Age 65 – 74 years               | 1.34           | 0.064   | 1.86  | 0.98 – 1.84  | 1.42 (1.05 – 1.92)             |
| - Age ≥ 75 years                  | 2.32           | <0.001  | 4.95  | 1.66 – 3.24  | 2.40 (1.74 – 3.31)             |
| Female gender                     | 1.09           | 0.417   | 0.81  | 0.89 – 1.34  | 1.12 (0.92 – 1.38)             |
| <b>TUG at Wave 1<sup>A</sup></b>  |                |         |       |              |                                |
| - TUG 2 <sup>nd</sup> Quartile    | 3.95           | <0.001  | 4.08  | 2.04 – 7.64  | 4.15 (2.18 – 7.87)             |
| - TUG 3 <sup>rd</sup> Quartile    | 8.51           | <0.001  | 6.63  | 4.51 – 16.05 | 8.43 (4.56 – 15.58)            |
| - TUG 4 <sup>th</sup> Quartile    | 12.62          | <0.001  | 7.85  | 6.69 – 23.80 | 12.97 (6.99 – 24.09)           |
| <b>CAGE Score:</b>                |                |         |       |              |                                |
| - CAGE=1                          | 0.69           | 0.119   | -1.56 | 0.43 – 1.10  | 0.71 (0.45 – 1.10)             |
| - CAGE=2                          | 1.28           | 0.176   | 1.35  | 0.90 – 1.83  | 1.07 (0.72 – 1.61)             |
| - CAGE=3                          | 0.62           | 0.310   | -1.02 | 0.25 – 1.56  | 0.49 (0.19 – 1.27)             |
| - CAGE=4                          | 1.09           | 0.851   | 0.19  | 0.46 – 2.58  | 1.22 (0.54 – 2.74)             |
| Falls in last year                | 0.96           | 0.756   | -0.31 | 0.76 – 1.22  | 1.05 (0.84 – 1.32)             |
| Lonely <sup>B</sup>               | 1.26           | 0.211   | 1.25  | 0.88 – 1.83  | 1.25 (0.89 – 1.76)             |
| Cardiac Disease <sup>C</sup>      | 1.24           | 0.054   | 1.93  | 1.00 – 1.54  | 1.28 (1.04 – 1.58)             |
| Stroke                            | 1.34           | 0.226   | 1.21  | 0.83 – 2.17  | 1.39 (0.86 – 2.26)             |
| Diabetes                          | 1.10           | 0.548   | 0.60  | 0.80 – 1.53  | 1.04 (0.76 – 1.42)             |
| Arthritis                         | 1.27           | 0.023   | 2.28  | 1.03 – 1.57  | 1.25 (1.02 – 1.53)             |
| Parkinson's Disease               | 1.27           | 0.422   | 0.80  | 0.71 – 2.25  | 1.04 (0.48 – 2.22)             |
| Antidepressant Use                | 1.21           | 0.323   | 0.99  | 0.83 – 1.77  | 1.23 (0.87 – 1.74)             |
| Cognitive Impairment <sup>D</sup> | 1.55           | 0.024   | 2.26  | 1.06 – 2.27  | 1.73 (1.20 – 2.49)             |

Notes: N = 2,342; Design DF=625

Abbreviations: IRR = Incidence Rate Ratio; Sx = symptoms; TUG = Timed Up and Go Test; CI = confidence interval; CES-D = Centre for Epidemiological Studies Depression Scale.

<sup>A</sup> TUG quartiles are as follows: 1<sup>st</sup> quartile = 4.8 – 7.9 seconds; 2<sup>nd</sup> quartile = 7.9 – 8.94 seconds; 3<sup>rd</sup> quartile = 8.96 – 10.38 seconds; 4<sup>th</sup> quartile > 10.38 seconds. <sup>B</sup> Lonely defined as answering either a 'moderate amount of time' or 'all of the time' when asked 'How often are you lonely?' <sup>C</sup> Cardiac disease defined as self-report of prior myocardial

*infarction, current cardiac failure, cardiac arrhythmia, hypertension or angina.*<sup>D</sup> *Cognitive impairment defined as Mini Mental State Examination score  $\leq 24$ .*

Addition of each of the additional Model 3 covariates one-by-one to Model 2 found that loneliness, arthritis and cognitive impairment caused the greatest attenuation in this association. Addition of only the loneliness variable to Model 2 saw a reduction in the IRR from 1.74 (1.25-2.43) to 1.55 (1.05-2.30), while addition of arthritis and cognitive impairment variables to Model 2 produced an IRR of 1.64 (1.18 – 2.30) and 1.65 (1.18 – 2.32) respectively.

## **8.6 Discussion**

This study demonstrates that baseline gait disturbance, measured by TUG, predicted incident depressive symptoms defined by CES-D, in a population-representative cohort of community-dwelling older people.

Baseline depressive symptoms predicted incident gait disturbance in unadjusted models but statistical significance was lost when adjusted for clinical covariates, particularly loneliness, arthritis and cognitive impairment.

Our findings are supported by longitudinal studies from Finland that have shown that reduced mobility, as well as a reduction in the intensity of physical activity increases the risk of depression (278, 279). Generally poor physical performance, including 4 metre gait speed, has also been shown to predict incident depression in later life (280). This study adds to the current evidence base by involving a large, well described population-based sample of older adults, using the most commonly employed clinical assessment of gait and controlling for a comprehensive range of covariates.

There are several factors which may underlie this observed association. Incident depression could represent a response to the physical limitations or loss of independence conferred by mobility problems. Additionally, there may also be a neurobiological basis for this association. WMH, bright foci seen in the parenchyma on brain MRI sequences, representing injury to white matter tracts, have been implicated in LLD, as well as in higher level gait disorders (114, 222). Furthermore it appears that this association between WMH and gait disturbance is more pronounced in the setting of LLD (281). It is likely that much of the effect we see in this study is related to higher level gait impairment as we controlled for the commonest causes of both middle and lower level gait problems (arthritis, alcohol, diabetes, stroke, Parkinson's disease).

Executive dysfunction, which often co-exists with depression in later life (213), may also be an important factor in this association as it has also been shown to influence performance on gait analysis such as the TUG (282). Additionally, WMH volume is independently associated with deficits in executive functioning and studies have described a specific phenotype characterised by slow gait, impaired executive function, and depressive symptoms in an older population with significant vascular disease (283).

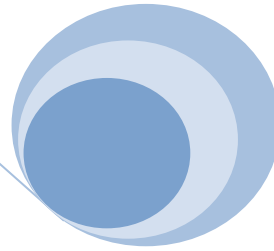
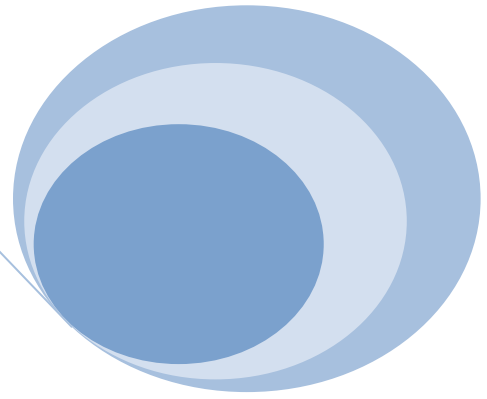
The modest results for average marginal effects we have shown do not support the use of gait analysis in isolation as an objective marker of depression risk in later life. It appears that a

combination of gait impairment and depression has an additive effect on the incidence of significant disability in later life however (284) and older people with co-existing gait problems and depression may therefore be an appropriate target for multimodal interventions aimed at reducing functional decline. The augmentation of antidepressant therapy with physical exercise has been shown to improve remission rates in LLD (285).

Furthermore, it must be noted that subsyndromal depressive symptoms remain the strongest predictor of incident depression in this cohort. Other significant predictors of incident depression include arthritis, another condition with significant effects on mobility.

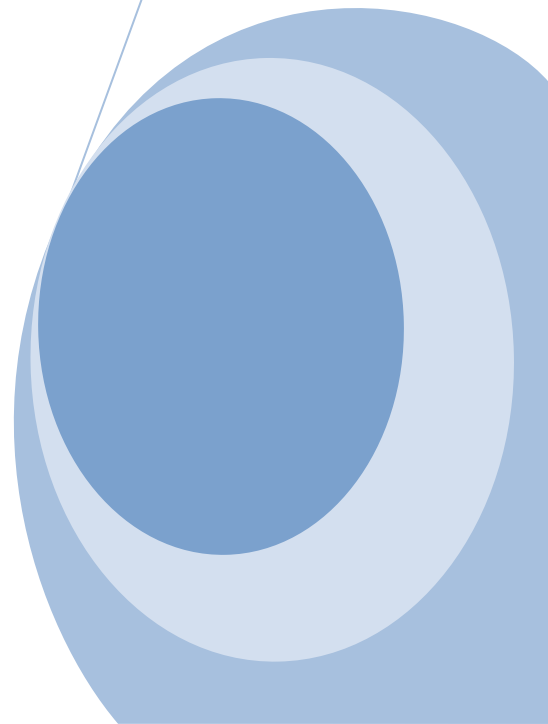
Our study has some limitations which should be noted. Diagnosis of depression was based on the CES-D, rather than the gold standard structured psychiatric interview. Similarly, gait disturbance was also defined based on a validated tool rather than a clinical diagnosis but the TUG is widely used in clinical settings. In the setting of a large longitudinal study such as this however individual clinical assessments are not feasible and both tools have been validated for use in an older population. Sufficient data on anxiety symptoms was not available to include in our analysis. The strengths of this study include the large population-based sample of community-dwelling older adults, with comprehensive health data available for analysis, including medical comorbidities, full medication lists, gait and cognitive testing.

In conclusion, this study demonstrates that baseline gait problems, measured by TUG, are associated with a two-fold increase of incident depressive symptoms in a population-based sample of older adults. Further studies are required to focus on a potentially common mechanistic pathway for this association involving WMH and executive dysfunction as potential mediators of this relationship.



## **CHAPTER 9:**

Study 6: Do Spatiotemporal Gait  
Parameters predict incident  
Depressive Symptoms in Later Life?



### **9.1 Key Findings**

- Older people who went on to develop significant depressive symptoms during follow-up walked on average almost 4cm/s slower than those who did not have incident depressive symptoms.
- Slower gait speed and shorter step length were both independently associated with a 50% increased likelihood of developing depressive symptoms.
- Findings remained robust after adjusting for important factors including socio-demographics, cardiovascular disease, blood pressure, smoking and alcohol excess.
- A possible mechanism for this association is cerebral WMH, particularly those involving the frontal lobe, as they are more prevalent in older people with both depression and gait problems, particularly higher level gait disorders.
- Higher level gait disorders also involve problems with gait ignition, and short shuffling steps, consistent with the reduced gait speed and step length we have demonstrated in this study.
- Additionally, these results raise the possibility that exercise could also be used as part of a multimodal preventative strategy for depression, alongside strategies that may help prevent accumulation of white matter disease in later life.
- This study was published in the Journal of the American Geriatrics Society: DOI 10.1111/jgs.15783.

## **9.2 Abstract**

### *Background*

There is growing interest in the association between gait disturbance and depression in later life. The aim of this study is to clarify the longitudinal relationship between specific gait parameters and incident depression within a population-representative sample of older people.

### *Methods*

This is a longitudinal analysis of spatiotemporal gait parameters at baseline (wave 1) and incident depression at 2 and 4 years (waves 2/3). Logistic regression models were used to assess the relationship between tertiles of gait parameters and incident depression. This study was embedded within TILDA with over 3,600 non-depressed community-dwelling people aged  $\geq 50$  years were included.

A score  $\geq 9$  on the CES-D-8 at wave 2 or 3 was indicative of incident depression. The GAITRite system was used to measure gait speed, step length, step width and double support phase during usual speed walking and under dual task conditions.

### *Results*

Participants with incident depressive symptoms (344/3,615) had slower gait speed (129.9 (95% CI:127.2 – 132.6) cm/s vs. 134.1 (95% CI:133.0 – 135.1) cm/s;  $F=8.82$ ;  $p=0.003$ ) and shorter step length (68.0 (95% CI:66.9 – 69.2) cm vs. 70.3 (69.9 – 70.7) cm;  $F=13.99$ ;  $p<0.001$ ) at baseline than those who did not develop depression.

Logistic Regression models demonstrated that those within the slowest tertile for gait speed and shortest tertile for step length had significantly increased likelihood of incident depression in fully adjusted models, with OR of 1.54 (95% CI:1.08 – 2.19) and 1.54 (95% CI:1.01 – 2.35) respectively. Measures of step width and double support time were not associated with depression.

### *Conclusion*

This study demonstrates that older people with incident depression have significantly slower gait speed, and shorter step length at initial assessment.

These findings are clinically significant given the impact both conditions have on functional status in later life, as well as the possibility that gait problems may represent a potentially modifiable risk factor for depression.

### **9.3 Background**

Gait disorders affect around one third of community-dwelling older people aged 60 years or more, with prevalence increasing significantly with advancing age(286). Given the wide range of processes that integrate to maintain gait and balance, there are multiple potential underlying causes of gait disturbance and these causes are generally defined as lower, middle or higher level, depending on the level of the sensorimotor deficit involved(287).

Causes of lower level gait problems include osteoarthritis and peripheral neuropathy, while conditions associated with focal neurological deficits such as stroke, Parkinson's disease or multiple sclerosis cause middle level deficits(114). Higher level gait disorders are those that cannot be explained by demonstrable deficits in the pyramidal, extrapyramidal, sensory or cerebellar systems, and are related to cerebrovascular disease, particularly frontal white matter disease(114).

Decline in gait is a consistent and reliable predictor of future functional status and mortality in later life(288-290). Gait problems, particularly higher level gait problems, are also closely linked with poorer brain health outcomes, increasing the risk of incident dementia, particularly vascular dementia(291, 292).

There is also growing evidence linking gait disturbance with depression in later life(116). Elevated late life depressive symptoms are associated with slower gait velocity and shorter stride length (115) and older adults with major depression have also been shown to have higher swing time variability than healthy controls(274). In a cohort of depressed older people, slower gait speed was associated with an increased chance of persistent depressive symptoms(293).

LLD is associated with an increased risk of falls, which may be related to gait disturbance(13). Importantly, cerebral white matter disease has also been shown to predict incidence of depression in later life, as well as poorer prognosis(294).

To date, most work examining gait patterns in LLD is cross-sectional. The aim of this study therefore is to clarify the longitudinal relationship between spatiotemporal gait parameters and incident depression within a large population-representative sample of community-dwelling older adults. Our hypothesis was that we could identify specific gait patterns, particularly slower walking speed and shorter step length as both are seen in higher level gait disorders, as a marker of an increased risk of incident depression as both conditions are strongly linked with frontal lobe white matter disease.

## **9.4 Methods**

This is a longitudinal study examining the relationship between spatiotemporal gait parameters at baseline (wave 1) and incident depression at 4-year follow-up (waves 2 and 3).

### *Ethics*

The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki. All health assessments were carried out by trained research nurses.

### *Study Design*

This study is embedded within TILDA, a large population-based study of a nationally representative sample of community dwelling adults aged  $\geq 50$  years. The TILDA study design has been outlined previously<sup>(117)</sup> but in short; participants were recruited using a stratified clustered procedure to randomly sample postal addresses from the Irish Geo-Directory (a listing of all residential addresses in the Republic of Ireland). All postal addresses in Ireland were assigned to one of 3155 geographic clusters; using RANSAM (a random sampling design for Ireland), a sample of 640 of these clusters was selected stratified by socioeconomic group and geography, where all household residents aged  $\geq 50$  years were eligible to participate.

We analysed data from the first, second and third waves of TILDA collected between 2009 and 2015. Participants were included in this analysis if they were aged 50 years or more with no pre-existing diagnosis of dementia at wave 1 completed screening for depression during the CAPI and underwent a health assessment at wave 1, with complete data for gait assessment. Pre-existing dementia was based on a prior doctor's diagnosis of dementia only, so it is possible that some patients with clinical dementia who had not yet received a formal doctor's diagnosis of same were included at wave 1.

Participants were excluded if they did not complete both 2 and 4-year follow-up, including assessment for depression at both waves 2 and 3.

### *Depression*

Depressive symptoms were assessed at wave 1 using the CES-D-20. A score  $\geq 16$  was used to define cases of depression<sup>(123)</sup>. Participants with depression at wave 1 were excluded from the study ( $n=332$ ).

At waves 2 and 3, the CES-D-8 was used to screen for depression. Previous work has confirmed its reliability in comparison to the CES-D-20 in terms of internal consistency and factor structure within the TILDA cohort(124). Therefore, the CES-D-8 was used to reduce the time taken to conduct participant assessments, as well as to reduce respondent burden and fatigue. Participants with a CES-D-8 score  $\geq 9$  at either wave 2 or 3 were defined as having incident depression(295).

Scales were administered in participant's own home by a trained interviewer.

### *Gait*

Spatiotemporal gait analysis was provided by the GAITRite system, a computerized mat with pressure-sensors(136). Participants started walking 2.5 metres before the mat and stopped 2 metres after the mat to allow for acceleration and deceleration. They completed two walks in each of three conditions: at usual walking pace; walking while carrying out a manual task (holding a glass of water) and walking while carrying out a cognitive task (reciting alternate letters of the alphabet, i.e. A-C-E, etc.). Data from the two walks in each condition were averaged, e.g. the two 'normal' walks were combined to yield one overall variable for normal walking; similarly the two manual task walks were averaged and so on, and the following gait variables were obtained: gait speed, step length, step width and double support phase.

Gait speed is defined as the distance covered by the body per unit time, and is measured in cm/second. Step length is the distance between corresponding successive points of heel contact of the opposite foot. Step width is the side-to-side distance measured between the midline midpoint of one foot to the midline midpoint of the opposite foot. Double support phase is the time spent with both feet in contact with the floor, expressed as a percentage of the total gait cycle.

### *Other Measures*

Further detailed social and biological data, including age, sex, educational attainment, smoking status, BMI etc. were also collected at wave 1. BP was measured twice in a seated position using the OMRON™ digital automatic BP monitor and the mean value was used for analysis. Alcohol use was assessed using the CAGE questionnaire(277). Cardiovascular disease was defined as self-reported doctor diagnosis of arrhythmia, angina, myocardial infarction or cardiac failure. Cognitive status was assessed with the MOCA. Medication records were also examined for antidepressant use, specifically those with Anatomic Therapeutic Chemical (ATC) Classification N06A, and benzodiazepine use (ATC N05BA).

*Statistical Analysis*

Data were analysed using Stata (Statacorp).

Analysis was weighted for attrition. These weights corrected for the systematic difference in attrition rates over subgroups and reduced the bias caused by this difference in attrition rates and were calculated based on the reciprocal of the probability of a wave 1 respondent taking part in wave 2 or wave 3. This probability was calculated using a logistic regression model. Factors in the model which were shown to affect attrition included measures of cognitive and behavioural health, marital status and several health measures.

Normally distributed continuous variables were compared across groups using Student's t-test with adjusted Wald test used post-estimation. Proportional estimation was used for categorical variables with Z score calculated post-estimation.

Multilevel models with 8-item CES-D score as the dependent variable nested within participant were used to compare data across specific time points by gait abnormalities, specifically tertiles of gait speed, and average marginal effects were calculated, and graphed.

Logistic regression models, presenting OR, were used to assess the longitudinal relationship between tertiles of gait parameters (Gait Speed, Step Length, Step Width and Double Support Time) and incident depression (developed depression/did not develop depression at either wave 2 or wave 3).

Three regression models were tested: the first model was unadjusted; the second model adjusted for age, sex, educational attainment, BMI, smoking status and excess alcohol intake; and the third model adjusted for baseline subthreshold depressive symptoms and additional clinical covariates such as cardiac disease, cognitive impairment and stroke. Variables were chosen a priori based on their likely probability of modifying the index relationship between gait and depression.

In order to exclude the effect of antidepressant use, models were re-run excluding all antidepressant users, regardless of their baseline depression status based on the CES-D.

A p value  $\leq 0.05$  was considered statistically significant.

## **9.5 Results**

After exclusion of those meeting criteria for depression at wave 1, there were 4,235 participants eligible for inclusion in the longitudinal analysis for incident depressive symptoms. Of these, 15% (620/4,235) did not complete 4-year follow-up and were therefore excluded, yielding a final study sample of 3,615 participants who were included in the longitudinal analysis. 9% of study participants were aged 75 years or more at initial assessment, while 28% and 63% were aged 65-74 years and 50-64 years respectively.

Almost 10% (344/3,615) of the study sample met criteria for incident depressive symptoms during follow-up, i.e. they scored  $\geq 9$  on the 8-item CES-D at either wave 2 or wave 3. Those who had incident depressive symptoms were more likely to be females with lower levels of educational attainment and had a higher prevalence of BMI  $\geq 30$ . See table 9.1.

As shown in table 9.2, participants who subsequently met criteria for incident depressive symptoms had significantly slower gait speed and shorter step length under normal and manual task conditions. They also had a marginally shorter step width during cognitive dual task walking only. There was no difference in percentage of time spent in double support phase between groups during any of the walking conditions.

Figure 9.1 illustrates the significant difference in trajectory of depressive symptoms, as measured by 8-item CES-D during 4-year follow-up, when stratified by tertiles of gait speed at wave 1. While there were no significant differences at baseline, those with a gait speed  $< 129.6$  cm/s had a significantly higher burden of depressive symptoms at wave 2 (compared to those in the highest tertile of gait speed) and wave 3 (compared to both the middle and highest gait speed tertiles) after controlling for covariates.

**Table 9.1: Baseline Characteristics by Incident Depressive Symptoms**

| Variable                                            | Incident Depressive Symptoms | Not depressed         |                      |
|-----------------------------------------------------|------------------------------|-----------------------|----------------------|
|                                                     | n = 344                      | n = 3,271             |                      |
| Age, Mean (95% CI), years                           | 63.3 (61.8 – 64.8)           | 63.6 (63.1 – 64.1)    | F = 0.15; p = 0.701  |
| Female, Prop (95% CI)                               | 0.58 (0.52 – 0.65)           | 0.50 (0.48 – 0.51)    | Z = 2.82; p = 0.004  |
| Educational attainment, Prop (95% CI):              |                              |                       |                      |
| - Primary                                           | 0.40 (0.34 – 0.47)           | 0.27 (0.25 – 0.30)    | Z = 5.10; p < 0.001  |
| - Secondary                                         | 0.40 (0.34 – 0.46)           | 0.48 (0.46 – 0.50)    | Z = -2.83; p = 0.005 |
| - Tertiary                                          | 0.20 (0.16 – 0.24)           | 0.24 (0.23 – 0.26)    | Z = -1.66; p = 0.096 |
| Body Mass Index, Prop (95% CI), kg/m <sup>2</sup> : |                              |                       |                      |
| - BMI <24.9                                         | 0.23 (0.18 – 0.28)           | 0.21 (0.20 – 0.23)    | Z = 0.86; p = 0.389  |
| - BMI 25.0 – 29.9                                   | 0.37 (0.31 – 0.43)           | 0.47 (0.45 – 0.49)    | Z = -3.54; p < 0.001 |
| - BMI ≥ 30.0                                        | 0.40 (0.34 – 0.47)           | 0.32 (0.30 – 0.34)    | Z = 3.01; p = 0.003  |
| Current Smoker, Prop (95% CI)                       | 0.21 (0.16 – 0.27)           | 0.15 (0.13 – 0.16)    | Z = 2.92; p = 0.004  |
| CAGE Score ≥2, Prop (95% CI) <sup>A</sup>           | 0.14 (0.10 – 0.18)           | 0.11 (0.10 – 0.12)    | Z = 1.68; p = 0.095  |
| Sys BP, Mean (95% CI), mm Hg <sup>B</sup>           | 135.3 (132.6 – 138.0)        | 136.5 (135.6 – 137.3) | F = 0.67; p = 0.413  |
| Cardiovascular Disease, Prop (95% CI) <sup>C</sup>  | 0.15 (0.11 – 0.21)           | 0.14 (0.12 – 0.15)    | Z = 0.51; p = 0.610  |
| Stroke, Prop (95% CI)                               | 0.01 (0.00 – 0.03)           | 0.01 (0.01 – 0.02)    | Z = 0.00; p = 1.000  |
| Osteoarthritis, Prop (95% CI)                       | 0.17 (0.13 – 0.22)           | 0.13 (0.12 – 0.15)    | Z = 2.10; p = 0.038  |
| MOCA, Mean (95% CI)                                 | 24.6 (24.1 – 25.0)           | 24.9 (24.8 – 25.1)    | F = 1.97; p = 0.161  |
| Antidepressant Use, Prop (95% CI)                   | 0.12 (0.08 – 0.16)           | 0.04 (0.03 – 0.05)    | Z = 6.63; p < 0.001  |
| Benzodiazepine Use, Prop (95% CI)                   | 0.06 (0.03 – 0.10)           | 0.02 (0.01 – 0.02)    | Z = 4.60; p < 0.001  |

**Notes:**

Incident depression is 8-item CES-D score ≥ 9 at either wave 2 or wave 3, i.e. 2 and/or 4 year follow-up.

Student's t-test used for continuous variables with adjusted Wald test post-estimation. Proportional estimation used for categorical variables with Z score calculated post-estimation.

Abbreviations: CI = confidence interval; Prop = proportional estimation; Sys BP = Systolic Blood Pressure; MOCA = Montreal Cognitive Assessment.

A CAGE Alcohol Scale for Alcohol Problem; B Systolic BP measured twice in seated position using Omron digital cuff and average of 2 readings taken C Cardiovascular Disease defined as self-report of angina, cardiac failure, myocardial infarction or arrhythmia.

**Table 9.2: Comparison of baseline gait characteristics by incident Depressive Symptoms**

| <u>Gait Variable</u>                     | <u>Incident Depressive Symptoms</u><br>n = 344 | <u>Non-depressed</u><br>n = 3,271 |                      |
|------------------------------------------|------------------------------------------------|-----------------------------------|----------------------|
| <b>Gait Speed, Mean (95% CI), cm/s :</b> |                                                |                                   |                      |
| - Normal Walking                         | 129.9 (127.2 – 132.6)                          | 134.1 (133.0 – 135.1)             | F = 8.82; p = 0.003  |
| - Manual Task                            | 126.6 (123.6 – 129.6)                          | 131.5 (130.5 – 132.5)             | F = 9.93; p = 0.002  |
| - Cognitive Task                         | 107.0 (103.8 – 110.1)                          | 109.1 (107.8 – 110.3)             | F = 1.56; p = 0.212  |
| <b>Step Length, Mean (95% CI), cm :</b>  |                                                |                                   |                      |
| - Normal Walking                         | 68.0 (66.9 – 69.2)                             | 70.3 (69.9 – 70.7)                | F = 13.99; p < 0.001 |
| - Manual Task                            | 66.3 (65.1 – 67.5)                             | 68.9 (68.5 – 69.3)                | F = 17.58; p < 0.001 |
| - Cognitive Task                         | 63.5 (62.1 – 64.9)                             | 66.3 (65.8 – 66.8)                | F = 14.14; p < 0.001 |
| <b>Step Width, Mean (95% CI), cm :</b>   |                                                |                                   |                      |
| - Normal Walking                         | 8.3 (8.1 – 8.5)                                | 8.5 (8.4 – 8.6)                   | F = 3.66; p = 0.056  |
| - Manual Task                            | 8.3 (8.1 – 8.5)                                | 8.6 (8.4 – 8.7)                   | F = 3.59; p = 0.059  |
| - Cognitive Task                         | 8.4 (8.1 – 8.6)                                | 8.6 (8.5 – 8.8)                   | F = 4.59; p = 0.033  |
| <b>Double Support Phase, % (95% CI):</b> |                                                |                                   |                      |
| - Normal Walking                         | 25.5 (24.9 – 26.2)                             | 25.4 (25.1 – 25.6)                | F = 0.28; p = 0.590  |
| - Manual Task                            | 26.1 (25.5 – 26.8)                             | 25.8 (25.6 – 26.1)                | F = 0.72; p = 0.398  |
| - Cognitive Task                         | 27.2 (26.5 – 28.0)                             | 26.9 (26.6 – 27.3)                | F = 0.50; p = 0.478  |

Notes:

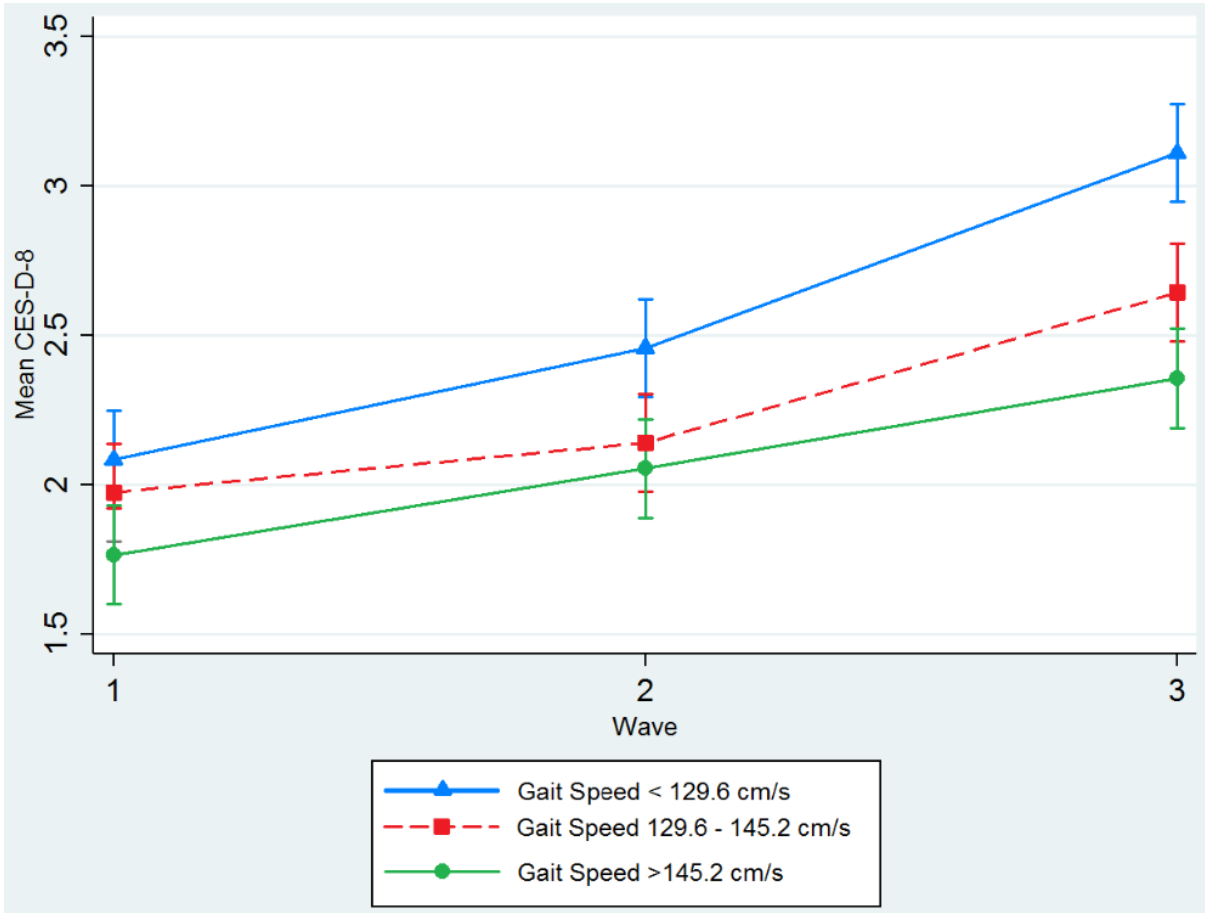
Incident depression is 8-item CES-D score  $\geq 9$  at either wave 2 or wave 3, i.e. 2 or 4 year follow-up.

Abbreviations: CI = confidence interval.

Student's t-test used for continuous variables with adjusted Wald test post-estimation.

Gait speed, step length, step width and double support phase measured using Gaitrite system. Manual task involves carrying a glass of water. Cognitive task involves reciting alternate letters of the alphabet, i.e. A-C-E, etc.

**Figure 9.1: Mean 8-item CES-D at Waves 1, 2 and 3 by Gait Speed Tertiles**



Notes:

*N* = 3,615.

Multilevel model demonstrating trajectory of mean 8-item CES-D scores at waves 1, 2 and 3, i.e. baseline, 2 and 4 year follow-up by tertiles of baseline gait speed at wave 1.

Analysis controls for age, sex, educational attainment, body mass index, systolic blood pressure, alcohol excess (CAGE score  $\geq 2$ ), cardiovascular disease (self-report of angina, cardiac failure, myocardial infarction or arrhythmia), stroke, cognitive impairment (MMSE score  $\leq 24$ ), and antidepressant use.

Logistic Regression models demonstrate that those within the slowest tertile for gait speed (<126.9 cm/s) and shortest tertile for step length (<67.5 cm) have a significantly increased risk of incident depression in fully adjusted models. These findings remained consistent after removing participants taking antidepressants (n=154) at baseline assessment from the analysis. There was no association with tertiles of step width and double support. See table 9.3.

The fully adjusted logistic regression output with incident depressive symptoms as the dependent variable and gait speed as the independent variable of interest is shown in table 9.4. Other variables significantly associated with incident depression include educational attainment, baseline subthreshold depressive symptoms and benzodiazepine use.

**Table 9.3: Logistic Regression with incident Depressive Symptoms as dependent variable**

|                                     | <u>Model 1</u>       | <u>Model 2</u>      | <u>Model 3</u>      | <u>Model 4</u>      |
|-------------------------------------|----------------------|---------------------|---------------------|---------------------|
| <b>Gait Speed cm/s</b>              |                      |                     |                     |                     |
| <b>- Reference: GS&gt; 145.2</b>    |                      |                     |                     |                     |
| <b>- Gait Speed 129.6 – 145.2</b>   | 1.26 (0.86 – 1.83)   | 1.24 (0.84 – 1.81)  | 1.17 (0.80 – 1.71)  | 1.24 (0.84 – 1.84)  |
| <b>- Gait Speed &lt;129.6</b>       | 1.78 (1.30 – 2.44)** | 1.72 (1.22 – 2.43)* | 1.54 (1.08 – 2.19)* | 1.53 (1.05 – 2.25)* |
| <b>Step Length cm</b>               |                      |                     |                     |                     |
| <b>- Reference: SL &gt;74.8</b>     |                      |                     |                     |                     |
| <b>- Step Length 67.5 – 74.8</b>    | 1.47 (1.02 – 2.12)*  | 1.37 (0.93 – 2.03)  | 1.32 (0.89 – 1.95)  | 1.32 (0.87 – 2.00)  |
| <b>- Step Length &lt; 67.5</b>      | 1.96 (1.42 – 2.70)** | 1.81 (1.20 – 2.74)* | 1.54 (1.01 – 2.35)* | 1.70 (1.09 – 2.64)* |
| <b>Step Width cm</b>                |                      |                     |                     |                     |
| <b>- Reference: SW&gt; 9.4</b>      |                      |                     |                     |                     |
| <b>- Step Width 7.7 – 9.4</b>       | 1.18 (0.83 – 1.68)   | 1.07 (0.74 – 1.56)  | 1.12 (0.76 – 1.65)  | 1.09 (0.73 – 1.64)  |
| <b>- Step Width &lt; 7.7</b>        | 1.33 (0.95 – 1.86)   | 1.11 (0.71 – 1.72)  | 1.19 (0.76 – 1.85)  | 1.13 (0.71 – 1.81)  |
| <b>Double Support %</b>             |                      |                     |                     |                     |
| <b>- Reference: DS&gt;26.9</b>      |                      |                     |                     |                     |
| <b>- Double Support 23.5 – 26.9</b> | 0.77 (0.54 – 1.08)   | 0.83 (0.58 – 1.19)  | 0.86 (0.59 – 1.25)  | 0.80 (0.54 – 1.17)  |
| <b>- Double Support &lt; 23.5</b>   | 0.81 (0.59 – 1.11)   | 0.89 (0.63 – 1.27)  | 0.92 (0.64 – 1.31)  | 0.95 (0.66 – 1.36)  |

Notes:

N = 3,615 (Incident Depression, n = 344; Not depressed, n = 3,271).

Logistic regression models with incident depression as dependent variable and gait parameters as independent variables. Reporting odds ratios with 95% confidence intervals. \* denotes p Value < 0.05, \*\* denotes p Value < 0.001.

Model 1 is unadjusted; Model 2 controls for age, sex, body mass index, educational attainment, smoking status and alcohol excess; Model 3 controls for model 2 covariates, as well as subthreshold depressive symptoms, cardiovascular disease (self-report of angina, cardiac failure, myocardial infarction or arrhythmia), stroke, osteoarthritis, benzodiazepine use, MOCA score and systolic blood pressure; Model 4 controls for model 3 covariates but excludes antidepressant users (n=154) from analysis.

Gait speed, step length, step width and double support time measured using Gaitrite system.

**Table 9.4: Fully Adjusted Logistic Regression Model with Incident Depressive Symptoms as Dependent Variable and Gait Speed as Independent Variable of Interest**

| Independent Variable                                    | Odds Ratio (95% CI) | t     | p Value |
|---------------------------------------------------------|---------------------|-------|---------|
| <b>Gait Speed (Ref: Gait Speed &gt;145.2 cm/s):</b>     |                     |       |         |
| - Gait Speed 129.6 – 145.2 cm/s                         | 1.17 (0.80 – 1.72)  | 0.82  | 0.410   |
| - Gait Speed <129.6 cm/s                                | 1.54 (1.08 – 2.19)  | 2.42  | 0.016   |
| <b>Age ( Ref; 50-64 years):</b>                         |                     |       |         |
| - Age 65 – 74 years                                     | 0.68 (0.48 – 0.96)  | -2.20 | 0.028   |
| - Age ≥ 75 years                                        | 0.91 (0.53 – 1.57)  | -0.34 | 0.733   |
| Female Sex                                              | 1.29 (0.95 – 1.75)  | 1.65  | 0.099   |
| <b>Educational Attainment (Ref: Primary)</b>            |                     |       |         |
| - Secondary Level                                       | 0.56 (0.40 – 0.76)  | -3.61 | < 0.001 |
| - Tertiary Level                                        | 0.60 (0.42– 0.86)   | -2.75 | 0.006   |
| Body Mass Index                                         | 1.20 (0.96 – 1.49)  | 1.61  | 0.107   |
| Current Smoker                                          | 1.26 (0.84 – 1.88)  | 1.12  | 0.263   |
| <b>CAGE Alcohol Status (Ref: CAGE 0-1) <sup>A</sup></b> |                     |       |         |
| - CAGE 2-4                                              | 1.35 (0.89 – 2.02)  | 1.43  | 0.153   |
| - Did not complete                                      | 1.26 (0.78 – 2.04)  | 0.95  | 0.340   |
| <b>Baseline CES-D Score (Ref: 0-5)</b>                  |                     |       |         |
| - CES-D 6-10                                            | 2.18 (1.56 – 3.05)  | 4.57  | <0.001  |
| - CES-D 11-15                                           | 5.10 (3.42 – 7.60)  | 8.02  | <0.001  |
| <b>Systolic BP (Ref: 120-139 mm Hg) <sup>B</sup></b>    |                     |       |         |
| - Sys BP < 120 mm Hg                                    | 0.85 (0.58 – 1.24)  | -0.86 | 0.390   |
| - Sys BP 140 – 159 mm Hg                                | 0.85 (0.60 – 1.19)  | -0.95 | 0.342   |
| - Sys BP ≥ 160 mm Hg                                    | 0.81 (0.48 – 1.39)  | -0.76 | 0.449   |
| Cardiovascular Disease <sup>C</sup>                     | 0.95 (0.60 – 1.51)  | -0.22 | 0.827   |
| Stroke                                                  | 0.52 (0.13 – 2.14)  | -0.91 | 0.365   |
| MOCA                                                    | 0.99 (0.95 – 1.04)  | -0.26 | 0.793   |
| Osteoarthritis                                          | 1.10 (0.76 – 1.59)  | 0.48  | 0.630   |
| Benzodiazepine Use                                      | 2.45 (1.16 – 5.20)  | 2.34  | 0.019   |

Notes: A CAGE Alcohol Scale for Alcohol Problem; B Systolic BP measured twice in seated position using Omron digital cuff and average of 2 readings taken C Cardiovascular Disease defined as self-report of angina, cardiac failure, myocardial infarction or arrhythmia.

## **9.6 Discussion**

This study demonstrates that older people with incident depressive symptoms over 4-year follow-up period have significantly slower gait speed, and shorter step length, but no difference in step width or double support phase at initial assessment. On average, they walk over 4 cm/s slower than their peers who do not develop depression. Slower gait speed and shorter step length were associated with an increased risk of depressive symptoms. The associations with these gait parameters remained significant after controlling for important covariates including socio-demographics, cardiovascular disease, systolic BP, smoking and alcohol excess. Furthermore, findings did not change significantly when participants taking antidepressants at baseline were excluded from the analysis.

To our knowledge, this is the first longitudinal study to analyse the association between specific spatiotemporal gait measures and incident depressive symptoms. We have previously shown that abnormal TUG predicted incident depression within the TILDA cohort(260). Furthermore, longitudinal studies have demonstrated a close relationship between gait speed (analysed during 2.5 - 3M walk) and depressive symptoms but did not analyse specific spatiotemporal gait parameters(275, 276). This study also adds significantly to the evidence-base in this field as it involves a large well-described cohort of community-dwelling older people and importantly the comprehensive TILDA dataset allows us to control for a wide range of covariates, including subthreshold depressive symptoms, and cardiovascular markers.

A possible mechanism for the association we have found is cerebral white matter disease, reflected by WMH on brain MRI. WMH, particularly involving the frontal lobe, are more prevalent in older people with both depression and gait problems(294, 296). In parallel with gait disturbance, an increasing burden of white matter disease is also a marker for an increased risk of chronic depressive symptoms, and lower remission rates(37). Importantly, the characteristic higher level gait disorder seen in this context involves problems with gait initiation, and short shuffling steps, consistent with the reduced gait speed and step length we have demonstrated in this study(114).

Executive dysfunction, which is implicated in gait problems in later life (297) is a common clinical feature of LLD, and often related to cerebral WMH(298). It has been suggested as a potential mediator for the link between depression and gait problems(283). While some smaller studies have demonstrated a relationship between dual task gait and depression(299,

300), we found no association between gait speed and incident depression during the cognitive dual task walk, although the association with step length remained significant. An alternative explanation for the longitudinal relationship we have identified is that mobility restriction has an adverse effect on mood and well-being as a response to the limitations it imposes on independence and functional status in later life.

These findings are significant because, given current and future demographic shifts and increasing worldwide longevity(301), unravelling and understanding associations between common late life conditions that impact significantly on functional status is imperative(302). Both depression and gait problems commonly co-exist in later life(283) and it appears that older people with a combination of both conditions are at particularly high risk of functional decline(284).

Additionally, these findings raise the possibility that gait analysis could be used as a tool to identify those at higher risk of LLD. Depression in later life is difficult to diagnose and older people are much less likely to present to a healthcare professional with mood-related symptoms(11). Given the adverse outcomes associated with untreated depression in later life, including early mortality and functional decline(303, 304), it is important to identify older individuals at higher risk of developing depression in order to improve case finding and promote early intervention. It must be noted however that any such tool would need to be tested against a clinical depression diagnosis rather than a tool such as the CES-D.

Furthermore, given recent evidence that physical exercise may be an effective adjunctive therapy in LLD(285, 305), this study also raises the possibility that exercise could also be used as a preventative strategy for depression, due to the beneficial effect it can have on gait and mobility in later life(306). This hypothesis would need to be tested in carefully planned interventional studies however.

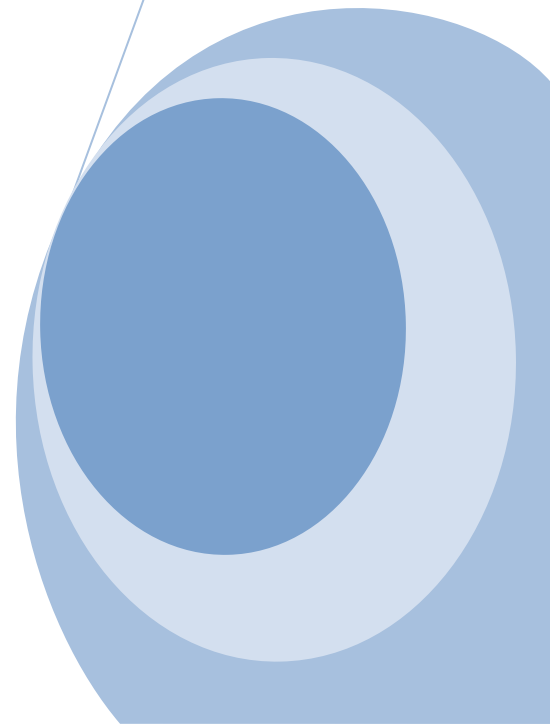
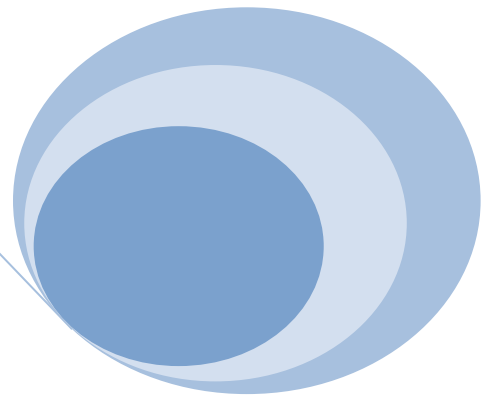
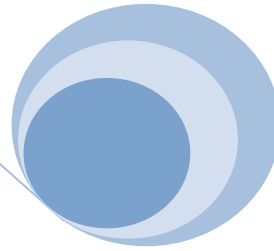
There are some important limitations of this study which should be noted. Depression diagnosis is based on the CES-D, which has been validated for use in an older population but is not the gold standard for depression diagnosis, which remains a structured clinical interview. In addition, self-reported doctor diagnosis was used to define cardiovascular disease and may therefore be subject to response bias. Furthermore, as stated previously, exclusion of participants with dementia at baseline was based on a prior doctor's diagnosis only so therefore this study may include some participants with undiagnosed dementia. Additionally participants did not undergo clinical examination to exclude incipient dementia as part of this study. While it is difficult therefore to account for the fact that participants may develop

dementia during follow-up, we controlled for MOCA at wave 1 in regression models, and by wave 3 only 3 participants included in the study had a new doctor's diagnosis of dementia.

Strengths of this study include the large, well-described population of older adults who underwent advanced gait analysis, as well as robust 2 and 4-year follow-up assessment.

In conclusion, this study demonstrates that reduced step length and slower gait speed are independent predictors of incident depressive symptoms in a large, non-depressed cohort of community-dwelling adults aged 50 and over. These findings are important given the high prevalence of both gait problems and depression in later life, as well as the significant impact both conditions have on functional status, and further work examining the role of cerebral white matter disease, which is common to both conditions and may explain these findings, would be welcome.

## **CHAPTER 10:** Discussion



### **10.1 Overview of Key Findings**

The key findings from these studies are:

- Lower BP and symptomatic OH both independently predict incident depressive symptoms in a large cohort of community-dwelling older people
- Depressive symptoms in later life are associated with significantly lower frontal lobe perfusion which is BP-dependant
- Cerebral WMH burden is higher in depressed older adults but only in those with lower BP or OH
- Gait problems, specifically prolonged TUG, slower gait speed and shorter step length, independently predict incident depressive symptoms in later life

While cross-sectional studies have shown a consistent relationship between lower BP and depression in later life, results from longitudinal studies are less consistent and are limited by not adjusting for important covariates such as subclinical depressive symptoms at baseline and cardiovascular disease (102). Our study found that sBP values less than 130 mm Hg were associated with a 40% increased risk of incident depressive symptoms (241). We further demonstrated that sOH-30 conferred a two-fold higher risk of incident depressive symptoms during 4-year follow-up (242). This is the first longitudinal analysis of this relationship and findings are supported by prior cross-sectional studies involving smaller numbers of participants (102).

Study 3 examining cerebral perfusion measured by NIRS found that participants with depressive symptoms had lower frontal lobe perfusion after standing, and that lower systolic BP in depressed individuals may be the predominant driver of this association (269). Prior neuroradiological studies have demonstrated cerebral hypoperfusion in older depressed participants but are generally based on a static supine assessment which is not linked with BP values (71, 72). Additionally, in accordance with prior studies (44) we show that LLD is closely associated with cerebral white matter burden on brain MRI. However, we also demonstrate in two-way interaction models that this relationship is only significant in those with lower BP or with OH.

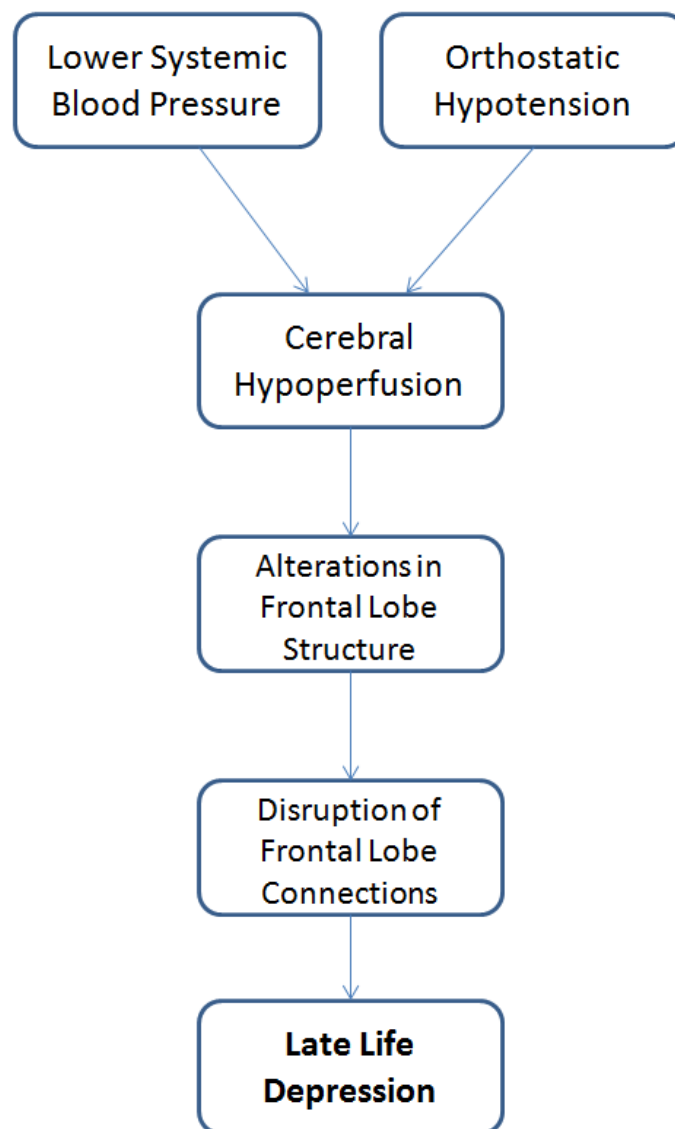
Participants with a TUG  $\geq 12$  seconds at baseline assessment have a two-fold higher risk of incident depressive symptoms, and those who develop depression walk on average 4cm/s slower and have a step length 2.3cm shorter than their peers who do not develop depressive symptoms (260, 307). These are the first studies to demonstrate the longitudinal association between comprehensive gait analysis, including spatiotemporal gait parameters, and incident depression in an older population.

## **10.2 Depression & Cerebral Perfusion**

We hypothesised that conditions such as orthostatic and systemic hypotension, which predispose to cerebral hypoperfusion, increase the risk of depression in later life.

We found that both systolic BP < 130 mm Hg (study 1) and symptomatic OH (study 2) predict incident depressive symptoms in fully adjusted models. Secondly, study 3 demonstrates that participants with depression had lower frontal lobe perfusion after standing, and that this was BP-dependant. Finally, study 4 shows that while cerebral WMH burden is higher in depressed participants, that this was only significant in those with either lower BP or OH. These findings have informed the schematic representation shown in figure 10.1.

**Figure 10.1: How does lower blood pressure lead to depression?**



These findings are supported by prior studies which have demonstrated cerebral perfusion deficits in depression, albeit using techniques such as MRI or TCD and not bedside testing(69, 71, 243).

We specifically measured frontal lobe perfusion in this study and this region is of particular interest as disruption of frontal networks has been identified as a key process underpinning LLD(33). Understanding this link between depression and frontal perfusion is important because CBF is potentially modifiable. While we have identified BP as a key factor in determining CBF, our study also highlighted other important factors associated with cerebral perfusion, including heart disease and weight. Other studies have suggested that alcohol intake, cognitive training and exercise may also influence CBF(257, 308).

### **10.3 Depression & Gait**

We also hypothesised that gait disturbance was closely associated with depression, and planned to clarify the longitudinal relationship between these two common syndromes of later life.

Gait problems, particularly higher level gait problems, are also closely linked with cognitive decline. For example, older people with neurological gait abnormalities have a two-fold higher risk of dementia (309). To date, the prospective link with depression was less well-defined however.

In study 5 we examined the bidirectional relationship between TUG and depression and found that those with TUG  $\geq 12$  seconds had a two-fold higher risk of depression in fully adjusted models(260). Depression did not predict incident gait disturbance after adjustment however.

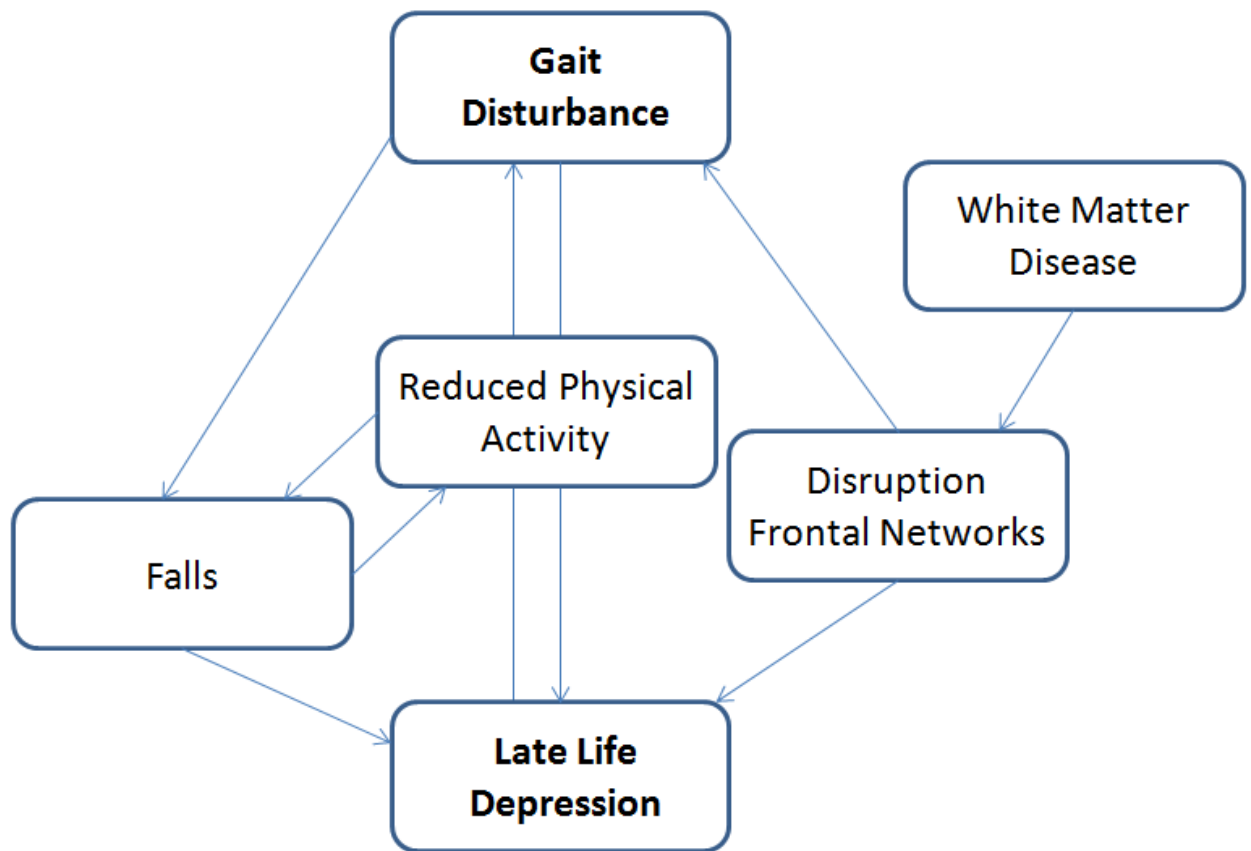
Across these studies we adjusted for the most frequent causes of both middle and lower gait problems (arthritis, alcohol, diabetes, stroke, Parkinson's disease), so it is likely that much of the effect we see in these studies is related to higher level gait impairment. Additionally, like depression, structural and functional frontal lobe changes, particularly white matter disease, appear to have an important role in higher level gait problems, suggesting a common mechanistic pathway may exist(114).

Further mechanisms that may link gait problems with depression in later life are shown in figure 10.2. Gait problems can lead to functional decline, which significantly increases the risk of depression. Depression in later life is also closely associated with falls risk (13), and the interaction between mobility problems, falls and low mood may also be an important factor in this relationship.

Clinically, higher level gait problems present with slower walking speed and short, shuffling, magnetic steps and can sometimes be difficult to distinguish clinically from Parkinsonism(114). It is interesting therefore that the gait parameters predictive of incident depressive symptoms in study 6 were gait speed and step length, further supporting our hypothesis of a common biological basis for both conditions.

Both depression and gait problems commonly co-exist in the clinical setting and it appears that older people with a combination of both conditions are at particularly high risk of functional decline(284). Unravelling and understanding associations between common late life conditions that impact significantly on functional status is important in order to inform strategies aimed at better identification and prevention in older people at risk of poor clinical outcomes.

**Figure 10.2: How are Gait Disturbance and Depression linked?**



#### **10.4 Clinical Relevance of Findings**

##### *Modifiable Risk Factors*

The findings from these studies are important because they highlight potentially modifiable pathways leading to LLD.

Conditions predisposing to cerebral hypoperfusion may cause alterations in frontal lobe structure and function, which ultimately leads to the clinical syndrome of LLD(33). Hypotension, resulting in cerebral hypoperfusion, is often amenable to treatment (80), and appropriate intervention could therefore reduce incidence of depression in later life. This would need to be tested in dedicated prospective studies however.

It must also be noted that if this does represent a modifiable pathway to incident depression, it is likely to account for only a relatively small proportion of cases. For example, our analysis suggests that symptomatic OH increases the probability of incident depression by 6% after adjusting for covariates. When we consider that OH affects up to 30% of older people however (310), the associated risk may be substantial.

Additionally, gait and balance impairment significantly increases the risk of incident depressive symptoms. Depression could represent a response to the physical limitations imposed by mobility issues or there could be a common mechanistic pathway between the conditions, with a focus on disruption of important frontal lobe networks(33). There is emerging evidence however, that physical exercise may be an effective adjunctive therapy in LLD(258, 285), and these studies raise the possibility that exercise could also be used as a preventative strategy for depression, due to the beneficial effect it can have on gait and mobility in later life(306).

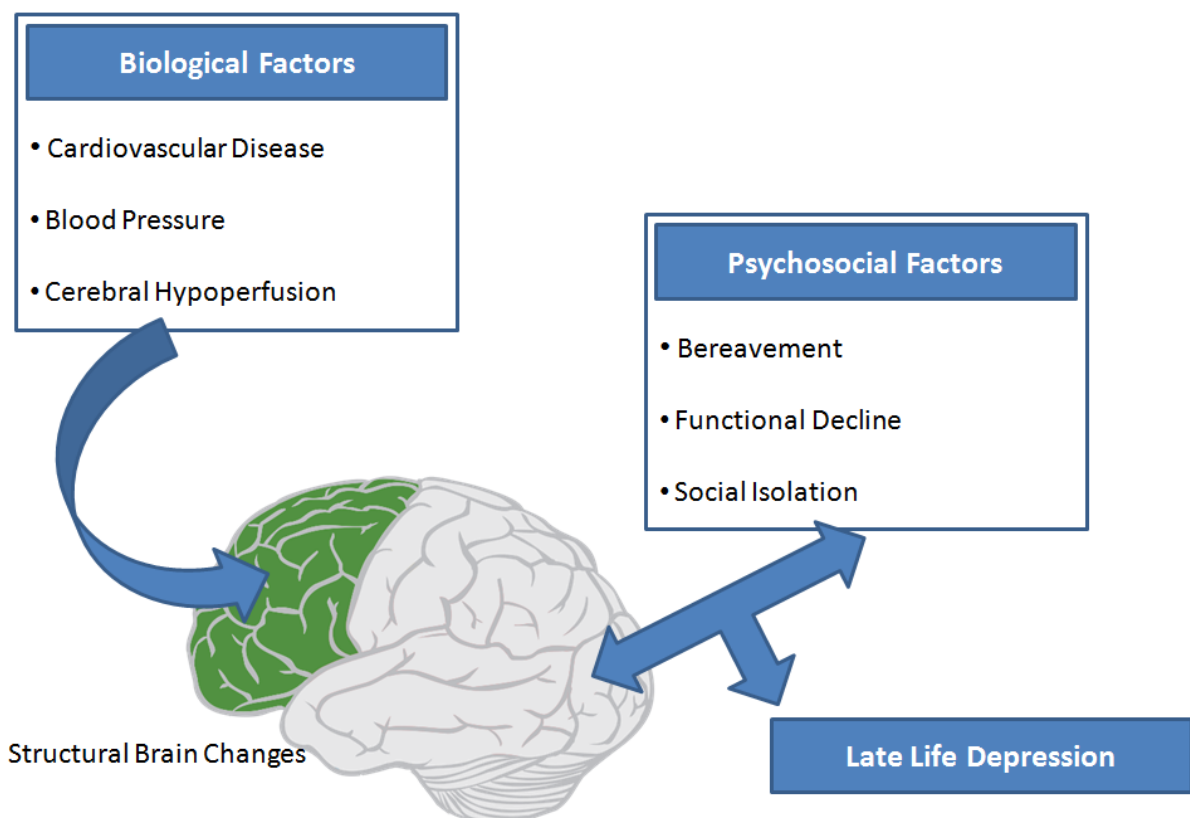
### Multimodal Prevention

While identification of potentially modifiable risk factors is important, it is unlikely that targeting a single modifiable risk factor or pathway in LLD will be successful, and integration of these findings into a multimodal intervention is likely to be more beneficial.

The adverse impact of LLD is considerable, at the individual level where it is a potent risk factor for functional decline and early mortality, but also at a societal level with significant indirect impact on population health (17). Interventions aimed at prevention should therefore be a priority (311).

LLD is a particularly complex illness however, where biological factors such as structural brain changes interact with psychosocial factors like bereavement to influence clinical expression of the illness (155)(figure 10.2). Preventative strategies are therefore likely to work only if they are multi-modal, addressing a combination of relevant biological and psychosocial risk factors.

**Figure 10.2: The Interaction of Biological and Psychosocial Factors in Late Life Depression**



*Notes: Interaction between biological factors, which lead to structural brain changes, conferring a vulnerability to depression and psychosocial stressors, such as bereavement.*

Multi-modal interventions now have a growing evidence base in later life, with programmes such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability demonstrating improvement or maintenance of cognitive functioning in at-risk older people over 2 years (312).

Findings from work such as ours, along with other population based findings in terms of depression risks in later life could be used as a basis for a similar dedicated prevention programme for depression. While interventions such as these can be costly and require careful economic evaluation (313), the healthcare cost burden associated with LLD should make them attractive to policymakers (314).

### *Case Identification*

Our findings may also have implications in terms of identification of older people with depression.

Depression in later life is often difficult to diagnose. Diagnosis is clinical and can be complicated by atypical presentation, multimorbidity and cognitive impairment. Only one third of older people with significant depressive symptoms present to their general practitioner for example.

Gait analysis may therefore potentially be used as an objective marker to identify those at risk of depression and improve case finding, as abnormalities at baseline in a non-depressed cohort reliably predicted incident depressive symptoms.

Additionally, several neuroradiological studies have identified frontal lobe hypoperfusion in the context of LLD using techniques such as MRI, CT or TCD. There is also some evidence using these techniques that perfusion deficits may resolve with appropriate treatment and remission of LLD. NIRS is a relatively inexpensive, bedside test that could be applied in clinic to measure frontal lobe perfusion non-invasively and could therefore be used to track similar progress at the bedside, potentially as a biomarker of response to treatment in LLD.

### *Blood Pressure Targets*

Our findings are also relevant in relation to hypertension treatment targets in later life. The SPRINT study demonstrates benefits in targeting a systolic BP of less than 120 mm Hg results in a reduction in the rate of fatal and non-fatal cardiac events. We have demonstrated however that BP values lower than this are independently associated with a higher risk of incident depressive symptoms in a population-based sample.

### **10.5 Strengths & Limitations**

There are some limitations of our studies which should be noted. Rather than the gold-standard structured clinical interview, we have used the CES-D to define cases of depression throughout. The CES-D has been well validated against clinical depression diagnosis specifically in an older population however.

Furthermore, while we discuss a potentially modifiable pathway causing frontal lobe hypoperfusion and ultimately leading to LLD, with strong evidence spread across studies and supported by other published work, we do not have sufficient evidence within our studies to imply causation as they are observational. Dedicated randomized trials assessing the relationship between BP, cerebral perfusion and depression would therefore be welcome.

Further work establishing the longitudinal relationship between cerebral perfusion measured by NIRS and depression is also important. While our study identifies a significant cross-sectional association, the direction of this association needs to be confirmed prospectively.

Strengths of these studies include the use of the well-described TILDA cohort of older people, with a wide breadth of demographic, social and biological data, including novel ambulatory measures such as spatiotemporal gait, continuous orthostatic BP and NIRS frontal lobe perfusion. The TILDA cohort is a large population-representative sample allowing robust longitudinal analyses, controlling for an extensive range of important covariates.

## **10.6 Conclusion**

Depression affects more than 300 million people worldwide, and LLD in particular confers a significant independent risk of functional decline, reduced quality of life and early mortality, including death by suicide. Depression in later life is often challenging to diagnose. Treatment can be complicated by co-existing illnesses and remission rate are relatively high.

Understanding the role of potentially modifiable risk factors that underpin LLD is therefore crucial in terms of population health. Across robust longitudinal studies, we have identified lower systemic BP and OH as significant independent risk factors for incident depressive symptoms in a large cohort of community-dwelling older people. This raises the possibility that hypotension may be a modifiable risk factor for depression in later life.

Furthermore, we have shown that older people with depression have reduced frontal lobe perfusion, as well as higher burden of cerebral white matter disease, both of which appear to be BP-dependant. This suggests that cerebral hypoperfusion may be the mechanism by which hypotension increases the risk of depression.

We have also shown that gait disturbance, specifically longer TUG, slower gait speed and shorter step length, is a strong predictor of incident depressive symptoms in this large cohort of non-depressed older people. These findings are relevant in the context of emerging evidence that physical activity may be beneficial as an adjunct to standard therapy in LLD, but also because physical activity has been shown to improve cerebral perfusion in later life.

These findings are novel, and underline the complex inter-relationship between heart health, brain health and physical health/function in later life, with a particular focus on frontal lobe integrity and function. Our intention is that the findings from these studies will inform a multimodal preventative program aimed at reducing the incidence of depression in older people at risk of mental health problems.

Enhanced life expectancy and greater longevity worldwide should be celebrated as important achievements but should also be accompanied by strategies targeting reduced morbidity in later life. Given that depression is now recognised as the leading cause of disability worldwide, and the complexities involved in identifying and treating depressed older adults, prevention of incident LLD should be a global public health priority.

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