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University of Dublin, Trinity College
School of Medicine,
Department of Medical Gerontology

Autonomic Function and Depression in Older Adults

Margaret Claire O Regan

Student ID 07132891

Submitted in fulfilment of the requirement of the degree of Doctor of Philosophy

2013
Declaration

I declare that no part of the material contained within my thesis has been submitted as an exercise for a degree in Trinity College Dublin or any other institution.

The material of this thesis forms part of the cross-sectional data analysis from a prospective longitudinal study entitled 'The Irish Longitudinal Study on Ageing' (TILDA). I certify that I performed all work contained within this thesis, from analysis and interpretation of data to manuscript preparation. The hypotheses, design and governance of the TILDA study is under the direction of Professor Rose Anne Kenny. Professor Rose Anne Kenny and Dr Patricia M Kearney provided guidance and direction to the issues addressed within this thesis and acted as supervisors. Dr Ciaran Finucane and John Frewen performed significant data processing of the neurocardiovascular signals obtained during the health assessment.

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Claire O Regan

Signed: [Signature]
Date: 07/10/2013
Overall Summary

The principle aims of this doctoral investigation were to provide new insights into the relationship between depression and cardiovascular disease (CVD) by investigating the functioning of the autonomic nervous system (ANS) in a population sample of older adults with depression.

Depression and CVD are leading burdens of disease worldwide and represent a major public health challenge. Despite the epidemiological evidence linking these conditions the mechanisms that underlie these associations are not well understood. The ANS is a candidate mechanism that may be particularly relevant in older adults; since there is evidence that deregulation of this system can cause CVD and contribute to the development of depression.

Initially I reviewed the literature on the cross-sectional and longitudinal association between measures of autonomic function and depression. To date a few studies have shown an association between orthostatic hypotension (OH) and depression; and consequently it has been suggested that OH induced hypoperfusion may be an important factor in the development of late-life depression. In addition there is evidence that heart rate variability (HRV) is reduced in depression and that this may lead to CVD. However, there is considerable debate about whether this is a consequence of the disorder or due to antidepressant medication.

The first study examined the prevalence of depression in The Irish longitudinal study on ageing (TILDA). We reported a weighted prevalence of 10% in this representative sample of community dwelling adults, aged 50 and over. The next two studies investigated the prevalence and severity of OH in older adults and the cross-sectional association between OH and depression. We defined OH using two measures - the first was centre based and recorded beat-to-beat blood pressure (BP) during orthostasis, using photoplethysmographic equipment. The second facilitated the inclusion of home based participants, by
recording BP in seated and standing positions, using a traditional cuff-based oscillometric device.

Results from the first study showed that participants with depression had a higher prevalence of symptomatic OH (SOH) and Initial OH relative to non-depressed controls; and participants who had not recovered their BP by 90 seconds post stand were, two times more likely to have depression. These findings were confirmed by the second study that showed higher levels of depression in participants with SOH. In both studies, the relationship between OH and depression was dependant on the presence of symptoms of hypoperfusion.

Finally, we compared time domain (standard deviation of normal-to-normal beats ms$^2$ [SDNN]) and frequency domain (High Frequency ms$^2$ [HF] power and Low Frequency ms$^2$ [LF] power) measures of HRV among those with and without depression and examined the influence of antidepressant medications on HRV. We found that participants on antidepressants (with or without depression) differed significantly from controls on measures of SDNN, LF and HF power. Depressed participants not taking antidepressants did not differ from controls on any indices of HRV. All antidepressants had a lowering effect on HRV; however, selective serotonin reuptake inhibitors (SSRIs) had a better HRV profile relative to tricyclic antidepressants (TCAs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) respectively.

In conclusion, our findings represent an original contribution to the limited literature on autonomic function and depression in older adults and advances our understanding of the complex relationship between depression and CVD.
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<th>Definition</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>Ach</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Ad</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>APOE</td>
<td>Apolipoprotein E</td>
</tr>
<tr>
<td>AS</td>
<td>Arterial stiffness</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BRS</td>
<td>Baroreflex sensitivity</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>CSH</td>
<td>Carotid sinus hypersensitivity</td>
</tr>
<tr>
<td>CSS</td>
<td>Carotid sinus syndrome</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>DWMHs</td>
<td>Deep white matter hyperintensities</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FFT</td>
<td>Fast fourier transform</td>
</tr>
<tr>
<td>GAD</td>
<td>Generalised anxiety disorder</td>
</tr>
<tr>
<td>HF</td>
<td>High frequency</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>LF</td>
<td>Low frequency</td>
</tr>
<tr>
<td>LLD</td>
<td>Late life depression</td>
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<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>MOCA</td>
<td>Montreal Cognitive assessment</td>
</tr>
<tr>
<td>NAd</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td>NCVI</td>
<td>Neurocardiovascular instability</td>
</tr>
<tr>
<td>OH</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>PNS</td>
<td>Parasympathetic nervous system</td>
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<tr>
<td>PSD</td>
<td>Power spectral density</td>
</tr>
<tr>
<td>PVHs</td>
<td>Periventricular hyperintensities</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RSA</td>
<td>Respiratory sinus arrhythmia</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDNN</td>
<td>Standard deviation of normal-normal intervals</td>
</tr>
<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
</tr>
<tr>
<td>TILDA</td>
<td>The Irish longitudinal study on ageing</td>
</tr>
<tr>
<td>VaD</td>
<td>Vascular dementia</td>
</tr>
<tr>
<td>VCD</td>
<td>Vascular cognitive disorder</td>
</tr>
<tr>
<td>WML</td>
<td>White matter lesions</td>
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<td>WHHs</td>
<td>White matter hyperintensities</td>
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</table>
1 Introduction

Chapter one provides an overview of late-life depression and existing literature linking depression and vascular disease. The current status of the vascular depression hypothesis is discussed and the assessment of depression in The Irish Longitudinal Study on Ageing (TILDA) is described. Chapter two provides a review of literature exploring the autonomic nervous system (ANS), common conditions of autonomic dysfunction and their relationship with depression, along with a detailed description of the methods used to assess autonomic function. The methodology underlying TILDA and the benefits of population studies are summarised and finally the objectives of my thesis are presented.

1.1 Late-Life Depression

1.1.1 Background
Depression imposes a heavy burden of morbidity and mortality on society and represents a major public health challenge. The Global Burden of Disease Study [1] predicts that depression will be the leading cause of disease burden by 2030 (see figure 1.1). A number of misconceptions still surround the illness in older adults; most commonly that depression is understandable or a realistic response to ageing and physical illness. This can lead to under-diagnosis and consequently the illness is frequently overlooked by non-specialist medical staff [2]. In the community it is estimated that less than 20% of cases are detected or treated [3].

Late-life depression (LLD) is commonly defined as a major depressive episode occurring in older adults usually after the age of 60 or 65 years [4]. As the
proportion of older people in the population expands; the adequate recognition and prevention of the causes and negative consequences of LLD is a research priority. In recent years the literature on LLD has increased and many gaps in our understanding have been filled. It is now believed that depression in older adults differs from that experienced by individuals earlier in the lifespan [5]. Presentation, aetiology, risk and protective factors all reflect aspects of the older adult's position in the lifespan. Knowledge of the ways in which age may alter the factors associated with the onset and progression of depression is essential for effective treatment of older adults [6].

**Figure 1.1 Ten leading causes of burden of disease in 2004 and predictions for 2030 [1]**

<table>
<thead>
<tr>
<th>2004 Disease or injury</th>
<th>As % of total DALYs</th>
<th>Rank</th>
<th>2030 Disease or injury</th>
<th>As % of total DALYs</th>
<th>Rank</th>
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<td>Unipolar depressive disorders</td>
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<td>3.2</td>
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<td>Hearing loss, adult onset</td>
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<tr>
<td>Birth asphyxia and birth trauma</td>
<td>2.7</td>
<td>8</td>
<td>Refractive errors</td>
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<td>1.3</td>
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</table>

12
1.1.2 Epidemiology
Life expectancy is increasing worldwide. In Ireland it is estimated that between 20 to 25 per cent of the population will be aged 65 years and over in 2041 compared with 11 per cent in 2006 [7]. The reported prevalence of LLD in international studies varies enormously. A 2006 review of 122 papers found that the prevalence ranged from 1% to 49% [8]. Although it is accepted that the true prevalence of LLD varies; several methodological factors are thought to contribute to the wide divergence in prevalence. Most importantly, the definition of depression is highly variable, with surveys that assessed major depression yielding lower prevalence rates than those investigating minor or subclinical depression. Sampling strategies also contributed significantly; whereby older people sampled from private households tended to yield lower estimates than samples drawn from nursing/residential homes or hospital settings.

In Ireland, there is also little consensus on the prevalence of depression in the older population. In 1999, the EURODEP study (n=451) reported a 12% prevalence of depression among a sample of adults aged 65 and over resident in Dublin [9]. Subsequently, the Health and Social Services for Older People surveys (HeSSOP I, n=937; HeSSOP II, n=1053) reported a prevalence of between 2 and 5% for severe depression and between 4 and 9% for borderline depression [10]. Most recently in 2007, the Surveys of Lifestyle, Attitudes and Nutrition survey (SLAN, n=1969) reported a 3% prevalence of major depressive disorder (MDD) among community-dwelling adults aged 65 and over [11]. Epidemiological studies have identified a wide variety of risk factors for LLD including lower income and socioeconomic status, cognitive
impairment and medical illness [12]. In addition bereavement, sleep disturbance, disability, and female gender are significant risk factors for depression in community dwelling older people [13]. Social and psychosocial risk factors are also important, however it has been suggested that those who survive into later life may actually be characterised by psychological resilience [14] resulting in an even greater focus on the biological factors that may lead to the development of depression in older adults.

1.1.3 Classification of Depression
Classification of depression is currently a matter of great debate regarding whether dimensional or categorical approaches are most appropriate [15]. The Diagnostic and Statistical Manual of the American Psychiatric Association Fourth Edition, text revision (DSM-IV-TR) is the dominant system employed in both clinical practice and research for the formal classification of depression [16] It will be replaced in May 2013 by the DSM-V.

The DSM-IV employs a categorical approach to psychiatric disorders, viewing major depression as a discrete disorder that occurs independently of other disorders. The DSM-IV includes emotional (depressed mood, anhedonia), cognitive (feelings of worthlessness or excessive/inappropriate guilt, diminished ability to think or concentrate, thoughts of death or dying or suicidal ideation), and somatic (weight loss or weight gain, insomnia or hypersomnia, fatigue or loss of energy, psychomotor retardation or agitation) symptoms of depression. According to the DSM-IV, a diagnosis of MDD requires the presence of at least five depressive symptoms for two weeks or longer, one of which must be depressed mood or anhedonia. Thus, depression
is conceptualised by the DSM-IV as comprising a group of related symptoms, some of which are seen as criteria for the disorder (e.g. depressed mood or anhedonia), while others are not [17]. As a consequence of requiring a certain number of symptoms, but not a specific group of symptoms, very different presentations can meet criteria for MDD.

The DSM-IV describes several depressive disorders including MDD, dysthymic disorder and bipolar disorder, however much attention has recently been given to the experience of depressive symptoms that do not fulfil the criteria for a diagnosis of MDD [18, 19]. Variously defined as minor, subsyndromal, or subthreshold depression these symptoms are associated with impairment similar to that of MDD [18-21]. In older adults these depressive symptoms seem especially relevant; as health and functional ability may be seriously impeded by a relatively small number of depressive symptoms [22, 23]. Therefore while the categorisation of specific subtypes and severity levels of depression is important for diagnostic purposes in older adults, any depressive symptoms that impair health, cognition or activities of daily living (ADLs) are clinically significant. Some researchers have argued that depression may occur on a spectrum, with symptoms that do not meet syndromal criteria for MDD representing a less severe manifestation of the same disorder [23].

Although subthreshold depression is not formally recognised in the nomenclature, DSM-IV [16] introduced a number of “subthreshold” diagnoses including “minor depressive disorder” in the Appendix as conditions requiring further study. LLD is also not classified by DSM-IV, but as mentioned earlier it
is commonly defined as a major depressive episode occurring in older adults usually after the age of 60 or 65 years [4].

1.1.4 Age of Onset
A growing body of evidence suggests that late-onset depression (depression occurring for the first time in later life) differs from early-onset (recurrent) depression in terms of clinical features, aetiology, neuroanatomical substrates and prognosis. However, there is no consensus on the age cut off (typically between 50 and 65 years). It does appear that half or more of older adults with MDD are experiencing a new condition arising for the first time in old age, whereas half or less have experienced their first episode of depression considerably before old age [24]. For example, in 2001 Brodaty et al found that half of all patients attending a geriatric mood disorders unit had their first onset of depression at age 60 or older [24]. Similarly, a study of older depressed home-care patients found that 71% of patients experienced their first episode of depression after age 60 [25].

Although scepticism exists regarding the divided classification of depression on the grounds of age at onset, (primarily owing to a lack of valid methods for pinpointing that age), late-onset depression is recognised to be aetiologically different from depression of early onset, and aetiologically heterogeneous in itself [26-28]. Older adults with late onset depression have less likelihood of a positive family history of depression, more neuropsychological impairment, stronger relationship with the development of subsequent dementia, and a higher association with brain changes on magnetic resonance imaging (MRI) [29, 30]. According to existing literature the term LLD encompasses both late-
onset cases as well as early-onset cases that recur or continue into later years of life [28, 31].

1.1.5 Clinical Features
In contrast to depression earlier in life, the presentation and treatment of LLD is complicated by higher rates of co-morbidity with medical illness and the presence of cognitive impairment. Older adults are less likely to endorse cognitive-affective symptoms of depression, including dysphoria (depressed mood) and worthlessness/guilt, than are younger adults [32-34]. Sleep disturbance, fatigue, psychomotor retardation, loss of interest in living, and hopelessness about the future are believed to be more prevalent in LLD than in depression in younger or middle-aged adults [35]. Subjective complaints of poor memory and concentration are also common among depressed older adults and cognitive processing speed and executive functions have been found to be impaired in objective testing [36]. Overall, there does not appear to be substantial differences by gender or ethnicity [8]. With respect to somatic symptoms, depressed older women report more appetite disturbance than do men, whereas older men report more agitation [37].

1.1.6 Co-morbidity
It is well established that LLD frequently occurs in the context of medical illness. Although virtually any serious or chronic condition can produce a depressive reaction, the conditions believed to be most strongly associated with depression include vascular disease and neurological conditions such as Alzheimer’s disease and Parkinson’s disease. The co-occurrence of anxiety with depression is particularly common in older adults. One study estimated that one third of the patients with MDD met inclusion criteria for generalised
anxiety disorder (GAD) [38] while another found that almost 50% of individuals with depression also met criteria for anxiety disorders [39]. Co-occurrence has been associated with higher levels of disability [40], suicide [41] and impaired social function [38] compared to non-anxious depressed people.

1.2 Vascular Disease as a Risk Factor for Depression

1.2.1 Depression and Cerebrovascular Disease
The association between depression and cerebrovascular disease was first described in 1905; however, it has only been possible to study brain changes in depression systematically in the last two decades due to advances in brain imaging techniques such as computer tomography (CT) and MRI scans. Subclinical cerebrovascular disease is generally accepted to be visualised as hyperintensities in MRI scans (see Figure 1.2). The hyperintensities appear as bright areas of increased signal intensity and are best visualised in T2 weighted and fluid attenuated inversion recovery (FLAIR) images. They are seen either in the sub cortical white matter (white matter hyperintensities [WMHs]) or deep gray matter. WMHs have been divided into 2 types: those adjacent to the ventricular system (periventricular hyperintensities [PVHs]) and those separate from the ventricles in the deep white matter (deep white matter hyperintensities [DWMHs]). Collectively, they are often referred to as white matter lesions (WML) [42].

1.2.1 White Matter Hyperintensities in LLD
A large number of studies have found a higher rate and severity of WMHs in individuals with LLD compared with healthy elderly controls [43-46].
Longitudinal findings from the Rotterdam study have shown that older adults with severe WMHs have 3 to 5 times the risk of depression compared to controls and the association was stronger for DWMHs rather than PVHs [47]. Likewise, after 7 years of follow up, the Cardiovascular Health Study [48] has shown that depressive symptoms are associated with small lesions of the basal ganglia and large cortical white matter lesions. Moreover, a meta-analysis of 98 studies confirmed that LLD was characterised by more frequent and intense white matter abnormalities; and in particular the odds of having white matter changes were four times greater for late compared with early onset depression [49]. WMHs appear most strongly linked to depression when they involve frontal-subcortical circuits that reciprocally link prefrontal areas (the dorsolateral prefrontal cortex [DLPFC] and the anterior cingulate cortex) to the basal ganglia [50].

*Figure 1.2 White matter hyperintensities on MRI: (left) minor white matter hyperintensities; (right) extensive white matter hyperintensities [51].*
WMHs are associated with age [52] and cerebrovascular risk factors, including diabetes, cardiac disease and hypertension [53-57]. WMHs have clinical importance, as they predict poorer response to antidepressant medication [58-60], long term disability, [61] and their increased severity is related to a more chronic course of depression [61, 62].

Neuropathology

The vascular basis of WML in depressed individuals has been shown in several studies. Seminal work by Thomas and colleagues showed that all deep WMHs in depressed subjects were due to ischemia compared to less than one third in controls [63]. Specifically, they found that larger lesions were usually ischemic in both groups; but the punctate lesions were predominantly ischemic in depressed elderly but not in control subjects. They also showed that lesions were more frequently located at DLPFC in depressed subjects. Similarly, studies of post-mortem tissue from depressed older adults, have shown increased levels of cellular adhesion molecules in the DLPFC. [64-66]. Cellular adhesion molecules are inflammatory markers whose expression is increased by ischemia, supporting a role for ischemia in LLD and highlighting a relationship between vascular and inflammatory processes.

The pathology underlying cerebral ischemia leading to WML is unclear. Large vessel atherosclerosis and small vessel arteriosclerosis are believed to play a role. More recently, research has focused on the contribution of transient decreases in local perfusion because of cerebral autoregulatory dysfunction associated with ageing [51, 67].
1.2.2 Mechanism Linking Cerebrovascular Disease and Depression

A number of explanations have been advanced to explain the link between depression and cerebrovascular disease. The dominant view is that vascular risk factors cause cerebral ischemia and WML, leading to disruption of frontal subcortical circuits resulting in depression. A model of LLD with brain dysfunction is described by Alexopoulos [28] by which age-, disease- and stress-related neurobiological changes serve as etiological factors, contributing to alterations in circuits regulating mood and cognition [28]. These etiological factors may lead to depression only after crossing a certain threshold, above which, they acquire a dose-effect relationship (see Figure 1.3). In this conceptualisation, single or multiple etiological factors may reach an initial severity threshold and contribute to LLD vulnerability due to frontolimbic compromise. This can be observed through imaging or abnormal performance on cognitive or affective tasks [28, 56]. When etiological factors further increase in severity and cross a second threshold, they may have a greater and direct effect on mood circuit function, leading to affective and cognitive symptomatology.

This threshold model accounts for multi-factorial contributions to LLD. It also provides some explanation as to why putative clinical and biological factors only predict a modest part of the variance in distinguishing LLD from controls; and in predicting treatment response, as any individual measure may itself not cross a crucial threshold. This model allows for mixed syndromes of multiple etiological
contributors, if each disturbance alone or in combination is strong enough to cross the threshold required to induce neural circuit changes mediating LLD [28, 56].

**Figure 1.3 Proposed progression of etiological processes affecting fronto limbic function.**

The role vascular disease and WMHs can be interpreted within this framework. Greater WMHs severity would represent a state of vascular compromise and ischemic injury in specific regions. Depending on severity and how strongly they effect affective and cognitive circuitry, such damage may predispose older adults to depressive episodes [56].

**Hypoperfusion, White Matter Hyperintensites and Late-Life Depression**

Vascular dysregulation is common in LLD [65, 66, 68-70] and reductions in cerebral blood flow (CBF) can impair regional brain function, contributing to affective and cognitive symptoms. Regional cerebral metabolic activity is correlated with CBF, which is regulated by local interactions between neurons,
glia and the vasculature [71, 72]. Blood flow to the brain is influenced by systemic hemodynamics and cerebrovascular autoregulation with cerebral arteries contracting or dilating in response to changes in arterial pressure. These processes interact to maintain stable perfusion but are impaired in the context of vascular disease.

Perfusion deficits do not need to cause ischemia in order to influence brain function. Reduced CBF impairs protein synthesis [73] that is crucial for cognitive and affective processing [74, 75] and for maintaining the integrity of cortical functional maps. [76] Thus, mild CBF reduction may impair cognitive and affective processes, while greater CBF reduction in the context of autoregulatory deficits may cause ischemic injury. The subcortical white matter is particularly sensitive to these changes because it is supplied by terminal arterioles with limited collateral flow [77] and so is more susceptible to minor changes in flow due to impaired autoregulation and consequent infarction [78]. Greater WMH severity may be a marker of broader deficits in perfusion and autoregulation as individuals with greater WMH severity exhibit reduced CBF in both white matter and gray matter regions [79-81]. Depressed older adults with greater WMH severity also exhibit decreased perfusion in the cingulate gyrus [82] a region involved in cognitive and affective processing [83]. Advanced age is itself associated with decreased frontotemporal CBF [84] an effect which is mediated by vascular risk factors [85].

**Vascular Depression Hypothesis**

Repeated evidence of a relationship between depression and vascular disease led to the ‘Vascular Depression hypothesis’ which posits that cerebrovascular
disease may predispose, precipitate or perpetuate some geriatric depressive syndromes [29]. In the fifteen years since it was proposed the hypothesis has stimulated much research that laid the foundation for examining the specific mechanisms by which vascular disease influences the development and course of depression [56]. As a result, an updated model has recently been proposed [56] which suggests three mechanistic paths to 'vascular depression.' It includes a 'disconnection' hypothesis' an 'inflammation hypothesis' and of key relevance to the current thesis a 'hypoperfusion hypothesis' (see figure 1.4).

**Figure 1.4 Updated model of vascular depression [56]**

![Updated model of vascular depression](image-url)
The model holds that the processes of these pathways could proceed independently, but they are complementary and interconnected and so may all contribute to LLD. Hence, vascular disease may contribute to altered brain function either through structural damage adversely affecting connectivity, through perfusion deficits altering regional function, or both. Proinflammatory processes increase vascular risk, but may also affect brain function through independent processes. In this model, vascular disease is an important and central contributor to LLD. Not only is vascular disease common and perhaps unavoidable in later life, but it also interacts with other pathological processes related to depression [56].

Naturally, the authors acknowledge that vascular disease is not the only contributor to LLD. Other biological and environmental factors can increase the risk for depression by altering neural circuit structure and function. Similarly, genetic influences may increase risk of depression by altering function of neural circuits, changing the biological response to stress, adding to vascular risk, or predisposing to proinflammatory states. Nonvascular factors clearly contribute to LLD; the same genetic, epigenetic and environmental factors that contribute to depression in younger adults continue to confer vulnerability to depression in later life [86].

1.3 Depression as a Risk Factor for Vascular Disease

According to the World Health Survey, depression produces the greatest decrement in health compared with other chronic conditions; even those conditions with greater levels of associated disability [87].
1.3.1 Depression and CVD Risk in Healthy People

In 1996, the Baltimore Epidemiologic Catchment Area Study [88] found that people with MDD had four times the risk of MI relative to non-depressed controls. In the United Kingdom, a prospective cohort study of people initially free of heart disease, revealed MDD to be associated with a higher rate of death from ischemic heart disease (IHD) [89]. Specifically, they found that patients who had depression currently, or in the past 12 months, were three times more likely to die from IHD than those who had never had depression or who had had it more than 12 months previously. A recent meta-analysis [90] of 28 epidemiologic studies with nearly 80,000 patients showed MDD to be an independent risk factor for incident cardiovascular disease.

1.3.2 Depression and CVD Risk in People with Existing CVD

A landmark study by Frasure-Smith et al [91] showed that patients who were depressed at 1 week after an MI were three to four times more likely to die in the next 6 months compared to non-depressed post-MI patients. Moreover, they found that even after 18 months, depression remained an independent risk factor for cardiac-related death [92]. Seven recent systematic reviews of the literature [93-95], including two meta-analyses [96, 97] have investigated the link between depression and adverse outcomes in patients with existing CHD. A total of 23,005 men and women between the ages of 24 and 88 years were followed for between four months and 19 years. All seven reviews concluded that there is strong and consistent evidence that depression is associated with increased all-cause mortality and/or fatal and non-fatal CHD events in people with existing CHD. The relative risks for all-cause mortality reported in the individual studies included in the systematic reviews ranged
from 1.08 to 6.64. The relative risk for the two meta analyses was 2.38 [96] and 2.24 [97] respectively.

In summary, the volume, strength and consistency of the association, the dose-effect relationship of the risk and the plausibility of the potential pathophysiological mechanisms have led to the conclusion that depression is an independent etiological and prognostic risk factor in CVD. Furthermore, it has been argued [98] that the magnitude of increased risk incurred by depression on both the etiology and prognosis of CVD is equal to many of the conventional cardiac risk factors such as smoking, high cholesterol and hypertension.

### 1.3.3 Mechanisms Linking Depression and Vascular Disease

There is no proven behavioural or biological mechanism by which depression contributes to the development of CVD but a variety of promising hypotheses have emerged over the past several years. These include reduced adherence to treatment regimens, increased prevalence of smoking and diabetes, platelet dysfunction and coagulant processes, inflammatory processes, alterations in the hypothalamic-pituitary-adrenal axis (HPA axis) and ANS dysfunction. Table 1.1 summarises the mechanisms that are proposed to link depression with adverse outcome in CVD. Any or all of these might contribute to the increased risk for cardiac morbidity and mortality in depressed patients.

In older adults dysregulation of the ANS is believed to be one of the most plausible candidate mechanisms especially since autonomic function is known to decline with age [99]. Reduced parasympathetic and increased sympathetic nervous system (SNS) activity has been shown to lower the threshold for
myocardial ischemia, ventricular tachycardia/fibrillation and sudden cardiac death [99]. Neurohormonal dysregulation in MDD may impair autonomic activity [100, 101]. Dysfunction of the HPA axis observed in depressed patients leads to overproduction of catecholamines (epinephrine [Ad] and norepinephrine [NAd]) by the adrenal gland. High levels of circulating catecholamines may result in CVD by causing excessive stimulation of the SNS and potentiating platelet activation [102, 103]. Coronary artery disease is a

Table 1.1 Possible mechanisms linking depression and cardiovascular disease

<table>
<thead>
<tr>
<th>Possible mechanisms</th>
<th>Specific disturbances</th>
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| Serotonergic dysfunction | ↑ Sensitivity of platelet aggregation  
| | ↑ Platelet activation, secretion, and aggregation |
| Systemic inflammation and immune activation | ↑ Proinflammatory cytokines, such as interleukin-6  
| | ↑ C-reactive protein  
| | ↑ Levels of inflammatory markers  
| | ↓ levels of anti-inflammatory molecules |
| Autonomic nervous system dysfunction & Hypothalamic-pituitary-adrenal axis and | Disturbance in autonomic tone  
| | ↑ Activation of hypothalamic-pituitary-adrenal axis  
| | ↑ Systemic sympathetic activation  
| | ↑ Heart rate  
| | ↓ Heart rate variability |
| Vascular changes | Endothelial dysfunction  
| | Reduced vasodilation  
| | Decreased levels of nitric oxide metabolites |
| Omega-3 fatty acids | Low omega-3 fatty acid consumption or level in both diseases |
| Genetics | Short allele of serotonin transporter gene-linked polymorphic region  
| | Variation in vWF gene |
| Psychosocial | ↓ Adherence  
| | ↑ Cigarette smoking  
| | ↑ Weight and obesity, including visceral fat accumulation  
| | ↓ Exercise and physical activity |
chronic inflammatory process that is triggered by injury to the vascular endothelium [104, 105]. Increased levels of catecholamines may also contribute to recurrent endothelial injury [104]. MDD is associated with excessive secretion of proinflammatory cytokines interleukin-1, tumor necrosis factor and interferon [106-108]. These influence the release and metabolism of several neurotransmitters that are involved in the autonomic control of the CVS (see Figure 1.5 for an illustration).

**Figure 1.5 Relationship between depression and cardiovascular disease**

*The central nervous system is proposed to play a major role in the etiology of both depression and CV dysregulation via positive and negative feedback systems. Autonomic nervous system changes are likely mediated by brain mechanisms that can lead to specific cardiac events. Feedback from the cardiovascular system to the brain perpetuates the cycle of dysregulation.*
1.4 Assessment of Depression in TILDA

Depression was assessed in TILDA using the Center for Epidemiologic Studies Depression (CES-D) scale. The CES-D was developed to measure the frequency of depressive symptoms in the general population and was designed for inclusion in population surveys [109]. The twenty items that comprise the full scale are symptoms associated with depression which have been used in previously validated longer scales. Individuals evaluate how frequently they experienced each of the twenty items during the past week, from none or almost none of the time, some of the time, most of the time, to all/almost all of the time (see Appendix 1). The CES-D generates a total score with a range between 0 and 60 with higher scores indicating greater depressive symptoms. A cut-off score of 16 has been shown to have a sensitivity of 100% and specificity of 88% for major depressive disorder in an elderly population [110].
2 LITERATURE REVIEW

2.1 The Autonomic Nervous System
The Autonomic Nervous System (ANS) is a complex system of interconnected neurons which controls bodily functions that are engaged in homeostasis. The system mainly regulates autonomic processes in the body such as sweating, heart rate frequency, pupil reflexes, energy regulation, digestion, and renal function. It is largely an involuntary system with its pathways permeating all organ systems [111].

The autonomic network is divided into the central network and the peripheral autonomic nervous system. The central autonomic network is an interconnected network in several forebrain and brainstem areas. These structures also control endocrine and motor outputs that, together with the autonomic output, participate in integrated responses to internal and external stimuli [112]. The peripheral autonomic nervous system is composed of two separate divisions or branches; the sympathetic and parasympathetic systems (see Figure 2.1). In general, activation of the sympathetic system causes an increase in cardiac output, constriction of blood vessels, a reduction in gastrointestinal motility and constriction of the sphincters. It prepares the human body for action in times of danger and stress and is therefore defined with the term “fright, flight, fight’. Activation of the parasympathetic system causes the opposite response. It regulates the resting state of the body and is therefore known as the “rest and digest” branch [111, 113].
The sympathetic and parasympathetic divisions of the ANS are depicted in the left and right panels, respectively, and the targets of innervation are schematically depicted in or near the center panel. All brain pathways are schematically depicted. On the left (sympathetic) side, depicted brain pathways include those to the thalamus from the ALS of the spinal cord, output from the thalamus to the neocortex, insula, and amygdala, bidirectional pathways between the hypothalamus and both the amygdala and frontal cortex, output from the hypothalamus to the NTS, and output from the amygdala to the ALS and brainstem. The small bifurcated arrow to the hypothalamus on each side schematically represents the entire set of inputs from cortical and subcortical structures to the hypothalamus. On the right (parasympathetic) side, depicted pathways include those to the thalamus from the NTS, output from the thalamus to the neocortex, insula, and amygdala, and bidirectional pathways between the hypothalamus and amygdala. Roman numerals III, VII, IX, and X (vagus) designate cranial nerves. Three vagal nuclei in the brainstem, including the NTS, nucleus ambiguus and dorsal vagal nucleus, are also depicted. ANS = autonomic nervous system; ALS = anterolateral system; NTS = nucleus tractus solitarius.
2.1.1 The Sympathetic Nervous System
The sympathetic nervous system nerve cell bodies are located in the spinal cord. These pre-ganglionic neurons have myelinated axons and utilize acetylcholine as neurotransmitter. Acetylcholine mediates excitatory inputs from pre-ganglionic sympathetic and parasympathetic neurons via ganglion type nicotine receptors. The post-ganglionic neurons are non-myelinated. The primary neurotransmitter of sympathetic ganglion neurons is noradrenaline (NAd). NAd acts via three families of adrenergic receptors (\(\alpha_1\), \(\alpha_2\) and \(\beta\) receptors). The sympathetic system controls patterns of responses to specific internal or external stresses, such as postural changes, exercise, hypoglycaemia, dehydration, exposure to heat or cold, and stress. Sympathetic output is critical for maintenance of arterial pressure, response to stress, exercise, and thermoregulation [111].

2.1.2 The Parasympathetic Nervous System
The parasympathetic pre-ganglionic neurons are located in the brain stem and spinal cord. The most important cranial pre-ganglionic parasympathetic output is carried by the vagus nerve (cranial nerve X). The primary neurotransmitter of the parasympathetic system is acetylcholine. However, many effects are also mediated by nitric oxide, adenosine triphosphate, and several neuropeptides. Acetylcholine acts via muscarinic receptors in the parasympathetic nervous system. Muscarinic receptors are present in presynaptic terminals of autonomic ganglia and target organs. In contrast to sympathetic outflow, the different parasympathetic outflows are activated in an organ-specific fashion by specific stimuli that control each organ separately. The vagus nerve exerts a beat-to-beat control of the heart rate and facilitates motility of, and secretion in the gastrointestinal tract.
The autonomic nervous system is extensive and is involved in the function of virtually every organ in the body [115]. The clinical manifestations of autonomic dysfunction can therefore be quite diverse in nature and the ANS may be involved in virtually all diseases [112]. Any structural pathologic process affecting the brain (whether infectious, inherited, neoplastic or degenerative in nature) may result in an autonomic dysfunction [112]. People with autonomic failure experience symptoms such as postural dizziness, falls, syncope, urinary incontinence, constipation and sexual dysfunction.

2.2 Cerebral Autoregulation
Cerebral autoregulation (CA) modulates CBF in order to meet regional perfusion demands despite variations in arterial blood pressure associated with daily activities [116]. Dynamic CA refers to the rapid response of cerebral vasculature to transient BP fluctuations. In general, autoregulation maintains a stable perfusion across mean systemic pressures between 50/60 and 150/160 mmHg [117]. Impaired autoregulation results in the relationship between CBF and BP becoming more linear whereby the BP range within which perfusion remains optimal is narrowed and perfusion becomes more dependent on arterial BP (see Figure 2.2). In this context, vasodilatation in response to low BP is often reduced, and vasoconstriction in response to high BP is increased [118]. Several mechanisms control CA including the sympathetic, parasympathetic and trigeminovascular systems. Autoregulation is affected by several age-related conditions including vascular disease, stroke [119], hypertension [120] and hypotension [117].
Figure 2.2 Normal cerebral autoregulation curve with its lower (50 mmHg) and upper (150 mmHg) limits of mean arterial pressure (green line), and a narrowed range with a steeper curve (red dashed line) [118].

The evaluation of autonomic function is primarily by physiological assessments. Current physiological assessments include cardiovascular reflex tests, the thermoregulatory sweat test, and time frequency and power spectral analysis of heart rate variability. Plasma catecholine is the main neurochemical index used to assess autonomic function.
2.3 Heart Rate Variability

Heart rate variability (HRV) is the temporal variation between consecutive heartbeats during sinus rhythm. HRV indices are calculated from the RR interval of an ECG [121]. The RR interval is the time period between two successive R waves (i.e. the peak of the QRS complex, see Figure 2.3).

Figure 2.3 Waveform of ECG in normal sinus rhythm [122]

HRV is a marker of cardiovascular autonomic function [123] and ANS modulation [124, 125]. It is controlled predominantly by parasympathetic and sympathetic arms of the ANS. HRV is thought to reflect the heart’s ability to adapt to changing circumstances by detecting and quickly responding to unpredictable stimuli [126]. Beat-to-beat variability of the heart primarily emerges through the activity of the individual branches of the ANS during respiration. Low HRV suggests excessive cardiac sympathetic modulation, diminished cardiac parasympathetic modulation, or both. HRV analysis allows for a much more sensitive determination of the function of the ANS than HR. HRV is also a particularly good indicator of changes in ANS activity in response to stress [126].
2.3.1 Measurement of Heart Rate Variability

Variations in HR can be evaluated using a number of techniques. The most straightforward technique for HRV analysis involves characterising the statistical variability in the beat-to-beat time series (time domain). HRV data is also commonly analysed using frequency domain analysis, which evaluates the frequency spectrum of the HR signal. Conversion to the frequency domain is done via the fast fourier transform algorithm, which can quantify the spectral content of the signal in defined frequency ranges (e.g. high, low, and very low frequencies [127, 128]). Standardisation of measurements and interpretation of HRV indices was performed by The Taskforce of the European Society of Cardiology and the North American Society of Pacing in 1996 [129]. Short term 5 minute recordings or nominal 24 hour recordings are most commonly used.

Time Domain Measurements

In these methods, either the heart rate at any point in time or the intervals between successive normal complexes are determined. In a continuous ECG record, each QRS complex is detected, and the so-called normal-to-normal (NN) intervals (all intervals between adjacent QRS complexes resulting from sinus node depolarisations) are determined. Time domain measurements are divided into those derived from the direct measurements of NN intervals and those derived from the differences between NN intervals. The NN interval is defined as the time in milliseconds between two successive R waves on the ECG recording.
The simplest variable to calculate is the standard deviation of NN intervals (SDNN). SDNN represents overall HRV and encompasses all frequency components responsible for HRV in the period of recording [130, 131]. The most commonly used variables derived from interval differences include the square root of the mean squared difference of successive NN intervals (RMSSD) and the proportion of successive NN intervals greater than 50ms (pNN50). These measurements of short term variation estimate high frequency variation and are highly correlated [130]

Figure 2.4 Graph of Power Spectral Analysis of Heart rate Variability
**Frequency Domain Measurements**

This technique provides information regarding the distribution of power (variance) as a function of the frequency, independent of the method used. Spectral analysis of short term readings of ≤ 5 minutes produces several prominent peaks or frequency bands (see Figure 2.4). Three main spectral components are very low frequency (VLF), low frequency (LF) and high frequency (HF). However, the physiological basis of VLF is poorly defined. The HF component is eliminated by high dose atropine and is therefore believed to represent parasympathetic activity (> 0.15 Hz). Sympathetic stimulation increases the LF component of HRV. However, high dose atropine also eliminates LF indicating this component represents predominantly sympathetic activity but there are some parasympathetic contributions (0.04-0.15Hz). The LF/HF ratio has been proposed as an index of sympathovagal balance, although this assertion remains controversial [130, 131]

**Determinants of HRV**

Physiological components such as ventilation are responsible for a cyclic fluctuation of HF power, mediated by changes in vagal outflow, termed respiratory sinus arrhythmia (RSA). During inspiration, there is a slight increase, and during expiration, a slight decrease in heart rate. A comparison of free and paced breathing measures of HRV reported that paced breathing at 12 cycles/min resulted in a stronger relationship between the \( \log_e \) of HF (InHF) and RR interval, indicating InHF to be a valid index of vagal outflow and hence a protocol of paced breathing is recommended [132]. HRV absolute values decrease with age in healthy subjects [133], and studies are inconclusive regarding the role of gender in HRV [134, 135].
2.3.2 Depression and HRV

HRV and CVD

A large body of evidence suggests that autonomic imbalance, in which typically the sympathetic system is hyperactive and the parasympathetic system is hypoactive, is associated with various pathological conditions. In particular, when the sympathetic branch dominates for long periods of time, the energy demands on the system become excessive and ultimately cannot be met. Premature aging and disease characterise a system dominated by autonomic imbalance [136].

A landmark study by Kleiger et al [137] showed that HRV was a significant independent predictor of mortality among post-myocardial infarction patients. Numerous studies have since supported the notion that decreased vagal activity, as indexed by HRV, predicts mortality in high risk as well as low risk populations [138-141] and HRV has been identified as providing the best measure for predicting fatal or near-fatal cardiac arrhythmia [142].

HRV and Depression

Most relevant studies have documented decreased HRV in patients with depression [143-148]. This relationship has been observed in depressed individuals with CVD [96, 97] and without CVD [149]. Currently, the debate is centred on inconsistent findings concerning whether HRV is reduced in depression per se [150] or whether these reductions are driven by antidepressant medication [151]. In their study of physically healthy patients with and without MDD, all of whom were unmedicated, Kemp and colleagues
found that HRV was reduced in those with MDD compared to the non-depressed controls [150]. In contrast, the Netherlands Study of Depression and Anxiety (NESDA) [152, 153] has reported (cross-sectionally and longitudinally) that while depression was associated with significantly lowered HRV, the association was found to be mainly driven by the effect of antidepressants.

**Role of Antidepressant Medications**

Antidepressants are a particularly relevant source of potential confounding when examining the association between depression and HRV. There is evidence that tricyclic antidepressants (TCAs) reduce parasympathetic activity and therefore HRV [144, 154, 155] due to their anticholinergic and 1-adrenergic properties [156, 157]. Other antidepressants with milder anticholinergic properties might also decrease HRV [158]. However, other lines of research suggest that antidepressant treatment (particularly non-TCA) might provide HRV-mediated cardiac protective effects [159] or at least have a benign cardiovascular profile [160]. A recent meta-analysis on the impact of antidepressant treatment on HRV concluded that TCAs are associated with a large decrease in HRV but that the data for SSRIs and other antidepressants were not clear [161].

In fact, it is unknown whether antidepressants are advantageous or hazardous for the heart. For example, the US Department of Veterans Affairs cohort study showed a lower risk for myocardial infarction in those using antidepressants (hazard ratio: 0.50 to 0.66) [162] whereas in the Nurse’s Health Study, the use of antidepressants more than tripled the risk of sudden
cardiac death [163]. In addition, the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) trial showed that sertraline (an SSRI) was not superior to placebo in improving any cardiovascular outcome [164]. Some antidepressant classes might act as platelet inhibitors, thus having a protective effect in the increased platelet activity of infarction [165]; on the other hand, antidepressants are also related to increased levels of cytokines such as interleukin-6 [166] and tumor necrosis factor-α [167]. So while antidepressants are effective for reducing depression symptoms, their putative favourable impact on cardiovascular risk is questionable. It is possible that they impair autonomic function by increasing sympathetic and decreasing parasympathetic activity alternatively; autonomic dysfunction may be caused by the severity of depression and this is indexed by antidepressant use [168]. Longitudinal evidence is lacking to inform this debate, apart from one recent study by Litch and colleagues. Over 2 years of follow up they found that all antidepressants reduced HRV and participants who discontinued antidepressants showed recovery in indices of HRV [153].

HRV and Depression in Older Adults

Most existing research on HRV and depression has been conducted on young and middle-aged patients with depression. Although valuable, it has been suggested that research in older adults who have a greater risk of heart disease may have greater applicability [169]. Because normal aging is associated with reduced HRV [170] it has been hypothesised that depression in old age may further reduce HRV, potentially posing an increased risk of cardiovascular morbidity and mortality [169]. Of the studies that have investigated HRV specifically in depressed older adults (see Table 2.1 for a
review) the results are conflicting; with some studies providing evidence of reduced HRV in depression [147, 171-174] and others reporting no association [169, 175]. Notably, none of these studies have investigated the role of individual antidepressants classes on HRV. Moreover, the role of co-morbid anxiety has not often been considered. Recent evidence suggests that patients with co-morbid GAD have greater reductions in HRV compared to MDD patients without co-morbid anxiety or controls [150]. GAD is the most prevalent anxiety disorder among older adults [176] and a high prevalence of co-morbid depression and anxiety is observed in this age group [38].

2.4 Orthostatic Hypotension
Orthostatic hypotension is a sudden reduction in blood pressure or central venous pressure commonly associated with either prolonged upright stance or a change in posture from a lying or seated to standing position.

Cardiovascular Response to Orthostatic Stress
Blood pressure is defined as the product of cardiac output (heart rate x stroke volume) and total peripheral resistance. In humans upright posture results in a gravitational displacement of 300-800ml of blood into the vasculature below the diaphragm, leading to a decrease in venous return to the heart with a consequent decrease in cardiac output and an immediate drop in BP [113, 177, 178]. The ANS plays a principal role in BP regulation and the maintenance of BP during changes in posture (see Figure 2.5). The BP drop during upright posture causes baroreflex activation. The baroreceptors are stretch receptors located in the carotid sinus and ascending aorta. In order to maintain blood pressure, the baroreceptors activate the sympathetic nervous
system with a resultant increase in HR, cardiac contractility and peripheral vascular resistance. The primary role of the baroreflex is to facilitate a rapid adjustment of BP on a beat-to-beat basis. Changes in peripheral vascular resistance rather than changes in cardiac output are thought to be primarily responsible for maintaining BP during orthostatic challenges [113, 177, 178]. Failure of mechanisms in the body to maintain BP during the upright position can result in OH [180]. Characteristic symptoms of OH are mostly due to cerebral hypoperfusion and include feelings of weakness, fatigue, blurred vision, light-headedness, dizziness and loss of consciousness [177, 180].

OH occurs frequently in elderly patients because of age related physiological changes in the neuro-humoral systems, therapy (vasoactive drugs, dopamine and agonists, antidepressants), reduced fluid intake, and decreased ANS function [115]. The prevalence of OH increases with age. OH is more common in institutionalised (up to 70%) than community dwelling elderly (approx 6%) [115, 180]. In 2009, the European Society of Cardiology Guidelines for the diagnosis and management of syncope summarised the definitions and characteristics of the three main orthostatic syndromes in older adults namely classical, initial and delayed or progressive OH.

**Classical or consensus OH (COH):** is defined as a sustained reduction of systolic blood pressure (SBP) of at least 20mmHg or diastolic blood pressure (DBP) of 10mmHg within 3 min of standing [122]. OH is a clinical sign and may be symptomatic or asymptomatic.
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Age</th>
<th>Sample</th>
<th>Analysis of HRV</th>
<th>Time</th>
<th>Depression Diagnosis</th>
<th>Results</th>
<th>Antidepressant use</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Carney et al [171]</td>
<td>Mean age 59</td>
<td>380 depressed, 424 controls</td>
<td>Clinical trial of patients with acute MI</td>
<td>FD 5 mins 24 hr</td>
<td>DISH</td>
<td>VLF, ULF and LF measures of HRV were significantly lower in patients with depression than in patients without depression.</td>
<td>Excluded if on tricyclic or monoamine oxidase inhibitor antidepressants</td>
</tr>
<tr>
<td>2004</td>
<td>Guinjoan [172]</td>
<td>&gt;60 years</td>
<td>19 depressed, 37 controls</td>
<td>CCU patients with ACSs</td>
<td>TD &amp; FD 5 mins</td>
<td>DSM-IV</td>
<td>- HF, pNN50, rMSSN measures of HRV were decreased in patients with depression compared to controls - HF decreased with increasing depressive symptom severity.</td>
<td>Excluded if taking medications with anticholinergic activity within the week prior to testing</td>
</tr>
<tr>
<td>2005</td>
<td>Gehi et al [169]</td>
<td>Mean age 65</td>
<td>195 depression, 678 controls</td>
<td></td>
<td>TD &amp; FD 24 hr</td>
<td>DSM-3 PHQ</td>
<td>No difference in any measures of HRV between depressed and non depressed participants</td>
<td>Stratified analysis by antidepressants use with no effect</td>
</tr>
<tr>
<td>2004</td>
<td>Nashoni et al [179]</td>
<td>&gt;60 years</td>
<td>10 in-patients with MDD before and after ECT treatment</td>
<td>Clinical trial</td>
<td>TD &amp; FD 5 mins</td>
<td>DSM-IV</td>
<td>Only the responders to ECT exhibited a significant increase in time domain measure of HRV (PD2), which showed a tendency towards a correlation with symptom improvement Frequency domain measures did not show a significant difference after ECT.</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Van der Kooy et al [147]</td>
<td>&gt;55 years</td>
<td>136 depression, 136 controls</td>
<td>Case-control primary care study</td>
<td>TD &amp; FD 5 mins</td>
<td>DSM-IV</td>
<td>MDD patients had a reduced overall HRV (SDNN) and an reduced vagal tone (rMSSD, HF-power).</td>
<td>Excluded participants on antidepressants</td>
</tr>
<tr>
<td>2008</td>
<td>Jindal et al [175]</td>
<td>&gt;60 years</td>
<td>53 depression, 53 controls</td>
<td>Case control clinical study</td>
<td>TD &amp; FD 5 mins</td>
<td>DSM-4 MDD</td>
<td>- No between group differences in any measures of HRV. - Non depressed participants displayed decreasing cardiac vagal function with aging but there was no significant change in vagal function with age in the depressed group</td>
<td>Participants were free of all antidepressant and benzodiazepines for 2 weeks and fluoxetine for 6 weeks</td>
</tr>
<tr>
<td>2011</td>
<td>Vasudev et al [173]</td>
<td>&gt;60 years</td>
<td>42 depression, 31 controls</td>
<td>Case-control secondary care study</td>
<td>FD 10 mins</td>
<td>DSM-4 MDD</td>
<td>Depressed participants had lower LF measure of HRV.</td>
<td>Included participants on antidepressants</td>
</tr>
<tr>
<td>2012</td>
<td>Dauphinot et al [174]</td>
<td>&gt;65 years</td>
<td>67 current depressive symptoms, 228 history of depression</td>
<td>Population study</td>
<td>TD &amp; FD 24 hr</td>
<td>QD2A questionnaire</td>
<td>LF/HF ratio were lower among subjects with depressive symptoms and history of depression.</td>
<td>Included participants on antidepressants</td>
</tr>
</tbody>
</table>

**Notes:**
- **DSM** = Diagnostic and Statistical Manual of Mental Disorders
- **MDD** = major depressive disorder
- **HRV** = Heart Rate variability
- **ACSs** = acute coronary syndromes
- **DISH** = Depression Interview and Structured Hamilton
- **PHQ** = patient health questionnaire
- **CCU** = Coronary care unit
- **TD** = time domain measure of HRV
- **FD** = frequency domain measure of HRV
**Initial orthostatic hypotension (IOH):** is defined as a transient BP decrease of >40mmHg SBP and/or >20mmHg DBP within 15 seconds of standing, accompanied by symptoms of hypoperfusion. This BP fall can only be observed with continuous beat-to-beat blood pressure monitoring [178].

**Delayed orthostatic hypotension (DOH):** is defined as symptomatic COH that occurs beyond 3 min of standing.

### 2.4.1 Measures of Orthostatic Hypotension

In order to generate the physiological responses to standing (orthostasis) in a controlled environment, a number of different orthostatic challenges have been devised and tested. These include the Sit-to-Stand Test (STST), the Lying to Standing Test (LTST) and the Head-Up Tilt-Table Test (HUTT). The current European Society of Cardiology guidelines stipulate supine and upright measurements of BP for the diagnosis of OH [182]. Specifically, the patient should lay supine for a period of 5 minutes prior to assuming the upright posture and should thereafter have their BP measured every 30 seconds for a period of 3 minutes. This is a laborious practice consuming at least 8 minutes. For this reason, the use of once-off sitting and standing BP readings for the detection of OH are common in clinical practice.

The reference standard of BP monitoring for the diagnosis of OH is undoubtedly the use of continuous beat-to-beat plethysmography [183-186]. This provides an accurate account of instantaneous changes in BP and has been validated in the setting of orthostatic stress [187]. Indeed, this non-
Figure 2.5 Overview of the mechanisms underlying orthostasis [181].

Orthostasis

Cerebral Autoregulation

Cerebral blood flow is maintained

Skeletal Muscle Pump: propels blood from leg and gluteal muscles to increase venous return

Reduced venous return and cardiac output

Neurovascular adjustments:
- Baroreceptor reflex: pressure sensing carotid sinus, intima of aortic arch, heart chambers decrease firing rate
- Epinephrine and dopamine β-hydroxylase release
- Norepinephrine release
- Vasoconstriction in splanchnic bed and lower extremities

Neurohumoral effects

Atrial stretch receptors and arterial baroreceptors

Renin-Angiotensin-Aldosterone system

Vasopressin release

Blood volume increases

Blood pressure increases; venous return and cardiac output return to normal

Immediate response (seconds)

Delayed response (minutes)

Blood pressure increases; venous return and cardiac output return to normal

Heart rate increases (tachycardia)

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invasive technique has been suggested to be more specific than invasive measurements of BP due to the potential for vasovagal reactions to brachial artery cannulation in the latter [188]. For the assessment of orthostatic haemodynamic responses participants must undergo non-invasive beat-to-beat blood pressure monitoring.

### 2.4.1 Orthostatic Hypotension and Depression

**Orthostatic Hypotension and Vascular Disease**

Several studies have investigated the relationship between OH and both cardiovascular and cerebrovascular disease. The Atherosclerosis Risk in Communities Study (ARIC), a large population-based prospective cohort study of middle-aged participants (aged 45–65), found strong associations between OH and stroke, CHD and mortality [189-191]. In an older cohort, the Honolulu Heart Program, a prospective study of 3,741 men aged 71 to 93, found that OH increased the risk of all-cause mortality in elderly men [192].

The link between OH and CVD may have several explanations. Orthostatic challenge displaces blood to the lower body. This could decrease thoracic blood volume by 25 to 30% [193]. The secondary reduction in coronary and cerebral blood flow during a strong postural BP drop may cause myocardial and cerebral ischemia. OH could also be the expression of underlying CVD. Cerebral infarcts, MIs and heart failure [194, 195] could cause OH. Supine hypertension is common in patients with OH, affecting more than 50% of patients in some studies [196]. Hypertensive patients with greater postural BP changes have an increased risk of advanced silent brain lesions [197]. OH may occur after therapy for hypertension and supine hypertension may follow.
treatment of OH. In addition several studies have shown an association between OH and arterial stiffness [198, 199].

Orthostatic Hypotension and Depression

The "vascular depression" concept encompasses a range of possible vascular pathologies, but most work has focused on microvascular and large vessel disease [200]. Current research attention is focused on the role of hypoperfusion [56]; since older adults with depression may have a greater burden of OH leading to white matter ischemia [173, 201].

As described earlier, the ischemic basis of DWMH in adults with MDD was shown in a landmark study by Thomas and colleagues [63]. They found that the majority of DWMHs in older adults with MDD were due to ischemia, particularly when they are located at the level of the DLPFC. Animal studies have reported that low BP can cause WMHs [202]. Furthermore, LLD is associated with a higher burden of OH [67, 173] and greater falls in SBP on standing compared to adults without depression [201]. Most recently, a study by Colloby et al (2011), found evidence for an association between the degree of orthostatic SBP drop and volume of WMHs in depressed older adults [67]. Prior to the study by Colloby the relationship between orthostatic drops in BP and WMHs had rarely been examined; but one small pilot study did report an association between the degree of SBP drop on active stand and extent of WMHs in adults with dementia [203].

In summary, accumulating evidence suggests that OH may play an important role in the development of depression in older adults; however, evidence is
limited to only a few studies (see Table 2.2 for a review) that used small clinical samples of patients with MDD. Both animal models and human studies suggest a causal relationship between OH induced cerebral hypoperfusion and WMHs; but the longitudinal evidence needed to confirm this relationship has yet to be established.

<table>
<thead>
<tr>
<th>Year</th>
<th>Sample</th>
<th>OH Diagnosis</th>
<th>Depression Diagnosis</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Richardson et al [201]</td>
<td>&gt;60 years 17 depression 17 controls pilot community-dwelling study</td>
<td>DSM-4</td>
<td>Depressed group had higher proportion of OH compared to controls (94% versus 65%, X = 4.5, df = 1, p = 0.034) Orthostatic SBP drop was significantly greater in depressed group (t = 4.02, df = 32, p &lt;0.001; mean drop of 46 mm Hg).</td>
</tr>
<tr>
<td>2011</td>
<td>Vasudev et al [173]</td>
<td>&gt;60 years 42 depression 31 controls case-control secondary care study</td>
<td>DSM-4</td>
<td>Depressed group had significantly larger orthostatic drop in SBP</td>
</tr>
<tr>
<td>2011</td>
<td>Colloby et al [67]</td>
<td>&gt;60 years 38 depression 30 controls Primary care patients</td>
<td>DSM-IV</td>
<td>An association between orthostatic SBP drop and WMH volumes in temporal and parietal regions was found in the depression group (age-corrected partial correlation r' = 0.31–0.35, P&lt;0.05).</td>
</tr>
</tbody>
</table>

**DSM-4** = Diagnostic and Statistical Manual of Mental Disorders  
**MDD** = major depressive disorder  
**SBP** = systolic blood pressure  
**OH** = orthostatic hypotension  
**WMH** = white matter hyperintensities
2.5 Population studies
A population study is a study of a group of individuals taken from the general population who share a common characteristic, such as age, sex or health condition. A minimum proportion of the target population must be recruited to achieve reliability and validity. Because of their typically high cost and logistic complexities, population-based studies generally evaluate multiple hypotheses.

To ensure that responses from a population study are viewed as representative of the full population (regardless of response rate), the makeup of the data is compared to the makeup of the full population using demographic information. If the demographic percentages are similar, it can be assumed that the survey responses are representative of the total population. If not, then responses inaccurately reflect the population and weighting methods can be derived and applied to the sample cohort. This requires highlighting the demographic features which differ between the sample and the population and applying a higher weight to underrepresented respondents and a lower weight to overrepresented respondents. The higher the response rate on a population study the less there is a need to examine demographic percentages and makeup. Therefore with a population study, the overall response rate becomes the key factor in determining the validity of the responses gathered.

Population studies are hugely valuable as they provide reliable information regarding the true prevalence of health conditions and their epidemiological characteristics. Longitudinal analysis extends the scope of research to allow for investigation of the causal relationship between systems and understand
the pathophysiology underlying disease development. Population based studies provide scientists and policy makers with greater confidence in their findings, when compared to clinical case control studies [204].

2.5.1 The Irish Longitudinal Study on Ageing (TILDA)
The Irish Longitudinal Study on Ageing is a prospective study on the well-being, health and functioning of older people in Ireland. It is a major inter-institutional initiative led by Trinity College Dublin which aims to produce a significant improvement in the quantity and quality of data, relating to older people and ageing in Ireland. The objectives of TILDA are to describe the social, economic and health status of older Irish adults and to try to identify the factors that influence healthy ageing.

The study involves interviews on a two yearly basis with a large cohort of people aged 50 years and over. It collects detailed information on all aspects of their lives, including the economic aspects (pensions, employment, and living standards), health (physical, mental, service needs and usage) and social aspects (contact with friends and kin, formal and informal care, social participation). Participants firstly complete a computer-assisted personal interview (CAPI) in their own homes and are then invited to a health centre for a comprehensive health assessment. Participants who were unable or unwilling to attend a health centre are offered a modified assessment in their own home. Ethical approval for the first wave of the study was obtained from the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin.
In 2009, TILDA recruited a stratified clustered sample of 8,175 individuals' representative of the community living Irish population aged 50 years and over (i.e. wave 1 of the study). Younger spouses and partners were also invited to participate, primarily to provide information regarding family and financial circumstances.

The overall response rate to the study was 62.0%. The sampling frame used to select subjects was the RANSAM system; based on the Geodirectory designed by the Economic and Social Research institute of Ireland (ESRI) [205]. All postal addresses in Ireland were assigned to one of 3,155 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 (see figure 2.6). 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 (25,600 addresses were required to achieve the required sample size of 8,000). 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. All individuals aged 50 or over in each selected household and their partners were invited to be included in the study.
Assessment of Health in TILDA

The TILDA health centre assessment took an average of 2-3 hours to complete and included the following measures:

- **Anthropometric measurements**: height, weight and waist circumference
- **Cardiovascular measurements**: heart rate variability, blood pressure and pulse wave velocity
- **Gait and balance measurements**: timed up and go, gait assessment
- **Sensory measurements**: vision and hearing
- **Bone and muscle strength**: grip strength, heel ultrasound
- **Cognitive measurements**: sustained attention, executive function, visual memory, speed of processing, global cognition
- **Venous blood samples**
A modified assessment was provided in the home for those participants who were unable or unwilling to attend a health centre. This home assessment took approximately 1 ½ hours to complete. A full listing of all measures undertaken in wave 1 of the TILDA study is provided in Appendix 2.

2.6 Conclusion

It is clear from the data reviewed that the relationship between vascular disease and depression is bi-directional. Although various plausible biological explanations have been proposed to explain the relationship in both directions the mechanisms involved are far from understood.

Autonomic function declines with age and may result in OH. Consequent hypotensive episodes may lead to the development of WMHs and depression but the evidence base for this is limited. Previous studies confirming an association between OH and depression were conducted on small clinical cohorts using hospital based digital photoplethysmographic measures of phasic BP. It is not known whether the association would persist in the general population where lower prevalence and severity rates for these conditions are observed; or if the association could be detected using traditional oscillometric measures of BP. Further research is therefore required to determine if OH is an important factor in the association between vascular disease and depression in older adults.

Depression is believed to impair autonomic function as indexed by reduced HRV; however, the role of antidepressants in this relationship is not clear. Community studies examining HRV in depressed older adults are rare. These
may be critical to advancing our understanding of the link between depression and cardiovascular disease; especially given that older adults are at greater risk of heart disease. The effect of different types of antidepressants and co-morbid anxiety on HRV is not well studied in older adults.

Consequently, the overall aim of this thesis is to examine the relationship between OH and depression in a large community sample of older adults and examine the relationship between depression and HRV, with particular emphasis on the role of antidepressant use and co-morbid anxiety. TILDA provides a unique opportunity to achieve this aim.
2.7 Objectives of my Doctorate Thesis

The objectives of my thesis are to investigate the following research questions using data from the first wave of the TILDA study:

1. Examine the prevalence of depression in a population sample of adults aged fifty and over

2. Using active stand test and continuous blood pressure monitoring to detect OH:
   a) investigate the prevalence and severity of OH
   b) examine the cross-sectional relationship between OH and depression

3. Using a sit-to-stand test and a cuff-based oscillometric device to detect OH
   a) investigate the prevalence of OH
   b) examine the cross-sectional relationship between OH and depression

4. a) examine the cross-sectional relationship between depression and HRV
   b) examine the extent to which any associations observed are explained by the use of antidepressant medication and/or co-morbid anxiety
3 Age and sex differences in prevalence and clinical correlates of depression - first results from the Irish Longitudinal Study on Ageing (TILDA)

3.1 Abstract

OBJECTIVE

The risk of depression is increased by physical illness however the nature of this relationship is complex and unclear. Here we explore the prevalence and clinical correlates of depression; with particular emphasis on factors representing consequences or physical manifestations of disease and identify age and gender differences in their effects.

METHODS

A population-representative sample of 8,175 community-dwelling adults aged 50 years and older participated in the first wave of The Irish Longitudinal Study on Ageing (TILDA). The primary outcome measure was clinically significant depressive symptoms defined by a score of 16 or greater on the 20-item Centre for Epidemiologic Studies Depression scale (CES-D).

RESULTS

Overall, 10% (95%CI: 9-11%) of adults reported clinically significant depressive symptoms. Physical illness is associated with depressive symptoms only in adults aged 65 and over; in adults aged 50-64 years the association is mediated by medication use and this age difference is statistically significant (p<0.00). Irrespective of age, chronic pain and incontinence were stronger predictors of depression in men (interaction effects p<0.00)

CONCLUSIONS

Our findings identify age and gender specific clinical markers for depression risk among the older population, which may identify those more likely to present with depression in community settings.
3.2 Introduction
Depression is a leading cause of morbidity and mortality worldwide [206] but knowledge about prevention is lacking, especially among older people for whom under-diagnosis and under-treatment is a significant issue [207]. In older adults, physical illness has been well established as one of the most important risk factors for depression and its dominant role may be one of the most significant differences between late-life depression and depression in younger adults [208, 209]. A number of diseases have been shown to have direct aetiological links with depression, for example vascular disease [50] and Parkinson's disease [210]. However, findings from community-based studies suggest that general aspects of physical health, such as the level of functional impairment and perceived health are more important correlates of depression than specific diagnoses [211, 212].

The prevalence of major depressive disorder ranges from 1% to 5% among community-dwelling older adults [213] and approximately 15% experience clinically significant depressive symptoms [5]. The prevalence of major depression appears to diminish as people get older; however, the incidence of clinically significant non major forms of depression increases with advancing age [214]. At least half of all older adults with major depression are experiencing a new condition arising for the first time in old age [24, 25]. It is therefore important to identify factors that lead to depression in older adults so that prevention can be targeted at high risk groups. Previous studies have focused on risk factors for depression in all adults aged 55 and over, or 65 and over [20, 215], or explored risk factors in the 'oldest old' (i.e. adults ages 75 or 80 and over) [216]. While not directly comparing young-old and old-old
cohorts, these studies suggest that longstanding vulnerability factors, such as family and personal histories of depression are less important in older adults while risk factors such as physical illness, cognitive decline and a diminishing social network become more significant with increasing age [6].

Although it is well recognised that women are more likely to suffer from depression than men [8] gender differences in risk factors for depression are not well studied in older people. Rates of depression appear to be higher in older women than older men but with a smaller gender gap than among younger people [8]. Many social and health related aspects of ageing differ between men and women; therefore identifying variables that indicate greater risk of depression in different genders, as well as investigating whether risk factors associated with depression differ by gender, are important tasks.

The present study sought to determine the prevalence of depressive symptoms in a large population-representative sample of community-dwelling older adults. We explore clinical correlates of depression with particular emphasis on factors representing consequences or physical manifestations of disease. Older adults are not a homogenous group; therefore we hypothesised that clinical correlates of depression would show age and gender specific patterns of distribution.
3.3 Methods

Study design

We analysed data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) collected between October 2009 and February 2011. Full details of the sampling procedure and response rate have been described elsewhere [217]. In short, TILDA is a study of people aged 50 and over (and their spouses or partners of any age) resident in Ireland. A nationally representative sample was drawn from the Irish Geodirectory. Participants completed a computer-assisted personal interview (CAPI) in their own homes which included detailed questions on their social, economic and health situation. The response rate to the study was 62%. The study was approved by the Faculty of Health Sciences Research Ethics Committee and subjects were required to provide written informed consent prior to participation in the study.

Measurements

The primary outcome measure for this analysis was case-level depressive symptoms defined by a score of 16 or greater on the 20-item Centre for Epidemiologic Studies Depression scale (CES-D). The CES-D generates a total score with a range between 0 and 60 with higher scores indicating greater depressive symptoms. A cut-off score of 16 has been shown to have a sensitivity of 100% and specificity of 88% for major depressive disorder in an elderly population [110].
In the present study we considered socio-demographic and clinical correlates of depression. Socio-demographic factors included age, gender, education and marital status. Clinical factors included chronic diseases, cognitive impairment, functional limitations, pain, sensory impairment, medication use and lifestyle characteristics (alcohol & substance abuse, smoking). Participants were asked whether a doctor ever told them they had any of the following diseases: heart attack, heart failure, angina, cataracts, hypertension, high cholesterol stroke, diabetes, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, peptic ulcer or hip fracture. The number of chronic diseases was calculated by summing up all specific diseases reported to be present by a participant. Participants also reported whether a doctor had ever told them they suffered from alcohol or substance abuse or whether they had suffered from urinary incontinence in the previous year.

Measures of cognitive function included immediate and delayed recall of 10 words to assess memory; and semantic verbal fluency (number of animal names generated in 1 minute) which is both a measure of executive function and language. These measures of cognitive function have been utilised in other large ageing studies for example the English Longitudinal Study on Ageing [218] and the Health and Retirement Study in America [219]. Low verbal fluency was defined as 1.5 SD below the weighted mean. This equated to ≤ 10 words in adults aged 50 to 64 (mean 21, SD 7) and ≤ 9 words in adults aged 65 and over (mean 18, SD 6). Disability was examined by asking participants whether they had any longstanding illness, disability or infirmity that had troubled them or was likely to affect them over a period of time. If the answer was yes, they were then asked whether the illness limited their
activities in any way. From the answers to these questions a variable was derived to indicate the presence of a limiting longstanding illness (LLI). Participants were asked to list all medications (prescription and non-prescription) that they took on a regular basis and the total number of medications was summed (excluding antidepressants). Chronic pain was assessed by asking participant if they often suffered from pain. If the answer was yes, they were asked whether most of the time the pain was mild, moderate or severe. Participants who reported moderate or severe pain were classified as suffering from chronic pain. Sensory impairment was examined by asking participants to rate their vision and hearing using a five point Likert scale ranging from excellent to poor. Adults who rated their vision/hearing as fair or poor were classified as having visual impairment.

**Statistical Analysis**

Univariate logistic regression was used to identify correlates of depressive symptoms. These factors were then added into a multivariate model in three blocks to assess possible mediating relationships between factors. The first block included socio-demographic factors. The second included chronic disease, cognitive impairment and lifestyle factors, while the third block included factors representing consequences or physical manifestations of disease.

To examine how correlates of depressive symptoms varied by age and sex, multivariate models were estimated separately in four groups defined by gender and age (50-64 vs 65+). In order to test whether factors were significantly different between age and gender groups, a final model was then
estimated based on all participants including the interaction terms. Sample weights were calculated by comparing the TILDA sample with the Irish population with respect to age, sex and educational attainment [217].
3.4 Results

Sample Characteristics

The sample consisted of 8,175 older adults (mean age 64 years, SD 9.7 years, range 50-99 years, 52% female). 8,032 participants successfully completed the CES-D (98% of sample). People with known or suspected dementias were not recruited to the TILDA study at baseline so very few people are classified as having moderate or severe cognitive impairment in our study. Just over a third (38%) of participants had primary education (8 years or less of formal schooling) and just over two thirds (68%) of the sample were married (Table 3.1).

Prevalence of depressive symptoms by age and sex

The overall prevalence of depression in our sample was 10%. The highest prevalence of 10.7% (95% CI: 10-12%) was found among adults aged 50-64, declining to 9.1% (95% CI: 8-11%) for adults aged 65-74 and 8.7% (95% CI: 7-11%) in those aged 75 and over. Overall, females report more depression than men (12.5%, 95% CI: 11-14% versus 7.2%, 95% CI: 6-8%).

Correlates of depressive symptoms

There were significant differences in socio-demographic factors between participants with and without depressive symptoms (Table 3.1). Women had greater odds of being depressed than men (OR=1.85, 95% CI: 1.58, 2.16).
Table 3.1: Socio-demographic characteristics of older adults with and without depressive symptoms and univariate logistic regression analyses

<table>
<thead>
<tr>
<th></th>
<th>All sample</th>
<th>CES-D &lt;=15</th>
<th>CES-D &gt;= 16</th>
<th>OR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n *</td>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>64 (10)</td>
<td>64(10)</td>
<td>63(10)</td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>4606</td>
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<tr>
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</tr>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>male</td>
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</tr>
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<td>primary</td>
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<tr>
<td>Tertiary</td>
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</tr>
<tr>
<td>Marital status</td>
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</tr>
<tr>
<td>married</td>
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<td>5143</td>
<td>417</td>
<td>53.1</td>
</tr>
<tr>
<td>never married</td>
<td>766</td>
<td>677</td>
<td>99</td>
<td>12.8</td>
</tr>
<tr>
<td>widow/sep/divorce</td>
<td>1696</td>
<td>1439</td>
<td>257</td>
<td>34.2</td>
</tr>
<tr>
<td>Medical card</td>
<td>3948</td>
<td>3442</td>
<td>506</td>
<td>68.4</td>
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<tr>
<td>Private medical insurance</td>
<td>3246</td>
<td>3060</td>
<td>186</td>
<td>21.0</td>
</tr>
</tbody>
</table>

unweighted counts = weighted percentages * p=<0.05  **p=<0.001

Participants who had only completed primary level education were more likely than those with secondary or tertiary level to suffer with depressive symptoms (OR=1.62, 95% CI: 1.39, 1.89 for primary when compared with adults with tertiary education). Never having married or been widowed separated or divorced were associated with increased odds of being depressed (OR=1.44, 95% CI: 1.14, 1.79 for never married and OR=2.0, 95% CI: 1.71, 2.35, for been widowed separated or divorced when compared to been married).

Univariate logistic regression analyses of clinical characteristics on depressive symptoms can be seen in Table 3.2. The odds of depressive symptoms

67
increased as the number of chronic diseases increased (OR=1.31, 95% CI: 1.25, 1.37), and in the presence of a LLI (OR=4.18, 95% CI: 3.58, 4.86). Other health-related (smoking, number of medications, pain, urinary incontinence and sensory impairment) and cognitive (poor recall, poor verbal fluency) factors were also significantly related to increased odds of being depressed.

Table 3.2 Clinical characteristics of older adults with and without depressive symptoms and univariate logistic regression analyses.

<table>
<thead>
<tr>
<th></th>
<th>non-depressed CES-D &lt;=15</th>
<th>depression CES-D &gt;= 16</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of medications</td>
<td>2.4 (.03)</td>
<td>3.9 (.12)</td>
<td>1.17*</td>
<td>(1.15-1.20)</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>5.7 (.02)</td>
<td>5.3 (.06)</td>
<td>0.88**</td>
<td>(0.84-0.92)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>5.9 (.03)</td>
<td>5.3 (.08)</td>
<td>0.89**</td>
<td>(0.87-0.92)</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>1.6 (.02)</td>
<td>2.3 (.06)</td>
<td>1.31**</td>
<td>(1.25-1.37)</td>
</tr>
<tr>
<td>Low verbal fluency</td>
<td>393 (6.2)</td>
<td>75 (10.6)</td>
<td>1.92**</td>
<td>(1.48-2.47)</td>
</tr>
<tr>
<td>Limiting long illness</td>
<td>1442 (20.0)</td>
<td>395 (49.7)</td>
<td>4.18**</td>
<td>(3.59-4.86)</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>1610 (22.2)</td>
<td>396 (51.3)</td>
<td>3.69**</td>
<td>(3.17-4.30)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>582 (8.0)</td>
<td>161 (20.8)</td>
<td>3.02**</td>
<td>(2.49-3.66)</td>
</tr>
<tr>
<td>Smokes</td>
<td>1208 (16.6)</td>
<td>248 (31.9)</td>
<td>2.35**</td>
<td>(2.00-2.77)</td>
</tr>
<tr>
<td>Poor vision</td>
<td>2939 (40.4)</td>
<td>426 (54.8)</td>
<td>3.02**</td>
<td>(2.50-3.65)</td>
</tr>
<tr>
<td>Poor hearing</td>
<td>2832 (39.0)</td>
<td>359 (46.2)</td>
<td>1.51**</td>
<td>(1.24-1.82)</td>
</tr>
</tbody>
</table>

*a unweighted counts  b = weighted percentages
* p<0.05  **p<0.001

Multivariate analysis

The factors that attained statistical significance in the univariate analyses were then included in a series of multivariate logistic regression models for men and women separately and stratified by age group (Tables 3.3 & 3.4). Table 3.5 shows the p-values for tests of the interactions between each factor and age and sex when the final model was estimated across all participants.
In the first step of each regression analysis significant demographic variables were entered as predictors (age, only primary education and marital status). In the second step health related factors including verbal fluency, immediate recall, number of chronic conditions, alcohol/substance abuse and smoking were added to the model. In the presence of these additional factors, education remained significantly associated with depressive symptoms only in adult women aged 50-64 years, while all other associations remained stable. Step three involved adding factors associated with chronic conditions such as number of medications, presence of a LLI, chronic pain, incontinence and sensory impairment. Some associations seen in the fully adjusted models differed significantly by sex and age category.

**Age & sex differences in clinical factors**

*Cognitive function*

Verbal fluency was associated with depression only in men and women aged 65 and over. Immediate recall was associated with depression in women of all ages but no association was observed in men.

*Physical illness & medication use*

Physical illness was associated with depression in the partially adjusted model (model 2) for both men and women of all ages. However, in the fully adjusted model, physical illness was associated with depression only in men and women aged 65 and over.
Table 3.3 Multivariate logistic regression analysis of depression for male adults 50-64 and aged 65 and over

<table>
<thead>
<tr>
<th>Males</th>
<th>Model 1 OR (95% CI)</th>
<th>Model 2 OR (95% CI)</th>
<th>Model 3 OR (95% CI)</th>
<th>Model 1 OR (95% CI)</th>
<th>Model 2 OR (95% CI)</th>
<th>Model 3 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>.965 (0.93-1.01)</td>
<td>0.96 (0.92-1.00)</td>
<td>0.95* (0.90-0.94)</td>
<td>0.97 (0.93-1.00)</td>
<td>0.96* (0.92-0.99)</td>
<td>0.94* (0.90-0.98)</td>
</tr>
<tr>
<td>Primary edu</td>
<td>1.47* (1.00-2.16)</td>
<td>1.31 (0.88-1.95)</td>
<td>1.13 (0.73-1.73)</td>
<td>1.55* (1.01-2.37)</td>
<td>1.28 (0.81-2.02)</td>
<td>1.07 (0.66-1.75)</td>
</tr>
<tr>
<td>never married</td>
<td>3.19** (2.11-4.83)</td>
<td>2.87** (1.87-4.40)</td>
<td>2.69** (1.69-4.27)</td>
<td>2.07* (1.21-3.55)</td>
<td>1.86* (1.02-3.39)</td>
<td>2.23* (1.17-4.25)</td>
</tr>
<tr>
<td>widow/sep/divorce</td>
<td>2.86** (1.82-4.48)</td>
<td>2.06* (1.27-3.32)</td>
<td>1.92* (1.14-3.22)</td>
<td>1.52 (0.90-2.58)</td>
<td>1.38 (0.80-2.40)</td>
<td>1.38 (0.77-2.47)</td>
</tr>
<tr>
<td>low verbal fluency</td>
<td>0.70 (0.25-1.92)</td>
<td>0.80 (0.26-2.40)</td>
<td>2.37* (1.11-5.05)</td>
<td>2.64* (1.14-6.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>0.94 (0.84-1.04)</td>
<td>0.98 (0.87-1.11)</td>
<td>0.90 (0.78-1.04)</td>
<td>0.94 (0.80-1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no chronic conditions</td>
<td>1.25* (1.09-1.41)</td>
<td>0.85 (0.72-1.01)</td>
<td>1.53** (1.34-1.75)</td>
<td>1.24* (1.05-1.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcohol or sub abuse</td>
<td>5.28** (2.89-9.63)</td>
<td>4.24** (2.17-8.28)</td>
<td>2.94* (1.35-6.37)</td>
<td>2.29 (0.98-5.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>smokes</td>
<td>1.62** (1.11-2.36)</td>
<td>1.34 (0.89-2.02)</td>
<td>1.12 (0.64-1.99)</td>
<td>1.01 (0.55-1.87)</td>
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<tr>
<td>no of medications</td>
<td>1.18* (1.07-1.29)</td>
<td>1.38 (0.80-2.37)</td>
<td>3.42** (2.06-5.68)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>limiting long illness</td>
<td>1.98* (1.28-3.06)</td>
<td>3.12** (1.65-5.89)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>pain</td>
<td>2.67** (1.79-3.97)</td>
<td>3.15* (1.54-6.42)</td>
<td>1.92* (1.07-3.45)</td>
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<tr>
<td>incontinence</td>
<td>3.15* (1.54-6.42)</td>
<td>2.10* (1.29-3.42)</td>
<td>0.94 (0.56-1.58)</td>
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<td></td>
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</tr>
<tr>
<td>poor vision</td>
<td>1.00 (0.58-1.24)</td>
<td>1.04 (0.95-1.14)</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>
Table 3.4: Multivariate logistic regression analysis of depression for female adults 50-64 and aged 65 and over

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>50-64</th>
<th>Model 1</th>
<th>OR</th>
<th>95% CI</th>
<th>Model 2</th>
<th>OR</th>
<th>95% CI</th>
<th>Model 3</th>
<th>OR</th>
<th>95% CI</th>
<th>&gt;=65</th>
<th>Model 2</th>
<th>OR</th>
<th>95% CI</th>
<th>Model 3</th>
<th>OR</th>
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<td>age</td>
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<td></td>
<td>age</td>
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<td>(0.93-0.99)</td>
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<td>0.95*</td>
<td>(0.93-0.98)</td>
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<td>0.96*</td>
<td>(0.92-0.99)</td>
<td></td>
<td>.963</td>
<td>(0.94-0.99)</td>
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<td>0.94</td>
<td>(0.91-0.96)</td>
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<td></td>
<td></td>
<td>2.41**</td>
<td>(1.85-3.14)</td>
<td></td>
<td>1.65**</td>
<td>(1.23-2.20)</td>
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<td>1.35</td>
<td>(0.98-1.84)</td>
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<td>(1.27-2.38)</td>
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<td>(0.93-1.84)</td>
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<td>(0.78-1.92)</td>
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<td>1.21</td>
<td>(0.76-1.92)</td>
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<td>1.19</td>
<td>(0.74-1.93)</td>
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<td>1.83*</td>
<td>(1.00-3.33)</td>
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<td>1.63</td>
<td>(0.88-3.04)</td>
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<tr>
<td>widow/sep/divorce</td>
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<td>2.36**</td>
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<td>1.97**</td>
<td>(1.48-2.62)</td>
<td></td>
<td>1.83**</td>
<td>(1.35-2.48)</td>
<td></td>
<td>2.42**</td>
<td>(1.71-3.42)</td>
<td></td>
<td>2.13**</td>
<td>(1.48-3.07)</td>
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<td>(0.86-2.64)</td>
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<td>(1.14-3.24)</td>
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<td>1.88*</td>
<td>(1.08-3.26)</td>
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<tr>
<td>Immediate recall</td>
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<td>0.87*</td>
<td>(0.80-0.95)</td>
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<td>0.91*</td>
<td>(0.84-0.98)</td>
<td></td>
<td>0.83**</td>
<td>(0.70-0.92)</td>
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<td>0.85*</td>
<td>(0.76-0.95)</td>
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<td>(1.21-1.45)</td>
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<td>0.95</td>
<td>(0.85-1.07)</td>
<td></td>
<td>1.39**</td>
<td>(1.26-1.54)</td>
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<td>1.22*</td>
<td>(1.08-1.38)</td>
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<tr>
<td>alcohol or sub abuse</td>
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<td>(1.15-8.92)</td>
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<td>(1.10-30.9)</td>
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<td>11.2*</td>
<td>(1.76-71.4)</td>
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<tr>
<td>smokes</td>
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<td></td>
<td>2.13**</td>
<td>(1.64-2.76)</td>
<td></td>
<td>2.06**</td>
<td>(1.56-2.71)</td>
<td></td>
<td>1.85*</td>
<td>(1.24-2.75)</td>
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<td>1.74*</td>
<td>(1.15-2.65)</td>
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<td></td>
</tr>
<tr>
<td>no of medications</td>
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<td></td>
<td>1.13**</td>
<td>(1.06-1.20)</td>
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<td>0.97</td>
<td>(0.90-1.04)</td>
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<td></td>
</tr>
<tr>
<td>limiting long illness</td>
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<td>2.44**</td>
<td>(1.79-3.32)</td>
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<td>(1.16-2.50)</td>
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<tr>
<td>pain</td>
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<td>1.54*</td>
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<td>1.80*</td>
<td>(1.26-2.58)</td>
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</tr>
<tr>
<td>incontinence</td>
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<td></td>
<td></td>
<td></td>
<td>1.51*</td>
<td>(1.07-2.12)</td>
<td></td>
<td></td>
<td></td>
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<td>1.70*</td>
<td>(1.14-2.51)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>poor vision</td>
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<td></td>
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<td>1.57*</td>
<td>(1.05-2.33)</td>
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</tr>
<tr>
<td>poor hearing</td>
<td></td>
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<td></td>
<td></td>
<td>1.54</td>
<td>(0.99-2.39)</td>
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<td></td>
<td></td>
<td>1.21</td>
<td>(0.81-1.82)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*p<0.05   **p<0.001
The inclusion of medications in the full model caused the association between physical illness and depression to lose significance for younger adults aged 50-64yrs.

Differences in the effects of physical illness and medications use were significantly different by age group ($p<0.001$). The effects of pain and incontinence, while statistically significant in both sexes were significantly stronger predictors of depressive symptoms in men than women ($p<0.001$ for interaction terms). Smoking was associated with depressive symptoms only in women and this sex difference was stastically significant (see Table 3.5).

### Table 3.5 P-values for interactions terms in final model

<table>
<thead>
<tr>
<th></th>
<th>Age group p-value</th>
<th>Sex p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.40</td>
<td>0.76</td>
</tr>
<tr>
<td>Education</td>
<td>0.57</td>
<td>0.67</td>
</tr>
<tr>
<td>Never married</td>
<td>0.98</td>
<td>0.01</td>
</tr>
<tr>
<td>Windowed/Sep/Divorced</td>
<td>0.87</td>
<td>0.66</td>
</tr>
<tr>
<td>Low fluency</td>
<td>0.19</td>
<td>0.53</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>0.28</td>
<td>0.18</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>0.00</td>
<td>0.56</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>0.71</td>
<td>0.63</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.28</td>
<td>0.03</td>
</tr>
<tr>
<td>Medications</td>
<td>0.00</td>
<td>0.59</td>
</tr>
<tr>
<td>Limiting illness</td>
<td>0.13</td>
<td>0.43</td>
</tr>
<tr>
<td>Pain</td>
<td>0.42</td>
<td>0.00</td>
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<tr>
<td>Incontinence</td>
<td>0.63</td>
<td>0.00</td>
</tr>
<tr>
<td>Poor vision</td>
<td>0.92</td>
<td>0.25</td>
</tr>
<tr>
<td>Poor hearing</td>
<td>0.83</td>
<td>0.22</td>
</tr>
</tbody>
</table>
3.5 Discussion

Overall, the prevalence of depression in this population based study of adults aged 50 years and over was 10%. Women had a higher prevalence than men in all age groups.

Regardless of age and gender; chronic pain, disability, visual impairment and urinary incontinence are the most consistent correlates of depressive symptoms found in this study. Substantial evidence already exists in the literature linking pain and functional disability with depressive symptoms [220, 221]; however, the association between incontinence and depressive symptoms is not well documented, particularly in men. Urinary incontinence is a significant health problem for older adults and the prevalence increases significantly with age [222]. It is also a common reason for admission to residential care where the prevalence of depressive symptoms is known to be much higher. Some studies [223] suggest that incontinence is only associated with depressive symptoms in older women; however, our findings suggest that incontinence is strongly associated with depressive symptoms in both men and women and this finding is strengthened by the fact that the analysis controlled for limitations to physical mobility. Moreover, we found that among both age groups, incontinence was more strongly associated with depressive symptoms among men than women. Depression was seen in 20% of those reporting incontinence, suggesting that adults presenting for treatment of urinary incontinence should be screened for depression and greater awareness and treatment of incontinence in older adults could potentially reduce the prevalence of depression.
In our study, visual impairment was associated with depressive symptoms in all adults while hearing impairment was not associated with depressive symptoms after adjusting for all other factors. We might have expected visual impairment to be associated with depressive symptoms only in those aged 50-64, given the literature [224] suggesting it is the age at which individuals are dealing with loss that is critical to the development of depression. However, our results suggest that vision specific distress is associated with depressive symptoms in all adults regardless of age. Identifying older adults with high levels of distress from visual impairment could be a way to determine those at risk of depression and in need of early intervention. Older adults may benefit from early interventions focused on coping and dealing with the practical and social burden associated with visual impairment rather than being treated for depression.

In building our model of depression we developed three steps that represented socio-demographic variables, chronic disease factors and conditions or factors which may mediate the effect of chronic disease on depression. This procedure generated some statistically significant differences in the association between physical illness and medications across age groups. Among those aged 50-64 years, the relationship between physical illness and depressive symptoms appears to be accounted for by medication use. This is in direct contrast to what is observed in adults aged 65 and over; where physical illness remains significantly associated with depression, despite the inclusion of medications in the model. These results might suggest that in adults aged 50-64 years it is the medications taken for chronic diseases that account for some of the increased risk for depression associated with comorbid physical illness. Future
work will focus on whether this association is related to polypharmacy or the nature and dosage of specific medications.

Low verbal fluency was associated with depressive symptoms only in adults aged 65 and over, although this age difference was not statistically significant (interaction effect \( p=0.19 \)). These results are in keeping with previous findings of a strong association between depression and executive dysfunction in older adults [225]. Interestingly memory (measured by immediate recall) was associated with depressive symptoms only in women although again the gender difference was not statistically significant. The causal and temporal relationship between depressive symptoms and cognitive function is currently of great research interest and results thus far yield mixed findings [36, 226]. Future waves of TILDA will add to the evidence base in this area.

Depression is associated with cerebrovascular disease and as a result there is increasing interest in the potential role that risk factors for cerebrovascular disease might play in facilitating the clinical expression of depression [227]. Cigarette smoking is an important, but potentially reversible, risk factor for cardiovascular diseases. The link between smoking and depression has been well documented in young people; however, smoking research and intervention efforts have largely neglected older adults, with older women particularly underserved [228, 229]. Our results extend the evidence base by showing that current smoking is much more strongly associated with depressive symptoms in women than men (\( p \)-value for gender difference =0.03). Throughout adulthood, women show higher levels of depressive disorders than men and women are more prone to engage in negative affect-
related smoking and to show stronger relations of life stressors to smoking maintenance or relapse [230, 231]. For these reasons the most plausible interpretation of our results is that in older adult women it is depressed mood which increases smoking risk rather than smoking behaviour leading to depression, and that treatment of low mood may be a target for smoking cessation among older women.

Strengths of the present study are the very large nationally representative sample with a high response rate and the comprehensive assessment of health-related and socio-demographic factors. A response rate of 60% is used as the threshold of acceptability for most journals; therefore our response rate of 62% is robust for a study of older adults [232]. Limitations are that the data was analysed cross-sectionally and while we have used modification of regression effects to attempt to identify mediating relationships we cannot make any direct inferences about causality. Depression was not formally diagnosed in our study however the CES-D instrument has been shown to have good validity with respect to depression in the older population [110]. Additionally, findings from a recent review of risk factors for depression [233] showed no clear differences between risk factors for depressive symptoms and disorders, suggesting that these risk factors are significant for the whole continuum of severity of depression.

In summary, we have identified age and gender specific clinical correlates of depressive symptoms which may identify older adults most likely to present with depression in community settings. Some of the factors found to be associated with depression are potentially modifiable, in particular visual
impairment and incontinence. Given the rapidly expanding population of older adults and the burden of morbidity represented by depression, more research is needed to fully understand the effects of these potentially modifiable factors and how they can be targeted to alleviate depression in the older population.
4 Symptomatic Orthostatic Hypotension and Late-Life Depression

4.1 Abstract

BACKGROUND
Orthostatic drops in blood pressure may play an important role in the development of late-life depression; however, evidence is limited especially from population studies.

AIMS
To investigate the relationship between orthostatic hypotension (OH) and depression and examine the role of orthostatic symptoms in this relationship.

METHODS
We analysed data from the first wave of The Irish Longitudinal Study on Ageing (TILDA). Depression was assessed using the Center for Epidemiologic Studies – Depression scale and OH was assessed using continuous beat-to-beat blood pressure monitoring.

RESULTS
Depressed participants had a higher prevalence of symptomatic OH ($X^2 = 7.49$, $p=0.019$) and Initial OH ($X^2 = 4.93$, $p=0.026$). Sustained symptomatic OH was associated with a higher odds of been depressed (OR=1.80, 95% CI: 1.09-2.98 for 30 seconds; OR=1.99, 95% CI: 1.07-3.72 for 90 seconds).

CONCLUSIONS
The recognition of symptoms of hypoperfusion during standing may discriminate a subgroup of OH patients at greater risk for developing late-life depression.
4.2 Introduction

Orthostatic hypotension (OH) is a recently recognised risk factor for white matter hypertensities (WMHs) [67, 203] and accumulating evidence, although limited, suggests it may play an important role in the development of late life depression [67, 173, 201]. The importance of genetic predisposition to affective disorders declines in late-life depression (LLD) [234, 235]; and may be replaced by associations with structural abnormalities of the brain. Magnetic resonance imaging (MRI) studies have repeatedly found increases in WMHs in the frontal lobes [48, 236, 237] and basal ganglia [48] of older people with major depression. Although the pathology of WMHs varies, autopsy studies have shown that they are all due to ischemic change and tissue hypoxia in late-life major depression [63] and their presence has been interpreted as providing strong evidence for the role of cerebrovascular disease in LLD. In animal models cerebral white matter ischemia results from hypotension [202] and a few recent clinical studies have shown that OH occurs more frequently in late-life depression [67, 173, 201].

Hemodynamic homeostasis becomes less effective with aging and is associated with a decreased ability to regulate blood pressure (BP) [193]. After essential hypertension, OH is the most common disorder of BP regulation and in older adults the prevalence ranges between 5 and 30%, depending on the population studied and definition used [238]. OH can be asymptomatic or manifest as symptoms that range from dizziness and light-headedness to weakness and loss of consciousness. These symptoms are thought to arise from periods of hypoperfusion that have the potential to induce ischemic neurological impairment [238]. If OH causes cerebral ischemia and WMHs that
predispose older adults to depression, then the recognition of orthostatic symptoms may identify individuals at greater risk of depression.

The aim of this study was to investigate if the prevalence and severity of OH is associated with depression in a nationally representative, community dwelling sample of older adults. We hypothesised that participants with depression would have a greater burden of OH compared to participants without depression and that orthostatic symptoms would moderate the effect of OH on depression.
4.3 Methods

Study design

We analysed data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) collected between October 2009 and February 2011. Full details of the sampling procedure and response have been described elsewhere [217]. In short, TILDA is a study of people aged 50 and over (and their spouses or partners of any age) resident in Ireland. A nationally representative sample was selected from the Irish Geodirectory, a comprehensive and up-to-date listing and mapping of all residential addresses in the Republic of Ireland compiled by the Irish Postal Service and Ordnance Survey Ireland. People with known or suspected dementias were ineligible at baseline for participation in TILDA.

Participants completed a computer-assisted personal interview (CAPI) in their own homes administered by trained professional interviewers. The TILDA questionnaire includes detailed questions on many aspects of health, lifestyle, social interactions and financial circumstances. Each participant was then invited to travel to one of two health centres 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. All health assessments were carried out by trained nurses. The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, and participants were required to provide written informed consent prior to participation in the study. The measures specific to the current analysis are described in detail below.
Psychiatric Assessment

The primary outcome measure for this analysis was case-level depressive symptoms defined by a score of 16 or greater on the 20-item Centre for Epidemiologic Studies Depression scale (CES-D). The CES-D generates a total score with a range between 0 and 60 with higher scores indicating greater depressive symptoms. A cut-off score of 16 has been shown to have a sensitivity of 100% and specificity of 88% for MDD in an elderly population [110]. LLD is commonly defined as depression occurring in adults aged 60 or 65 years and over therefore only participant’s ≥ 60 years were included in the analysis. Participants taking antidepressants were excluded from this study.

Anxiety was assessed using the Hospital Anxiety Depression Scale – Anxiety subscale (HADS-A). Scores from this 7 item scale range from 0-21 with higher scores indicating greater anxiety symptoms. A cut-off score of ≥11 has been used to classify participants with clinically significant anxiety [239]. The Mini Mental State Examination (MMSE) was used to assess global cognition [240].

Measurement of Orthostatic Hypotension

Orthostatic BP was measured during the centre based health assessment using continuous beat-to-beat digital plethysmography (Finometer Midi, Amsterdam) during 5 minutes of supine rest followed by a stand for 2 minutes. Room ambient temperature was set between 21-24°C. The transition from supine to standing in each participant was completed within 5 seconds where possible. Participants were asked to report whether they had felt dizzy, light-headed or unsteady on standing (yes or no to any of the symptoms). Individual output was reviewed by a biomedical engineer and recordings with excessive
artefacts were excluded from analysis. Beat-to-beat recordings of 180 seconds duration beginning 60 seconds (s) before standing and lasting 120 seconds after standing were extracted. A 10 second moving average filter was used to smooth the beat-to-beat blood pressure variations [241]. Supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) was defined as the average SBP/DBP between 60 and 30 seconds before standing, nadir SBP/DBP as the lowest value during standing and delta SBP and DBP as the difference between nadir and supine SBP/DBP.

**Classification of Orthostatic Hypotension**

**Classical Orthostatic Hypotension:** In 1996, a consensus committee defined classical OH (COH) as a drop of at least 20mmHg in SBP or 10mmHg in DBP within the first 3 minutes of orthostasis [129]. In normal individuals, BP is expected to return to supine values within 30’s of standing. A deficit in recovery of SBP/DBP at 40’s post standing is considered abnormal [242]. Therefore to identify individuals with sustained OH, we calculated recovery deficits of SBP/DBP at 30’s, 40’s, 60’s 90’s and 110’s as the difference from supine SBP/DBP and expressed as OH_30, OH_40, OH_60, OH_90 and OH_110 respectively to reflect the BP pattern during standing.

**Symptomatic Orthostatic Hypotension:** Participants with a reduction of SBP of at least 20mmHg or DBP of 10mmHg accompanied by symptoms of dizziness/light-headedness within 2 minutes of standing were classified as having symptomatic OH (SOH). To identify individuals with sustained SOH, recovery deficits of SBP/DBP at 30’s, 40’s, 60’s 90’s and 110’s were calculated
as the difference from supine SBP/DBP accompanied by symptoms of dizziness/light-headedness and expressed as SOH_30, SOH_40, SOH_60, SOH_90 and SOH_110 respectively.

Asymptomatic Orthostatic Hypotension: Participants with a reduction of SBP of at least 20mmHg or DBP of 10mmHg without symptoms of dizziness/light-headedness within 2 minutes of standing were classified as having asymptomatic OH (AOH).

Initial Orthostatic Hypotension: Participants with a reduction of more than 40mmHg in SBP or more than 20mmHg in DBP, accompanied by symptoms of dizziness/light-headedness after standing were classified as having initial orthostatic hypotension (IOH) [177].

Measurement of Covariates

Other measures recorded during the CAPI home interview included age, gender, highest level of educational attainment (primary, secondary or tertiary), current smoking status, history of cardiovascular disease and medication use. Medication use was determined by recording medication names from the medicine bottles in the participant’s home during the CAPI interview. Medications were classified using the World Health Organization Anatomical Therapeutic Chemical (ATC) system [243]. A dichotomous variable for antihyperintensive medication was computed (1=yes, 0=no) with the following ATC codes: C02; diuretic drugs, C03; peripheral vasodilator drugs, C04; vasoprotective drugs, C05; β-blocking agents, C07; and calcium-channel
blockers C08. Psychotropic medications were classified by ATC code N05. In addition to the beat-to-beat BP measurements, SBP and DBP were recorded at rest using a digital automatic BP monitor (OMRON Model M10-IT). For descriptive purposes participants were classified as hypertensive if the mean of their two seated SBP measurements was ≥140 mmHg and/or if the mean of their two seated DBP measurements was ≥90 mmHg [244] or if they were currently taking antihypertensive medications [244]. Objective measures of weight (1 measure using SECA electronic floor scales) and height (1 measure using SECA 240 wall mounted measuring rod) were used to calculate body mass index (BMI). Total cholesterol was determined from a venous blood sample.

**Statistical Analysis**

Statistical analysis was performed using PASW statistics 18. Distribution of continuous variables was assessed using Q-Q plots and histograms. Normally distributed variables were described as means and standard errors (SE) and were compared using independent t-tests and categorical variables were compared using Chi-squared tests.

One-way analysis of variance was performed to evaluate differences among group means. Multivariate logistic regression analysis was used to assess the relationship between OH and depression with adjustment for potential confounders including age, sex, education level, MMSE, history of cardiovascular disease (angina, stroke, myocardial infarction), total cholesterol, smoking (0=non/previous smoker, 1=current smoker), BMI, antihypertensive and psychotropic drugs, SBP and DBP values as covariates.
Adjusted odds ratio (OR), 95% confidence intervals and significance levels are presented here. Differences with \( p \leq 0.05 \) (two-tailed) were considered statistically significant. Data was weighted with respect to age, sex and education to the Quarterly National Household Survey (2010) and further weighted to account for those who did not attend for a health assessment.
4.4 Results

Characteristics of the sample

Only participants who completed a health centre assessment were eligible for inclusion; given that beat-to-beat monitoring of BP during ‘active stand’ was only conducted in the health centre assessment. The study population used in this analysis is depicted in Figure 4.1 (coded blue). In total 2,560 participants were eligible for the current analyses. Of these, 52% were female with a mean age of 67.9, (SE .16, range 60-98).

Figure 4.1 TILDA population used in OH and depression analysis (Blue)
Table 4.1 Demographic and clinical characteristics of sample by depression status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No-depression (2400)</th>
<th>Depression (n=160)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SE</td>
<td>68.0 ± .17</td>
<td>67.1 ± .53</td>
<td>0.064</td>
</tr>
<tr>
<td>Female, % (n)</td>
<td>50.7 (1245)</td>
<td>64.4 (107)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>36.8 (675)</td>
<td>48.5 (63)</td>
<td>0.009</td>
</tr>
<tr>
<td>Secondary</td>
<td>42.3 (919)</td>
<td>35.4 (52)</td>
<td>0.112</td>
</tr>
<tr>
<td>Tertiary</td>
<td>21.0 (804)</td>
<td>16.1 (45)</td>
<td>0.072</td>
</tr>
<tr>
<td>Current Smoker, % (n)</td>
<td>11.2 (255)</td>
<td>22.4 (33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE ± SE</td>
<td>28.2 (.04)</td>
<td>27.6 (.18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Anxiety ± SE</td>
<td>3.5 (74)</td>
<td>31.2 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVRF's ± SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>6.6 (155)</td>
<td>9.8 (14)</td>
<td>0.144</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.8 (138)</td>
<td>7.8 (12)</td>
<td>0.306</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67.2 (1605)</td>
<td>69.4 (109)</td>
<td>0.566</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.9 (185)</td>
<td>8.9 (14)</td>
<td>0.617</td>
</tr>
<tr>
<td>Stroke/TIA ± SE</td>
<td>3.8 (91)</td>
<td>8.6 (12)</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SE</td>
<td>28.6 ± .10</td>
<td>29.0 ± .39</td>
<td>0.533</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L), mean ± SE</td>
<td>4.97 ± .06</td>
<td>4.95 ± .02</td>
<td>0.176</td>
</tr>
<tr>
<td>Taking anti-hypertensive medications, % (n)</td>
<td>43.8 (1039)</td>
<td>46.85 (71)</td>
<td>0.512</td>
</tr>
<tr>
<td>Taking psychotropic medications</td>
<td>4.5 (108)</td>
<td>26 (16.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood Pressure ± SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline systolic BP</td>
<td>139.2 (.56)</td>
<td>143.6 (2.3)</td>
<td>0.214</td>
</tr>
<tr>
<td>Baseline diastolic BP</td>
<td>72.7 (.26)</td>
<td>75.1 (1.2)</td>
<td>0.172</td>
</tr>
<tr>
<td>nadir systolic BP</td>
<td>97.4 (.60)</td>
<td>100.5 (2.5)</td>
<td>0.596</td>
</tr>
<tr>
<td>nadir diastolic BP</td>
<td>45.8 (.32)</td>
<td>47.4 (1.2)</td>
<td>0.527</td>
</tr>
<tr>
<td>delta SBP ± SE</td>
<td>-39.8 (.46)</td>
<td>-40.5 (1.9)</td>
<td>0.530</td>
</tr>
<tr>
<td>delta DBP ± SE</td>
<td>-25.6 (.26)</td>
<td>-26.0 (1.0)</td>
<td>0.773</td>
</tr>
</tbody>
</table>

*Mini Mental State Examination (range 0-30), †Hospital Anxiety and Depression scale ≥ 11 (range 0-21), ‡Cardiovascular risk factors §mean of 2 seated SBP is ≥140mmHg and/or mean of 2 seated DBP is ≥90 mmHg or currently taking antihypertensive medications, †Transient Ischaemic Attack, ‡Body Mass Index †Venous measurement †Blood pressure 1 Average change in SBP on standing (nadir SBP – baseline BP) 2 Average change in SBP on standing (nadir SBP – baseline BP) §Based on t-test comparing depressed and non-depressed groups for continuous variables and X² for categorical variables ∗denotes significance at p < .05
Table 4.1 shows demographic and clinical characteristics of participants by depression status. Excluding those on antidepressants, participants with depression were more likely to be women (p<0.001), had significantly more anxiety (p<0.001) and were more likely to smoke (p=0.002). No between group differences were observed for objectively measured vascular risk factors (BMI, total cholesterol, and hypertension). Both groups had similar prevalence of self reported angina, MI and diabetes however the prevalence of stroke/TIA was greater in participants with depression (p<0.006). No difference in anti-hypertensive medication use was observed between groups but participants with depression took more psychotropic drugs (p<0.001). Overall orthostatic blood pressure parameters did not differ significantly between groups.

The distribution of different classifications of OH (OH, SOH, IOH) by depression status is shown in Table 4.2. Participants with depression had a higher proportion of OH at 30 seconds post active stand and at all subsequent time points; however these differences were not statistically significant. Depressed older adults had a higher proportion of SOH at all recovery time points and these differences were statistically significant at 30, 40 and 90 seconds. Participants with depression had significantly higher levels of IOH.
Table 4.2 Prevalence of classical, symptomatic and Initial OH by depression status and univariate logistic regression analysis on depression

<table>
<thead>
<tr>
<th></th>
<th>No-depression</th>
<th>Depression</th>
<th>( X^2 )</th>
<th>P-value</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2400</td>
<td>N=160</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COH</td>
<td>2033</td>
<td>96.9</td>
<td>2033</td>
<td>.186</td>
<td>.682</td>
<td>.781</td>
</tr>
<tr>
<td>COH_30</td>
<td>479</td>
<td>23.1</td>
<td>479</td>
<td>1.96</td>
<td>.211</td>
<td>1.34</td>
</tr>
<tr>
<td>COH_40</td>
<td>374</td>
<td>18.1</td>
<td>374</td>
<td>2.33</td>
<td>.150</td>
<td>1.39</td>
</tr>
<tr>
<td>COH_60</td>
<td>310</td>
<td>14.8</td>
<td>310</td>
<td>1.53</td>
<td>.247</td>
<td>1.33</td>
</tr>
<tr>
<td>COH_90</td>
<td>299</td>
<td>14.7</td>
<td>299</td>
<td>.990</td>
<td>.362</td>
<td>1.19</td>
</tr>
<tr>
<td>COH_110</td>
<td>311</td>
<td>14.9</td>
<td>311</td>
<td>.127</td>
<td>.740</td>
<td>1.08</td>
</tr>
<tr>
<td>Orthostatic symptoms</td>
<td>815</td>
<td>34.0</td>
<td>815</td>
<td>.198</td>
<td>1.29</td>
<td>0.93-1.79</td>
</tr>
<tr>
<td>SOH</td>
<td>719</td>
<td>30.9</td>
<td>719</td>
<td>1.10</td>
<td>.362</td>
<td>1.20</td>
</tr>
<tr>
<td>SOH_30</td>
<td>194</td>
<td>8.2</td>
<td>194</td>
<td>14.6</td>
<td>.026</td>
<td>1.77*</td>
</tr>
<tr>
<td>SOH_40</td>
<td>155</td>
<td>6.6</td>
<td>155</td>
<td>11.6</td>
<td>.039</td>
<td>1.77*</td>
</tr>
<tr>
<td>SOH_60</td>
<td>120</td>
<td>5.1</td>
<td>120</td>
<td>7.1</td>
<td>.361</td>
<td>1.44</td>
</tr>
<tr>
<td>SOH_90</td>
<td>105</td>
<td>4.5</td>
<td>105</td>
<td>9.1</td>
<td>.019</td>
<td>1.99</td>
</tr>
<tr>
<td>SOH_110</td>
<td>106</td>
<td>4.6</td>
<td>106</td>
<td>8.1</td>
<td>.069</td>
<td>1.81</td>
</tr>
</tbody>
</table>

SOH                  a Classical Orthostatic Hypotension (Systolic drop in blood pressure of ≥20mmHg and/or diastolic drop in blood pressure of ≥10mmHg) participants who were classified as having classical OH 30 seconds after standing b participants who reported symptoms of dizziness, lightheadedness or unsteadiness on standing c Symptomatic Orthostatic Hypotension (Systolic drop in blood pressure of ≥20mmHg and/or diastolic drop in blood pressure of ≥10mmHg) participants who were classified as having symptomatic OH 30 seconds after standing d Initial Orthostatic Hypotension (Systolic drop in blood pressure of ≥40mmHg and/or diastolic drop in blood pressure of ≥20mmHg) participants who were classified as having initial OH 30 seconds after standing e Based on \( X^2 \) - test comparing depressed and non-depressed groups

Figure 4.2 (a-d) shows differences in recovery deficits between depressed and non-depressed participants with AOH and SOH. Depressed participants with SOH have a more impaired SBP and DBP recovery pattern compared to non-depressed participants with SOH or participants (depressed or non-depressed) with AOH.
Figure 4.2 (a-d) Systolic and diastolic recovery deficits by depression group

Figure 4.2a

Systolic BP recovery deficits by depression group

Asymptomatic OH

Figure 4.2b

Systolic BP recovery deficits by depression group

Symptomatic OH
Figure 4.2c

Diastolic BP recovery deficits by depression group

- No-depression
- Depression

Figure 4.2d

Diastolic BP recovery deficits by depression group

- No-depression
- Depression
Univariate logistic regression models showed that SOH at 30 seconds (OR=1.77, 95% CI: 1.09-2.87), 40 seconds (OR=1.77, 95% CI: 1.04-3.01) and 90 seconds (OR=1.99, 95% CI: 1.09-3.63) was associated with a significantly increased odds of depression. These associations persisted (Table 4.3) in the multivariate logistic regression models (30 seconds OR=1.80, 95% CI: 1.09-2.98, 40 seconds OR=1.94, 95% CI: 1.12-3.36 and 90 seconds OR=1.99, 95% CI: 1.07-3.72). When the individual components of SOH (i.e. participants with COH and participants with orthostatic symptoms) were entered into the model separately (data not shown) they were not independently associated with a significant effect on depression. However their combined effect resulted in a significant association with depression (OR=1.77, p=0.021).

Table 4.3 Multivariate logistic regression of symptomatic orthostatic hypotension on depression at various stages of BP recovery

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOH</td>
<td>1.23</td>
<td>(0.85-1.77)</td>
<td>0.260</td>
</tr>
<tr>
<td>SOH_30</td>
<td>1.87*</td>
<td>(1.12-3.09)</td>
<td>0.015</td>
</tr>
<tr>
<td>SOH_40</td>
<td>1.98*</td>
<td>(1.14-3.44)</td>
<td>0.015</td>
</tr>
<tr>
<td>SOH_60</td>
<td>1.54</td>
<td>(0.80-2.90)</td>
<td>0.192</td>
</tr>
<tr>
<td>SOH_90</td>
<td>2.02*</td>
<td>(1.08-3.78)</td>
<td>0.026</td>
</tr>
<tr>
<td>SOH_110</td>
<td>1.77</td>
<td>(0.93-3.38)</td>
<td>0.079</td>
</tr>
</tbody>
</table>

a adjusted for age, sex, education, MMSE, history cardiovascular disease (angina, stroke or myocardial infarction), smoking, total cholesterol, Body Mass Index, antihypertensive and psychotropic medications, systolic BP and diastolic BP.
b Symptomatic orthostatic Hypotension = Systolic drop in blood pressure of ≥20mmHg and/or diastolic drop in blood pressure of ≥10mmHg with symptoms of dizziness/light headed/unsteadiness on standing
c participants who were classified as having SOH 30 seconds after standing
4.5 Discussion
Our study shows that when OH is coupled with orthostatic symptoms it is independently associated with depression in community dwelling older adults. In contrast, OH defined by traditional methods is not associated with depression. Our results are broadly supportive of previous findings [67, 173, 201] but suggest that in the general population the presence of orthostatic symptoms may be important for identifying adults with OH who are at risk of developing depression. The occurrence of orthostatic symptoms in people with OH is likely to be due to cerebral hypoperfusion. In normal individuals, BP is expected to return to supine values within 30s of standing [242]. In our study depressed participants with SOH showed greater deficits in SBP and DBP at all stages of recovery compared to non-depressed adults with SOH or participants with AOH. Over time this impaired haemodynamic response to standing could cause cerebral ischaemia and WMHs that disrupt frontostriatal circuits and predispose individuals to the development of depression.

Just over a third (36%) of participants with OH reported symptoms of dizziness/light-headedness on standing. Cerebral autoregulation (CA) could explain why OH does not produce symptoms in all adults. CA acts as a safeguard to protect the brain against excessive oscillations of BP. Under normal physiologic conditions, changes in mean arterial BP between 60 and 160 mm Hg produce little or no change in cerebral blood flow (CBF). Beyond these limits, a sudden decrease in CBF occurs at the lower limit of autoregulation and likely manifests as orthostatic symptoms [117]. If the symptoms reported by participants in our study are a marker of impaired cerebral perfusion and cerebral hypoxia in people with OH, then it could
explain why only SOH was associated with depression in our analysis. In the context of depression, the presence of symptoms may discriminate a subgroup of OH patients at high risk for depression.

With the exception of smoking, no significant differences between depressed and non depressed participants were observed in self reported (angina, diabetes) or objectively measured (BMI, cholesterol, hypertension) cardiovascular risk factors. High rates of active treatment for hypertension and high cholesterol in this population could explain this lack of association. However, it is also possible that these risk factors are less relevant to the pattern of cerebrovascular disease observed in late life depression and that SOH is a more sensitive risk factor for this type of cerebrovascular disease. The prevalence of stroke/TIA was greater in the depressed group and this could have caused depression, [245] however in our fully adjusted model SOH was independently associated with depression even after controlling for angina, stroke and TIA’s. The use of antihypertensive medication did not differ between groups, and in healthy community-dwelling adults such as our participants these drugs are associated with only low rates of OH [246] making them unlikely to have confounded our findings. Participants currently taking antidepressants were excluded from our analysis. There is no simple way to ‘adjust’ for anti-depressant use in our baseline data since the model we are trying to estimate is essentially cyclical (i.e. our hypothesis is that OH causes depression, but we know depression results in anti-depressant use and anti-depressant use can cause OH). 6% of our target population were currently taking antidepressants and 80% of these were classified as not depressed by the CES-D (see figure 4.1).
One of the challenges in understanding the relationship between OH and depression relates to the optimal definition and measurement of OH. In our study the application of the COH definition to data obtained from continuous BP monitoring, resulted in 97% of participants been labelled as “pathological” which suggests a lack of specificity for the diagnosis of OH. The COH definition was primarily intended for use in clinical situations where OH is measured with sphygmomanometers or automatic oscillometric BP monitors.

Previous clinical studies investigating the relationship between OH and depression have used continuous BP monitoring and applied the COH definition [67, 173, 201]. However, our results suggest that in a large population study this definition does not easily reveal clinically meaningful differences. Applying the COH definition at 30s, 40s, 60s, 90 and 110s allowed us to identify participants with sustained OH and evaluate the relationship between abnormal BP recovery and depression. Moreover, some researchers have recommended that in older adults a definition of IOH be applied when taking continuous orthostatic BP measurements to more clearly discriminate between normal and abnormal groups [247]. IOH is defined as a transient BP decrease within 15 seconds after standing of more than 40mmHg in SBP, or more than 20mmHg in DBP accompanied by symptoms of cerebral hypoperfusion. We therefore also classified our sample using this definition and found that the burden of IOH was significantly greater in the depression group. IOH was associated with depression in the univariate logistic regression model (table 4.2) and the association was unchanged in the fully adjusted multivariate model (data not shown). Interestingly, when the OH group representing participants who had the BP drop associated with IOH (drop of at least
40mmHg in SBP or 20mmHg in DBP) but without orthostatic symptoms, were entered into the multivariate model, no significant association with depression was observed. This again suggests that the addition of indicators of hypoperfusion like dizziness/light-headedness during standing improves the predictive value of OH for late-life depression.

The main strengths of this study are the large population representative sample and comprehensive health assessment. We would expect the proposed link between OH and depression to be strongest among clinical samples where cases of depression and OH would be more prevalent and severe. It is therefore notable that we identified an association in this community sample where the lowest prevalence and severity rates for these conditions are observed. Limitations are that the data was analysed cross-sectionally so we cannot make any direct inferences about causality. Although many relevant risk factors were assessed and statistically controlled for in the analysis, the possibility of residual confounding cannot be ruled out. Depression was not formally diagnosed in our study although the CES-D instrument has good validity with respect to depression in the older population, and it is a well validated measure of depressive symptomatology [110, 248]. Although early MRI studies were carried out only on clinical samples with major depression, two large recent epidemiologic studies of community depression have shown that the prevalence of deep WMHs is also higher in this population [47, 48]. The proposed mechanism linking OH and depression through the development of WMH’s may therefore have wider relevance, including not only major depression but also milder forms of subclinical depression detected by symptom scales such as the CES-D. Our ability to identify a relationship
between OH and depression may have been limited by the fact that our depressed group contained both early and late-onset depression. It must also be acknowledged that in some participants vestibular dizziness rather than hypotension could have caused the symptoms of dizziness.

In summary, we found evidence of a relationship between symptomatic orthostatic hypotension and depression in a representative sample of community dwelling older adults. OH is an increasingly important topic in biomedical research given the aging demographics. A greater understanding of the biological processes linking vascular disease and depression will inform new approaches to the prevention and treatment of depression in older adults.
5 Oscillometric measure of blood pressure detects association between orthostatic hypotension and depression in a population based study of older adults

5.1 Abstract

Background: White matter hyperintensities may contribute to depression by disrupting neural connections among brain regions that regulate mood. Orthostatic hypotension (OH) may be a risk factor for white matter hyperintensities and accumulating evidence, although limited suggests it may play a role in the development of late-life depression. The aim of this study was to examine the relationship between an oscillometric measure of orthostatic hypotension and depression in population based sample of older adults.

Methods: We analysed data on adults aged 60 and over from the first wave of The Irish Longitudinal Study on Ageing (TILDA). Depression was assessed using the Center for Epidemiologic Studies – Depression (CES-D) scale and OH was assessed by a sit-to-stand orthostatic stress test; two seated blood pressure measurements were followed by a single standing blood pressure measurement. Participants self reported whether they felt dizzy, light-headed or unsteady on standing.

Results: Participants with symptomatic OH (SOH, n=20) had the highest mean CES-D score (mean 8.6, SE 1.6) when compared to participants with asymptomatic OH (AOH) (mean 5.6, SE .48) and participants with no OH (mean 5.2, SE .14) and this difference was significant for both comparisons (p<0.001). Linear regression analysis adjusted for socio-demographic and
clinical characteristics showed that SOH was associated with higher CES-D scores (unstandardised B coefficient = 2.24; 95% CI .301 - 4.79; p =0.05) compared to participants without OH. AOH was not associated with higher CES-D scores (unstandardised B coefficient = .162; 95% CI -.681, 1.00; p= 0.70).

**Conclusions:** Symptomatic orthostatic hypotension is associated with depression in older adults and needs to be considered in studies examining the relationship between vascular disease and depression in older adults.
5.2 Introduction
Depression is common in late life [8] and associated with diverse aetiological factors that are poorly understood. Evidence of an association between vascular disease and late-life depression (LLD) led to the 'vascular depression hypothesis' which proposed that structural damage to the frontostriatal tracts resulting from ischemic cerebrovascular disease creates a vulnerability to depression in late life [50, 249]. This hypothesis stimulated much research and laid the foundation for examining the mechanisms by which vascular disease influences the development of depression in older adults. As a result, a mechanistic model for vascular depression has recently been proposed that identifies hypoperfusion as a potential mechanistic path to vascular depression [56].

Blood flow to the brain is influenced by systemic hemodynamics and cerebrovascular autoregulation, whereby cerebral arteries contract or dilate in response to arterial blood pressure (BP) changes. These processes interact to maintain stable perfusion but are impaired in the context of vascular disease leading to perfusion deficits and potentially the development of white matter hyperintensities (WMHs) [56]. White matter is sensitive to transient ischemia because it is supplied by terminal arterioles with limited collateral flow and so is more susceptible to minor changes in flow due to impaired autoregulation and consequent infarction [77]. WMHs are believed to contribute to the pathogenesis of LLD since MRI studies have repeatedly found higher densities in the frontal lobes [48, 236, 237] and basal ganglia [48] of older people with major depression (MD) and these regions of the brain are known to regulate mood and cognition. Although the pathology of WMHs varies, autopsy studies
have shown that they are associated with ischemic damage and tissue hypoxia in patients with late-life major depression [63]. In animal models white matter ischemia results from drops in blood pressure [202] and a recent study [67] has shown a relationship between the degree of orthostatic drop in BP and WMH volume in LLD.

Hemodynamic homeostasis becomes less effective with aging and is associated with a decreased ability to regulate BP [193]. Orthostatic hypotension (OH) is an excessive fall in BP after standing which may result from inadequate intravascular volume, autonomic nervous system dysfunction, decreased venous return or an inability to increase cardiac output in response to postural changes [250]. After essential hypertension, OH is the most common disorder of BP regulation and in adults aged 65 years and older the prevalence ranges between 5 and 30%; depending on the population studied and definition used [238]. Prospective studies have shown that OH is predictive of ischemic stroke [251] and all-cause mortality in older adults [192].

In 1996, a consensus committee defined classical OH as a drop of at least 20mmHg in systolic blood pressure (SBP) or 10mmHg in diastolic blood pressure (DBP) within the first 3 minutes of standing [129]. This may reduce perfusion pressure of organs, especially above heart level, such as the brain. OH can be asymptomatic or manifest as symptoms that range from dizziness and light-headedness to weakness and loss of consciousness. These symptoms arise from periods of hypoperfusion that have the potential to induce ischemic damage and WMHs [180, 238]. For this reason, it has been suggested that OH
may play an important role in the development of depression and accumulating evidence, although limited shows that OH may be more frequent in late-life depression [173, 201]. Previous studies confirming an association between OH and depression were conducted on small clinical cohorts of patients with a formal diagnosis of MD and using hospital based digital photoplethysmographic measures of phasic BP. It is not known whether the association would persist in the general population; where lower prevalence and severity rates for these conditions are observed, and using traditional oscillometric measures of BP. Consequently, the aim of this study is to investigate if OH is associated with depression in a nationally representative sample of older adults utilising a standard test of OH and a self-report measure of depression.
5.3 Methods

Study design
We analysed data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) collected between October 2009 and February 2011. Full details of the sampling procedure and response have been described elsewhere [217]. In short TILDA is a study of community dwelling adults (nationally representative sample) aged 50 and over. Participants completed a computer-assisted personal interview (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. People with known or suspected dementias were ineligible at baseline for participation. All assessments were carried out by trained nurses. 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. The measures specific to the current analysis are described below.

Psychiatric Assessment
The primary outcome measure for this analysis was the mean score on the 20-item Centre for Epidemiologic Studies Depression scale (CES-D). The CES-D generates a total score with a range between 0 and 60 with higher scores indicating greater depressive symptoms. A cut-off of 16 has been shown to
have a sensitivity of 100% and a specificity of 88% for MD in older adults [110, 248]. LLD is commonly defined as depression occurring in adults aged 60 or 65 years and over therefore only participant’s ≥ 60 years were included in the analysis. Participants taking antidepressants were excluded from this study.

Anxiety was assessed using the Hospital Anxiety Depression Scale – Anxiety subscale. A cut-off of ≥11 was used to classify participants with anxiety [239]. The MMSE (Mini Mental State Examination) was used to assess cognition [240].

**Blood pressure measurement**

Participants underwent a sit-to-stand orthostatic stress test (STST).

*Seated blood pressure:* Two seated SBP and DBP measurements were obtained 1 minute apart using an OMRON™ digital automatic blood pressure monitor (Model M10-IT). Participants had been seated for at least 30 minutes and were a minimum of 1 hour pre or post lunch when the measurement was obtained. The means of the two sitting SBP and DBP readings were used in the analysis.

*Standing blood pressure:* Immediately after the second seated BP measurement, the participant was asked to stand and a single SBP and DBP measurement was obtained, using the same monitor with the cuff at heart level. Immediately after the standing BP measurement was complete,
participants were asked to report whether they had felt dizzy, light-headed or unsteady on standing (yes or no to any of the symptoms).

*Asymptomatic Orthostatic Hypotension:* Participants with a reduction of SBP of at least 20mmHg or DBP of 10mmHg without symptoms of dizziness/light-headedness after standing were classified as having asymptomatic OH (AOH).

*Symptomatic Orthostatic Hypotension:* Participants with a reduction of SBP of at least 20mmHg or DBP of 10mmHg accompanied by symptoms of dizziness/light-headedness after standing were classified as having symptomatic OH (SOH).

**Other Measures**

Other measures recorded during the home interview (CAPI) included age, gender, highest level of educational attainment (primary, secondary or tertiary), current smoking status, history of cardiovascular disease and medication use. Medication use was determined by recording medication names from the medicine bottles in the participant’s home during the CAPI interview. Medications were classified using the World Health Organization Anatomical Therapeutic Chemical (ATC) system [243]. A dichotomous variable for antihyperintensive medication was computed (1=yes, 0=no) with the following ATC codes: C02; diuretic drugs, C03; peripheral vasodilator drugs, C04; vasoprotective drugs, C05; β-blocking agents, C07; and calcium-channel blockers C08. Psychotropic medications were classified by ATC code N05. In addition to the beat-to-beat BP measurements SBP and DBP were recorded
during seated rest using a digital automatic BP monitor (OMRON Model M10-IT). For descriptive purposes, participants were classified as hypertensive if the mean of their two seated SBP measurements was ≥140 mmHg and/or if the mean of their two seated DBP measurements was ≥90 mmHg or if they were currently taking antihypertensive medications [244]. Objective measures of weight (1 measure using SECA electronic floor scales) and height (1 measure using SECA 240 wall mounted measuring rod) were used to calculate body mass index (BMI). Total cholesterol was determined from a venous blood sample.

**Statistical Analysis**

Only participants who completed a health assessment were eligible for inclusion. Statistical analysis was performed using SPSS version 20. Distribution of continuous variables was assessed using Q-Q plots and histograms. Normally distributed variables were described as means and standard errors (SE), and were compared using independent t-tests and categorical variables were compared using Chi-squared tests. AOH and SOH and were analysed separately a priori.

Multivariate linear regression analysis was used to assess the relationship between OH and depression with adjustment for potential confounders including age, sex, education level, MMSE, history of cardiovascular disease (angina, stroke, TIA, myocardial infarction), total cholesterol, smoking (0=non/previous smoker, 1=current smoker), BMI, SBP and DBP values, antihypertensive and psychotropic medications as covariates. Unstandardised regression coefficients, 95% confidence intervals and significance levels are
presented here. Differences with \( p<0.05 \) (two-tailed) were considered statistically significant. Sensitivity analysis was conducted to explore the impact of including participants on antidepressant medications. Data was weighted with respect to age, sex and education to the Quarterly National Household Survey (2010) and further weighted to account for those who did not attend for a health assessment (see TILDA wave 1 report for further information on the calculation of weights, [www.tilda.ie]).
5.4 Results

Characteristics of the sample
At baseline 8,175 participants were recruited to the TILDA study and the household response rate was 62%. 4,892 individuals were aged 60 and over and 3,437 of these completed a health assessment. The study population used in this analysis is depicted in Figure 5.1. In total 3,144 participants were eligible for the current analyses. Of these, 52% were female with a mean age of 70.0, (SE .01, range 60-98).

Figure 5.1 TILDA population used in OH and depression analysis (Blue)
Table 5.1 shows demographic and clinical characteristics of participants by orthostatic blood pressure group. 8% (n=240) of participants in our study had OH and 9% (n= 20) of these reported symptoms of dizziness, light-headedness or unsteadiness on standing. Symptoms were only reported by people who were classified with OH. Participants with OH were more likely to be female (p=0.01), had significantly more hypertension (p<0.001), lower BMI (p=0.01) and a lower MMSE score (p=0.04).

<table>
<thead>
<tr>
<th>Table 5.1 Demographic and clinical characteristics overall and by OH group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>N=3144</td>
</tr>
<tr>
<td>n</td>
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<td>-----</td>
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<tr>
<td><strong>Age</strong> mean (SE)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
</tr>
<tr>
<td>Education:</td>
</tr>
<tr>
<td>primary</td>
</tr>
<tr>
<td>secondary</td>
</tr>
<tr>
<td>tertiary</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td><strong>Antihypertensive meds</strong></td>
</tr>
<tr>
<td><strong>Psychotropic medication</strong></td>
</tr>
<tr>
<td><strong>History CVD</strong></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
</tr>
<tr>
<td><strong>Orthostatic symptoms</strong></td>
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<tr>
<td><strong>High cholesterol mean (SE)</strong></td>
</tr>
<tr>
<td><strong>BMI mean (SE)</strong></td>
</tr>
<tr>
<td><strong>MMSE mean (SE)</strong></td>
</tr>
</tbody>
</table>

*mean of 2 seated systolic blood pressures is ≥140mmHg and/or mean of 2 seated diastolic blood pressures is ≥90 mmHg or currently taking antihypertensive medications h history of angina, stroke or myocardial infarction j Hospital Anxiety and Depression Scale ≥ 11 (range 0-21) k symptoms of dizziness, lightheaded or unsteadiness on standing l measure obtained from venous sample m Body Mass Index n Mini Mental State Examination(range 0-30) h comparison of no OH and OH group based on t-test for continuous variables and X² for categorical variables
Figure 5.2 Mean change in systolic and diastolic BP on standing

![Graph showing mean change in systolic and diastolic BP on standing for different OH groups.]

Figure 5.3 Mean CES-D score by OH group

![Graph showing mean CES-D score by OH group.]

OH group

- AOH
- SOH

Mean change in SBP

Mean change in DBP

Mean change in CES-D score

OH group

- no OH
- AOH
- SOH
**OH and depression**

Table 5.2 shows BP measurements in participants with AOH and symptomatic SOH. Participants with SOH had greater drops in SBP and DBP compared to participants with AOH (see figure 5.2). Figure 5.3 shows mean CES-D score by OH group. Participants with SOH had the highest mean CES-D score (mean 8.6, SE 1.6) when compared to participants with AOH (mean 5.6, SE .48) and participants without OH (mean 5.2, SE .14). In multivariate linear regression analysis adjusted for socio-demographic and clinical characteristics, SOH was associated with higher levels of depressive symptoms (see Table 5.3). Mean CES-D score was over 2 points higher in participants with SOH compared to participants without OH. AOH was not associated with higher CES-D scores.

<table>
<thead>
<tr>
<th>Table 5.2 Blood pressure parameters by OH group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic OH</strong></td>
</tr>
<tr>
<td>N=220</td>
</tr>
<tr>
<td>Seated systolic BP</td>
</tr>
<tr>
<td>a</td>
</tr>
<tr>
<td>Seated diastolic BP</td>
</tr>
<tr>
<td>Standing systolic BP</td>
</tr>
<tr>
<td>Standing diastolic BP</td>
</tr>
<tr>
<td>Mean change in SBP</td>
</tr>
<tr>
<td>Mean change in DBP</td>
</tr>
</tbody>
</table>

*aaverage of 2 readings b mean of 2 seated SBP readings subtracted from 1 standing SBP reading c mean of 2 seated DBP readings subtracted from 1 standing DBP reading*
Table 5.3 Linear regression analysis of OH on CES-D score

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (^b)</th>
<th>Model 2 (^c)</th>
<th>Model 3 (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B coeff (^e)</td>
<td>95% CI</td>
<td>B coeff (^e)</td>
</tr>
<tr>
<td><strong>Asymptomatic OH(^a)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.333</td>
<td>-0.499-1.16</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptomatic OH(^a)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.83(^*)</td>
<td>0.173-5.48</td>
<td>0.03</td>
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</table>

\(^a\) comparison group is participants without OH (coefficient for AOH and SOH modelled concurrently)

\(^b\) univariate analysis

\(^c\) adjusted for age, sex, education

\(^d\) adjusted for age, sex, education, MMSE, History CVD, blood cholesterol, smoking, BMI, heart and psychotropic medications, seated systolic BP and seated diastolic BP

\(^e\) unstandardised B coefficient
5.5 Discussion

In this study, we found evidence of a relationship between orthostatic hypotension and depression in participants with OH who reported symptoms of hypoperfusion on standing. Emerging evidence suggests that hypoperfusion may be an important factor in the development of late-life vascular depression [56]. OH can lead to cerebral auto-dysregulation [252] which can impair cerebral blood flow (CBF) [117]. Perfusion deficits do not need to cause ischemia in order to influence brain function. Mild CBF reduction impairs protein synthesis [73] that is crucial for cognitive and affective processing while greater CBF reduction in the context of autoregulatory deficits may cause ischemic injury and WMHs [56]. Previous results linking OH and depression have been observed among clinical samples [67, 173, 201] where cases of OH and depression are respectively more prevalent and severe. Our findings suggest that in a representative sample of community dwelling older adults, the relationship is limited to those with more severe OH; since the association is dependent on the presence of symptoms of hypoperfusion.

9% of participants with OH reported symptoms of dizziness/light-headedness on standing. Cerebral autoregulation (CA) explains why OH does not produce symptoms in all adults. Under normal physiologic conditions, changes in mean arterial BP between 60 and 160 mmHg produce little or no change in CBF. Beyond these limits, a sudden decrease in CBF occurs at the lower limit of autoregulation and likely manifests as orthostatic symptoms [117]. In patients with OH, severe autoregulatory failure is believed to occur in approximately one in four patients and cerebral hypoperfusion occurs in
response to relatively small changes in BP [117]. Participants in our study with symptomatic OH may have impaired CA and more extreme changes in CBF resulting in orthostatic symptoms. In contrast, those with asymptomatic OH may have better preserved autoregulation centrally and therefore no symptoms of hypoperfusion from reduced CBF, despite clinically significant drops in BP during standing. While a causal relationship between WMH and cerebral hypoperfusion induced by OH has yet to be established, both animal models and human studies suggest that this exists [67, 202] and future waves of TILDA will investigate if OH at baseline predicts depression at follow up.

The prevalence of hypertension was higher in participants with OH which could have confounded results since hypertension is a known risk factor for OH [196] and WMHs [53]. However, hypertension was not associated with increased CES-D score in univariate analysis and the addition of systolic and diastolic BP levels to the model only slightly attenuated the association between SOH and depression. The use of antihypertensive medication was also somewhat higher in the OH group; however, the relationship between SOH and depression also persisted even after adjusting for these medications in the final model. In healthy community-dwelling adults such as our participants these drugs are associated with only low rates of orthostatic hypotension [67, 246] making them unlikely to have influenced our findings.

Participants currently taking antidepressants were excluded from our analysis. There is no simple way to 'adjust' for anti-depressant use in our baseline data since the model we are trying to estimate is essentially cyclical (i.e. our hypothesis is that OH causes depression, but we know depression results in
anti-depressant use and anti-depressant use can cause OH). 7% of our target population were currently taking antidepressants (see figure 5.1). Sensitivity analysis including participants on antidepressants (and controlling for antidepressants in the model) attenuated but did not eliminate the significant association between SOH and depression and overlapping confidences intervals between estimates derived from the sample with antidepressant users, and without them, suggests no significant difference between estimates (data not shown).

The STST is commonly used in everyday clinical practice, however it is believed to have inferior sensitivity for detecting OH compared to other orthostatic stress tests (Active Stand Test or the Head-Up Tilt-Table Test) [253]. Automated BP machines can take 25-40 seconds to record a measurement. We therefore expect that our findings underestimate the prevalence of OH (compared with prevalence rates estimated from phasic BP measurement) and potentially any associations uncovered; given that in some participants BP may have recovered before the recording was completed. Interestingly, orthostatic symptoms were only reported by participants with OH which would suggest that the STST has good sensitivity for detecting those with severe OH. Previous studies linking OH and depression have utilised continuous, beat-to-beat BP monitoring to measure OH in patients with MD at centre based assessments. Home respondents are known to differ markedly from the centre based attendees and in a TILDA pilot study we showed that participants who selected a home assessment had poorer physical health with higher levels depressive symptomology [254]. The STST is easily administered in an individual’s home therefore it maximised the participation of older
participants in our study and was effective for identifying the association between symptomatic OH and depression.

The main strengths of this study are the large population representative sample and comprehensive health assessment. Limitations are that the data was analysed cross-sectionally so we cannot make any direct inferences about temporality. Although many relevant risk factors were assessed and statistically controlled for in the analysis, the possibility of residual confounding exists. Depression was not formally diagnosed in our study although the CES-D instrument is a well validated measure of depressive symptomatology [110, 248]. The prevalence of MD in community samples of older adults ranges from 1-5%, with the majority of studies reporting prevalence in the lower end of the range [5, 6, 213, 255]. It is therefore likely that the CES-D overestimated the prevalence of MD and our measure of depression represents both major and subthreshold depression. Another limitation is that our primary conclusions were drawn from the SOH group which only included 20 individuals; the potential for spurious findings therefore exists. It must also be acknowledged that in some participant’s vestibular dizziness rather than hypotension could have caused the symptoms of dizziness although in our study all participants who reported symptoms had a clinically significant drop in blood pressure. Moreover, dizziness may also be a feature of anxiety which is highly co-morbid with depression in this age group [39].
Conclusion

In summary, we have identified an association between symptomatic OH and depression in a large community-based sample of older adults. Symptomatic orthostatic hypotension may be an important, but not widely recognised, risk factor for late-life depression which needs to be considered in studies examining the relationship between vascular disease and depression. Clinically, our results are important as they show that the relationship between SOH and depression is not limited to clinical samples but extends to the general population and potentially individuals with subthreshold depression. Clearly longitudinal studies are required to clarify the direction of this association.
6 Antidepressants Strongly Influence the Relationship between Depression and Heart Rate Variability: Findings from the Irish Longitudinal Study on Ageing

6.1 Abstract

CONTEXT
Heart rate variability (HRV) is known to be reduced in depression; however, is unclear whether this is a consequence of the disorder or due to antidepressant medication. Reduced HRV is believed to contribute to the increased risk of cardiac morbidity and mortality observed in patients with depression.

OBJECTIVE
To compare measures of HRV among those with and without depression in a large population sample of older adults and examine the influence of antidepressant medications in any associations observed.

DESIGN
Cross-sectional analysis from large prospective ageing study.

SETTING
The Irish Longitudinal Study on Ageing.

PARTICIPANTS
Four thousand seven hundred and fifty individuals (mean age, 61.6 years; 55% female) who participated in the first wave of The Irish Longitudinal Study on Ageing (TILDA). Depression was assessed using the Center for Epidemiologic Studies - Depression scale.

MAIN OUTCOME MEASURE
Time domain (standard deviation of normal-to-normal beats ms^2 [SDNN]) and frequency domain (High Frequency ms^2 [HF] power as an index of cardiac
vagal control and Low Frequency ms² [LF] power as an index of sympathetic and parasympathetic influence on the RR intervals) measures of HRV were derived from 3-lead surface electrocardiogram records obtained during 10 minutes of supine rest (5 minutes spontaneous breathing followed by 5 minutes paced breathing). Multivariate analyses were conducted to compare HRV measures across depression groups after adjustment for demographics, health, lifestyle, anxiety, and psychoactive medication.

RESULTS
Participants on antidepressants (with or without depression) differed significantly from controls on measures of SDNN, LF and HF power. Depressed participants not taking antidepressants did not differ from controls on all measures HRV. Linear regression models showed that selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were associated with reduced SDNN (unstandardised B coefficient = -0.053 95% CI -0.088, -0.017) and LF (B=-0.085 95% CI -0.139, -0.031). Only SNRIs were associated with reductions in the HF measure of HRV (B= -0.278 95% CI -0.417, -0.140).

CONCLUSION
Our results imply that reductions in HRV observed among depressed older adults are driven by the effects of antidepressant medications. SSRIs have less impact on HRV than other antidepressants with anticholinergic effects, but they do still reduce indices of HRV. Our findings also suggest that in older adults the use of SNRI antidepressants pose a particular risk to the cardiovascular system.
6.2 Introduction

By 2020 cardiovascular disease (CVD) and major depressive disorder (MDD) will be the leading causes of death and disability worldwide and there is increasing recognition that the two are related [256] Depression is a known risk factor for the development of CVD and an independent predictor of poor prognosis following a cardiac event [257]. Alterations in the autonomic nervous system (ANS) including a reduction in heart rate variability (HRV) may partly explain the increased risk of CVD, since low HRV is a known risk factor for myocardial infarction, arrhythmias, and cardiac mortality [152]. HRV reflects beat-to-beat changes in heart rate and is mediated by the parasympathetic nervous system which slows heart rate, and the sympathetic nervous system which accelerates it [111]. Normal patterns of HRV reflect a healthy ANS which is able to respond appropriately to environmental challenges [258] whereas impaired HRV is a marker of autonomic inflexibility and potential ill-health [126, 136]

While there is strong evidence that HRV is reduced in depression [148-150], it remains unclear whether these reductions are due to the effects of antidepressant medication or the disease per se. In their study of physically healthy individuals (mean age 36 years) with and without depression, all of whom were un-medicated, Kemp and colleagues found that HRV was reduced in individuals with MDD compared to a non-depressed control group [150]. In contrast, the Netherlands Study of Depression and Anxiety (NESDA, mean age 46 years) [152, 153] reported that while MDD was associated with lower HRV; the association was mainly driven by the effect of antidepressants
medications. In light of conflicting evidence regarding the role of antidepressants in the relationship between depression and HRV it is essential to address this issue in the current research by attempting to isolate the effects of depression and medication use on HRV.

Antidepressant treatment clearly impacts on HRV, although a precise picture has yet to emerge. There is evidence that tricyclic antidepressants (TCAs) reduce parasympathetic activity and thereby HRV [144, 154, 155] due to their anticholinergic and 1-adrenergic properties [156, 157]. In addition, other antidepressants with relatively milder anticholinergic properties such as paroxetine (a selective serotonin reuptake inhibitor [SSRI]) might decrease HRV [158]. However, there is also evidence that antidepressant treatment (particularly non-TCA) might provide HRV-mediated cardiac protective effects [159] or at least have a benign cardiovascular profile [160]. A recent meta-analysis on the impact of antidepressant treatment on HRV concluded that TCAs are associated with a large decrease in HRV but that the data for SSRIs and other antidepressants were not clear [161].

The influence of physical illness and lifestyle factors such as smoking, use of alcohol, high body mass index, and low physical activity also needs to be considered given that these factors occur more frequently in depression and are associated with decreased HRV [259, 260]. Some studies have been limited in their ability to control for these factors and this may have contributed to inconsistent findings [152]. Moreover, the need to examine the role of co-morbid anxiety in reducing HRV was highlighted by a recent study that found MDD patients with generalised anxiety disorder (GAD) showed the
greatest reductions in HRV compared to MDD patients without co-morbid anxiety and controls [150]. GAD is the most prevalent anxiety disorder among older adults [176] and a high prevalence of co-morbid depression and anxiety is observed in this age group [38].

To date, most of the research on depression and HRV has been conducted on young and middle-aged patients with depression. Although valuable, it has been suggested that research in older adults who have a greater risk of heart disease may have greater applicability [169]. Because normal ageing is associated with reduced HRV [170, 261, 262] it has been hypothesised that depression in old age may further reduce HRV, potentially posing an increased risk of cardiovascular morbidity and mortality [169]. Of the few studies that have investigated HRV specifically in depressed older adults the results are conflicting; with some studies providing evidence of reduced HRV in depression [263, 264] and others reporting no association [169, 175]. Notably, none of these studies have investigated the role of individual antidepressants classes on HRV; therefore, in older adults their effects on HRV are largely unknown. The aim of this study is to examine whether depression is associated with reduced HRV in older adults and if so, to examine the extent to which any associations observed are confounded by lifestyle, co-morbid anxiety or the effect of antidepressant medication.
6.3 Methods

Study design & participants

We analysed data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) collected between October 2009 and February 2011. Full details of the sampling procedure and response rate have been described elsewhere [217]. In brief, TILDA is a study of people aged 50 and over (and their spouses or partners of any age) resident in Ireland. A nationally representative sample was selected from the Irish Geodirectory, a comprehensive and up-to-date listing and mapping of all residential addresses in the Republic of Ireland compiled by the Irish Postal Service and Ordnance Survey Ireland. People with known or suspected dementia were ineligible at baseline for participation in TILDA.

Participants completed a computer-assisted personal interview (CAPI) in their own homes administered by trained professional interviewers. The TILDA questionnaire includes detailed questions on many aspects of health, lifestyle, social interactions and financial circumstances. Each participant was then invited to travel to one of two health centres 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. All health assessments were carried out by trained nurses. The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, and participants were required to provide written informed consent prior to participation in the study. The measures specific to the current analysis are described in detail below.
Psychiatric Assessment

Depression was assessed using the Center for Epidemiologic Studies – Depression scale (CES-D). The CES-D generates a total score with a range between 0 and 60 with higher scores indicating greater depressive symptoms. A cut-off score of 16 has been shown to have a sensitivity of 100% and specificity of 88% for major depressive disorder in an elderly population [110].

Anxiety was assessed using the Hospital Anxiety Depression Scale – Anxiety subscale (HADS-A). Scores from this 7 item scale range from 0-21 with higher scores indicating greater anxiety symptoms. A cut-off score of ≥11 has been used to classify participants with clinically significant anxiety [239].

Measurement of Heart Rate Variability

Heart rate variability was only assessed during the health centre assessment. A continuous 10 minute supine resting surface 3-lead electrocardiogram (ECG) was digitally recorded using the Medilog AR12 system (Schiller, Baar, Switzerland). Each recording was conducted in a comfortably lit, quiet room at ambient temperature (21-23°C). Subjects were instructed to breathe spontaneously for the first 5 minute period, and to control their breathing (paced) during the second 5 minute period according to a pre-recorded set of auditory instructions (set at a rate of 12 breaths/minute). Paced breathing experimentally controlled for the effect of respiratory rate on spectral HRV indices [265]. The acquired ECG was sampled at 4kHz, band-pass filtered and a proprietary algorithm was used to detect the R peak of each heart beat recorded on the ECG signal [266]. Supra-ventricular ectopic beats and noise
were excluded from the signal using linear interpolation. All recordings were screened for atrial fibrillation (AF) using criteria from the European Society of Cardiology (ESC) [267], and those identified with AF were subsequently excluded from analysis. Mean resting heart rate over 5 minutes of spontaneous breathing was calculated and controlled for in study analysis.

Time domain measures derived from each 5 minute epoch included the standard deviation of NN intervals (SDNN ms²). Frequency domain (FD) features were calculated from spectral estimates derived using an autoregressive (Burg transform) parametric algorithm. FD features were derived by integrating the power spectral density across two frequency bands: low frequency power (LF, 0.04-0.15Hz, ms²) and high frequency power (HF, 0.15-0.4Hz, ms²). High frequency measures are thought to reflect parasym pathetic activity while LF measures are thought to reflect both sympathetic and parasym pathetic activity.

**Measurement of Covariates**

Sociodemographic characteristics included age, sex, and highest level of educational attainment (primary [<8 years], secondary [8-12 years], tertiary [≥12]). In addition, the following health indicators were considered as covariates as these have been linked with both depression status and HRV. Objective measures of weight (1 measure using SECA electronic floor scales) and height (1 measure using SECA 240 wall mounted measuring rod) were used to calculate body mass index (BMI). Physical activity was assessed using the international physical activity questionnaire (IPAQ-short form, [268]).
Participants were classified into three groups representing low, medium and high levels of exercise in accordance with the IPAQ scoring protocol [268]. Participants self-reported how many standard alcoholic drinks they consumed in a week as well as whether they were a non-smoker, former smoker or current smoker. Self-reports were used to ascertain the presence of a doctors diagnosis of heart disease and other chronic conditions. Blood pressure (BP) was recorded using an automated oscillometric BP monitor (OMRON Model M10-IT). Participants were classified as hypertensive if the mean of their two seated systolic blood pressure (SBP) measurements was ≥140 mmHg and/or if the mean of their two seated diastolic blood pressure (DBP) measurements was ≥90 mmHg [244].

Medication use was determined by recording medication names from the medicine bottles in the participant’s home during the CAPI interview. Medications were classified using the World Health Organization Anatomical Therapeutic Chemical (ATC) system [243]. A dichotomous variable for cardioactive medication was computed (1=yes, 0=no) with the following ATC codes: antihypertensive drugs, C02; diuretic drugs, C03; peripheral vasodilator drugs, C04; vasoprotective drugs, C05; β-blocking agents, C07; and calcium-channel blockers C08. Dichotomous variables (1=yes, 0=no) for various classes of antidepressant medications were computed with the following ATC codes: selective serotonin reuptake inhibitors (SSRIs), N06AB; tricyclic antidepressants (TCAs), N06AA; Monoamine oxidase inhibitors (MAOIs), N06AF, Serotonin-norepinephrine reuptake inhibitors (SNRIs), N06AX (16, 17, 23, 21); Serotonin antagonist + reuptake inhibitors N06AX (05, 06). We also distinguished benzodiazepine drugs (ATC codes N03AE, N05BA, N05CD, and N05CF) and other non-depression-related psychoactive
medication such as anesthetic drugs, ATC code N01; analgesic drugs, ATC code N02; antiepileptic drugs, ATC code N03; anti-Parkinson disease drugs, ATC code N04; psycholeptic drugs, ATC code N05; psychostimulants, ATC code N06B; antidementia drugs, ATC code N06D; and other nervous system drugs, ATC code N07.

**Statistical Analysis**

Statistical analysis was performed using SPSS Version 20 (IBM Corp, Armonk, NY). Distribution of continuous variables was assessed using Q-Q plots and histograms. Non-normally distributed measures of HRV (SDNN, LF, and HF) were log transformed for graphs and analysis (values were back-transformed post analysis). Normally distributed variables were described as means and standard errors (SE), and were compared using independent t-tests and categorical variables were compared using Chi-squared tests.

Characteristics across the 4 depression groups were compared using analysis of variance. Linear regression was used to calculate mean values of HR, SDNN, LF and HF adjusted for age, sex, education, body mass index, smoking, alcohol use, physical activity, heart disease, cardioactive medications, number of chronic diseases and heart rate for each depression group.

In an attempt to understand the individual effects of various types of psychoactive medication on HRV, we distinguished between participants on various types of psychoactive medication (exclusively) and compared their adjusted mean HR and HRV values with un-medicated controls. Subsequently, the effect of anxiety and psychoactive medication on the relationship between depression and HRV was examined by entering information on these variables.
into a number of regression models with adjustment for potential confounders including age, sex, education level, physical activity, alcohol use, number of chronic conditions (diabetes, arthritis, cancer, chronic lung disease, liver disease, stomach ulcers and substance abuse), history of cardiovascular disease (angina, stroke, myocardial infarction), smoking (0=non/previous smoker, 1=current smoker), BMI, HR, and antihypertensive drugs as covariates. Unstandardised regression coefficients with 95% confidence intervals and significance levels are presented here. Differences with \( p < 0.05 \) (two-tailed) were considered statistically significant.
6.4 Results

At baseline 8,175 participants were recruited to the study. The household response rate was 62%. 5,034 (61%) participants who completed a health centre assessment were eligible for inclusion. Of these 96% successfully completed the CES-D and measurements of HRV giving the 4,750 included in the current analysis. The mean age of the study sample was 61.6 years (SD, 8.3 years) and 55% of participants were female.

To test whether measures of HRV differed across persons with and without depression and according to antidepressant use, 4 distinct depression groups were created for the present study: 4,107 controls without depression (score <16 on CES-D scale) or antidepressant use; 185 individuals without depression (score <16 on CES-D scale) but currently on antidepressants (remitted group); 317 individuals with depression but not currently on antidepressants; and 80 individuals with depression and currently on antidepressants. Table 6.1 presents demographic characteristics, disease status, lifestyle behaviours, and medication use according to depression groups. Relative to controls, participants with depression (current or remitted) were more likely to be female, had less education, were less physically active, were more likely to smoke and had more heart and other chronic diseases. Additionally, they had much higher levels of anxiety and medication use other than antidepressants (benzodiazepines, heart and blood pressure medications and other psychotropic medications).
### Table 6.1. Sample characteristics by depression group

<table>
<thead>
<tr>
<th></th>
<th>Non-depressed controls</th>
<th>Remitted Depression</th>
<th>Current Depression (no ads)</th>
<th>Current Depression (on ads)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 4107</td>
<td>N=185</td>
<td>N=317</td>
<td>N=80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age mean (SE)</td>
<td>61.7 (.13)</td>
<td>62.6 (.62)</td>
<td>60.4 (.43)</td>
<td>59.4 (.75)</td>
<td>.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>2179 (53.1)</td>
<td>124 (67.0)</td>
<td>212 (66.9)</td>
<td>58 (72.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary</td>
<td>828 (20.2)</td>
<td>46 (24.9)</td>
<td>91 (28.7)</td>
<td>27 (33.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Secondary</td>
<td>1743 (42.5)</td>
<td>80 (43.2)</td>
<td>117 (36.9)</td>
<td>33 (41.3)</td>
<td>.279</td>
</tr>
<tr>
<td>tertiary</td>
<td>1534 (37.4)</td>
<td>59 (31.9)</td>
<td>109 (34.4)</td>
<td>20 (25.0)</td>
<td>.045</td>
</tr>
<tr>
<td>BMI^mean (SE)</td>
<td>28.5 (.08)</td>
<td>28.8 (.41)</td>
<td>28.6 (.29)</td>
<td>29.3 (73)</td>
<td>.415</td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1045 (25.6)</td>
<td>68 (37.0)</td>
<td>123 (39.0)</td>
<td>34 (42.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>medium</td>
<td>1501 (36.8)</td>
<td>63 (34.2)</td>
<td>106 (33.7)</td>
<td>26 (32.5)</td>
<td>.522</td>
</tr>
<tr>
<td>High</td>
<td>1529 (37.5)</td>
<td>53 (28.8)</td>
<td>86 (27.3)</td>
<td>20 (25.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>1948 (47.4)</td>
<td>72 (38.9)</td>
<td>119 (37.5)</td>
<td>24 (30.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>former</td>
<td>1600 (39.0)</td>
<td>75 (40.5)</td>
<td>110 (34.7)</td>
<td>35 (43.8)</td>
<td>.341</td>
</tr>
<tr>
<td>current</td>
<td>559 (13.6)</td>
<td>38 (20.5)</td>
<td>88 (27.8)</td>
<td>21 (26.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5.98 (.15)</td>
<td>6.10 (.78)</td>
<td>5.25 (.55)</td>
<td>6.95 (2.2)</td>
<td>.493</td>
</tr>
<tr>
<td>Heart disease</td>
<td>443 (10.8)</td>
<td>30 (16.2)</td>
<td>45 (14.2)</td>
<td>16 (20.0)</td>
<td>.003</td>
</tr>
<tr>
<td>No Chronic conditions</td>
<td>.45 (.01)</td>
<td>.84 (.06)</td>
<td>.68 (.04)</td>
<td>.98 (.10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5 (.07)</td>
<td>6 (.38)</td>
<td>9 (.34)</td>
<td>11 (.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severity of depression</td>
<td>4 (.08)</td>
<td>6 (.43)</td>
<td>22 (.52)</td>
<td>25 (1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor (SSRI)</td>
<td>102 (55.1)</td>
<td>49 (61.2)</td>
<td>49 (61.2)</td>
<td>.463</td>
<td></td>
</tr>
<tr>
<td>Serotonin–norepinephrine reuptake inhibitors (SNRI)</td>
<td>36 (19.5)</td>
<td>17 (21.2)</td>
<td>17 (21.2)</td>
<td>.919</td>
<td></td>
</tr>
<tr>
<td>Serotonin antagonist + reuptake inhibitors</td>
<td>1 (0.5)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>.540</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants (TCA’s)</td>
<td>50 (27.0)</td>
<td>21 (26.3)</td>
<td>21 (26.3)</td>
<td>.896</td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors (MAOI)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td>.510</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>115 (2.8)</td>
<td>43 (23.2)</td>
<td>44 (13.9)</td>
<td>26 (32.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other psychotropic meds</td>
<td>244 (5.9)</td>
<td>42 (22.7)</td>
<td>59 (18.6)</td>
<td>20 (25.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart or blood pressure meds</td>
<td>1303 (31.7)</td>
<td>77 (41.6)</td>
<td>97 (30.6)</td>
<td>34 (42.5)</td>
<td>.007</td>
</tr>
</tbody>
</table>

*No depression = score <16 on CES-D scale, † Remitted = score <16 on CES-D scale & current antidepressant use, ‡ Current depression = score ≥16 on CES-D scale and not taking antidepressants, § Current depression = score ≥16 on CES-D scale and taking antidepressants, ° weight in kilograms divided by height in meters squared, † Physical Activity reported according the IPAQ (short form) scoring protocol, ‡ standard number of drinks a week (Standard drinks a day by weekly frequency), †† angina or myocardial infarction or heart failure or abnormal heart rhythm, †‡ number of chronic conditions (diabetes/stroke/arthritis/cancer/stomach ulcers/substance abuse or liver disease, †§ cutoff score ≥ 11 on Hospital Anxiety and Depression Scale – anxiety
Figure 6.1 (a-d) Mean heart rate and log measures of HRV during spontaneous and paced breathing conditions and across depression groups

Figure 6.1a

Mean heart rate during spontaneous and paced breathing across depression groups.

Figure 6.1b

Mean Log SDNN during spontaneous and paced breathing across depression groups.
Mean log LF during spontaneous and paced breathing across depression groups

Figure 6.1c

Mean log HF during spontaneous and paced breathing across depression groups

Figure 6.1d

Error Bars: 95% CI

Depression group
- no depression
- remitted
- current depression (no ads)
- current depression (ads)
Figure 6.1 shows mean values of HR, SDNN, LF and HF during spontaneous and paced breathing conditions for the 4 depression groups. As illustrated, HR is increased in participants taking antidepressants (with or without depression) compared to controls or participants with depression who were not taking antidepressants. A similar pattern emerges for measures of SDNN, LF and HF whereby depressed participants not taking antidepressants have similar measures of HRV to controls; and participants taking antidepressants (with or without depression) have significantly lower measures of HRV than controls. For conciseness, only measures of HRV obtained from the paced breathing condition (5 minutes) are presented in the subsequent analysis, since the pattern of findings was similar in both breathing conditions.

Table 6.2 presents unadjusted and adjusted means for HR, SDNN, LF and HF for the 4 depression groups. Participants on antidepressants (with or without depression) differed significantly from controls on adjusted measures of SDNN, LF and HF. Depressed participants who were not currently taking antidepressants did not differ significantly from controls on adjusted measures of HR, SDNN, or HF. Participants on antidepressants who were not classified as depressed by the CES-D (i.e. the ‘remitted’ group) had the lowest measures of HRV in our study.

Six mutually exclusive medications groups were created to examine the individual effects of various types of psychoactive medication on measures of HRV: 3,778 controls who were not depressed and not taking any psychoactive medication; 229 individuals with depression who were not taking any psychoactive medication; 91 individuals who were only taking SSRIs
Table 6.2 Mean HR, SDNN, LF and HF by depression group during the paced breathing condition

<table>
<thead>
<tr>
<th></th>
<th>Non-depressed controls</th>
<th>Remitted Depression no antidepressants</th>
<th>Current Depression on antidepressants</th>
<th>Controls Vs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Controls Vs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p-value^</td>
</tr>
<tr>
<td>HR beats/pm</td>
<td></td>
<td></td>
<td></td>
<td>p-value^</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>66.2 (.17)</td>
<td>69.4 (.98)</td>
<td>66.7 (.61)</td>
<td>.001**</td>
</tr>
<tr>
<td>Adjusted ^b</td>
<td>66.3 (.03)</td>
<td>66.7 (.16)</td>
<td>67.1 (.13)</td>
<td>.035*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.004**</td>
</tr>
<tr>
<td>Adjusted ^b</td>
<td></td>
<td></td>
<td></td>
<td>.004**</td>
</tr>
<tr>
<td>SDNN (SE) ms^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>40.7 (1.0)</td>
<td>32.3 (1.0)</td>
<td>38.9 (1.0)</td>
<td>.000*</td>
</tr>
<tr>
<td>Adjusted ^b</td>
<td>40.7 (1.0)</td>
<td>38.0 (1.0)</td>
<td>40.7 (1.0)</td>
<td>.001**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.563</td>
</tr>
<tr>
<td>Adjusted ^b</td>
<td></td>
<td></td>
<td></td>
<td>.050*</td>
</tr>
<tr>
<td>LF (SE) ms^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>151.3 (1.0)</td>
<td>83.1 (1.1)</td>
<td>128.8 (1.1)</td>
<td>.000**</td>
</tr>
<tr>
<td>Adjusted ^b</td>
<td>151.3 (1.0)</td>
<td>123.0 (1.0)</td>
<td>147.9 (1.0)</td>
<td>.000**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.315</td>
</tr>
<tr>
<td>Adjusted ^b</td>
<td></td>
<td></td>
<td></td>
<td>.018*</td>
</tr>
<tr>
<td>HF (SE) ms^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>158.4 (1.0)</td>
<td>97.7 (1.1)</td>
<td>147.9 (1.1)</td>
<td>.000**</td>
</tr>
<tr>
<td>Adjusted ^b</td>
<td>158.4 (1.0)</td>
<td>134.8 (1.1)</td>
<td>154.8 (1.0)</td>
<td>.009**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.602</td>
</tr>
</tbody>
</table>

^ adjusted for age, sex, education, BMI, physical activity, smoking, alcohol use, heart disease, chronic disease, heart medication, anxiety, HR.

^b Based on t-test
antidepressants; 34 individuals who were only taking TCAs antidepressants; 31 individuals who were only taking SNRIs antidepressants; 119 individuals who were only taking benzodiazepines and 263 participants who were taking medications collapsed into the group labelled 'other psychotropic medications'.

**Figure 6.2 (a-b)** shows values of HR, SDNN, LF and HF for each of these groups. Relative to controls, mean heart rates are significantly higher ($p<.001$) in participants on SNRIs and TCAs; whereas mean heart rates in participants on SSRIs are similar to controls. Once more a similar pattern emerged for the effect of antidepressant medication on indices of HRV; whereby a graded decrease in HRV, dependant on antidepressant type was observed among participants. Almost all measures of HRV were significantly lower in participants on antidepressants. Participants on SNRIs had the lowest measures of HRV observed in our study. Among participants on antidepressant medication, SSRIs were associated with the highest measures of HRV. Participants on benzodiazepines did not differ significantly from controls on measures of HRV; however, participants using 'other psychoactive medication' had significantly lower measures of HRV relative to controls.

**Table 6.3** presents linear regression models examining the relationship between depression and HRV and the role of anxiety and psychoactive medication. In univariate analysis (Model A) anxiety, TCAs and SNRIs are associated with increased HR and associations persist for TCAs and SNRIs in the fully adjusted model (Model D). Depression (score $\geq 16$ on CES-D scale) and all medication classes are associated with lower HRV in univariate analysis; however, in the fully adjusted model only SNRIs, SSRIs and other
Psychotropic medications are associated with significantly lower SDNN and LF and only SNRIs and other psychotropic medications are associated with lower HF (Model D). TCAs are associated with lower SDNN and HF when the analysis does not control for baseline HR (Model C). However, once baseline HR is considered, TCAs are not associated with significantly lower measures of SDNN or HF.

**Figure 6.2a Mean heart rate by depression and medication group**

![Mean heart rate by depression and medication group](image)
Figure 6.2b Mean Log SDNN/LF/HF by depression and medication group
Table 6.3 Linear regression models of depression, anxiety and medications on HR and measures of HRV

<table>
<thead>
<tr>
<th></th>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
<th>Model D</th>
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<tbody>
<tr>
<td></td>
<td>unstandardised B coeff 95% CI</td>
<td>unstandardised B coeff 95% CI</td>
<td>unstandardised B coeff 95% CI</td>
<td>unstandardised B coeff 95% CI</td>
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<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>.886 (-.246, 2.01)</td>
<td>.034 (-1.26, 1.33)</td>
<td>.310 (-1.66, 1.04)</td>
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<tr>
<td>Anxiety</td>
<td>1.33* (.175, 2.50)</td>
<td>.736 (-.495, 2.02)</td>
<td>.666 (-.627, 1.96)</td>
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<tr>
<td>SSRI</td>
<td>-.373 (-2.17, 1.43)</td>
<td>-.405 (-2.42, 1.61)</td>
<td>-.717 (-2.82, 1.39)</td>
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</tr>
<tr>
<td>TCA's</td>
<td>5.04** (2.39, 7.70)</td>
<td>3.78** (.918, 6.64)</td>
<td>3.54** (.546, 6.53)</td>
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<tr>
<td>SNRI</td>
<td>10.07** (7.10, 13.0)</td>
<td>11.1** (8.01, 14.2)</td>
<td>11.5** (8.35, 14.7)</td>
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</tr>
<tr>
<td>Benzodiazepines</td>
<td>1.29 (-1.70, 2.75)</td>
<td>.419 (-1.25, 2.09)</td>
<td>.525 (-1.20, 2.26)</td>
<td></td>
</tr>
<tr>
<td>Other psychotics</td>
<td>1.04 (-1.37, 2.22)</td>
<td>.574 (-.710, 1.85)</td>
<td>.368 (-.991, 1.72)</td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-1.06** (-1.12, -1.01)</td>
<td>-1.04 (-1.11, 1.01)</td>
<td>-1.03 (-1.09, 1.02)</td>
<td>-1.03 (-1.09, 1.01)</td>
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<tr>
<td>Anxiety</td>
<td>1.00 (-1.04, 1.06)</td>
<td>1.04 (-1.00, 1.10)</td>
<td>1.01 (-1.03, 1.07)</td>
<td>1.03 (-1.01, 1.08)</td>
</tr>
<tr>
<td>SSRI</td>
<td>-1.16** (-1.26, -1.07)</td>
<td>-1.12** (-1.23, -1.03)</td>
<td>-1.09* (-1.20, -1.00)</td>
<td>-1.12* (-1.22, -1.03)</td>
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<tr>
<td>TCA's</td>
<td>-1.26** (-1.42, -1.12)</td>
<td>-1.17** (-1.33, -1.03)</td>
<td>-1.51** (-1.35, -1.03)</td>
<td>-1.09 (-1.23, 1.02)</td>
</tr>
<tr>
<td>SNRI</td>
<td>-1.42** (-1.62, -1.24)</td>
<td>-1.44** (-1.66, -1.25)</td>
<td>-1.80** (-1.73, -1.58)</td>
<td>-1.21** (-1.37, -1.07)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
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<td>-1.00 (-1.08, 1.06)</td>
<td>-1.01 (-1.05, 1.09)</td>
<td>1.03 (-1.03, 1.10)</td>
</tr>
<tr>
<td>Other psychotics</td>
<td>-1.15** (-1.21, -1.09)</td>
<td>-1.11** (-1.18, -1.05)</td>
<td>-1.09** (-1.16, -1.03)</td>
<td>-1.07** (-1.13, -1.02)</td>
</tr>
</tbody>
</table>

a univariate analysis of depression, anxiety and medications on HR and log measures of HRV
b B values adjusted for depression, anxiety and antidepressants
c model B additionally adjusted for age, sex, education, BMI, physical activity, smoking, alcohol use, heart disease, number of chronic conditions, heart medications
d model C additionally adjusted for HR
<table>
<thead>
<tr>
<th></th>
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<th>Model C</th>
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<td></td>
<td>unstandardised B coeff</td>
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<td>unstandardised B coeff</td>
<td>unstandardised B coeff</td>
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<td></td>
<td>95% CI</td>
<td>95% CI</td>
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<td>95% CI</td>
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<tr>
<td><strong>LF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-1.19** (-1.34, -1.05)</td>
<td>-1.14* (-1.30, -1.00)</td>
<td>-1.11 (-1.28, 1.02)</td>
<td>-1.12 (-1.28, 1.00)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.03 (-1.08, 1.17)</td>
<td>1.19 (1.05, 1.36)</td>
<td>1.09 (-1.04, 1.24)</td>
<td>1.12 (-1.00, 1.26)</td>
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<tr>
<td>SSRI</td>
<td>-1.50** (-1.81, -1.24)</td>
<td>-1.35** (-1.67, -1.10)</td>
<td>-1.22 (-1.51, 1.00)</td>
<td>-1.29* (-1.57, -1.05)</td>
</tr>
<tr>
<td>TCA's</td>
<td>-1.71** (-2.25, -1.29)</td>
<td>-1.38* (-1.87, -1.03)</td>
<td>-1.30 (-1.76, 1.03)</td>
<td>-1.14 (1.51, 1.16)</td>
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<td>-2.50** (-3.41, -1.83)</td>
<td>-2.67** (-3.71, -1.93)</td>
<td>-2.86** (-3.95, -2.07)</td>
<td>-1.95** (-2.65, -1.44)</td>
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<td>-1.33** (-1.55, -1.14)</td>
<td>-1.03 (-1.56, -1.19)</td>
<td>1.08 (-1.09, 1.29)</td>
<td>1.11 (-1.05, 1.31)</td>
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<tr>
<td>Other psychotics</td>
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<td>-1.36** (-1.36, -1.19)</td>
<td>-1.29** (-1.48, -1.12)</td>
<td>-1.26** (-1.44, -1.11)</td>
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<tr>
<td><strong>HF</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-1.12 (-1.28, 1.00)</td>
<td>-1.04 (-1.20, 1.11)</td>
<td>-1.05 (-1.23, 1.09)</td>
<td>-1.07 (-1.22, 1.06)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.05 (-1.20, 1.08)</td>
<td>1.04 (-1.10, 1.20)</td>
<td>-1.12 (-1.30, 1.02)</td>
<td>-1.08 (-1.23, 1.04)</td>
</tr>
<tr>
<td>SSRI</td>
<td>-1.29* (-1.59, -1.05)</td>
<td>-1.19 (-1.50, 1.05)</td>
<td>-1.13 (-1.43, 1.11)</td>
<td>-1.21 (-1.50, 1.00)</td>
</tr>
<tr>
<td>TCA's</td>
<td>-1.67** (-2.26, -1.23)</td>
<td>-1.36** (-1.89, 1.02)</td>
<td>-1.42* (-1.99, 1.01)</td>
<td>-1.18 (-1.58, 1.14)</td>
</tr>
<tr>
<td>SNRI</td>
<td>-2.79** (-3.92, -1.99)</td>
<td>-3.01** (-4.31, -2.20)</td>
<td>-3.22** (-4.60, -2.25)</td>
<td>-1.89** (-2.61, -1.38)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>-1.19* (-1.41, -1.01)</td>
<td>1.03 (-1.17, 1.25)</td>
<td>1.10 (-1.09, 1.34)</td>
<td>1.15 (-1.02, 1.37)</td>
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<td>Other psychotics</td>
<td>-1.45** (-1.66, -1.27)</td>
<td>-1.37** (-1.59, -1.18)</td>
<td>-1.37** (-1.59, -1.18)</td>
<td>-1.33** (-1.52, -1.16)</td>
</tr>
</tbody>
</table>

- **univariate analysis of depression, anxiety and medications on HR and log measures of HRV**
- **Values adjusted for depression, anxiety and antidepressants**
- **Model B additionally adjusted for age, sex, education, BMI, physical activity, smoking, alcohol use, heart disease, number of chronic conditions, heart medications**
- **Model C additionally adjusted for HR**
6.5 Discussion

HRV in depression is now an important issue since both depression and decreased HRV have been shown, to be predictors of cardiac morbidity and mortality [269]. As a result, there has been substantial interest in the relationship between HRV and depression and the role, if any, of antidepressant medications. Our study has shown that depression is not associated with lower HRV in older adults; however, our results indicate that the use of antidepressants had a significant impact on HR and HRV. Emerging longitudinal evidence from the NESDA study [153] provides support for our findings; by demonstrating in a cohort of middle aged adults, a causal lowering effect of all antidepressants on cardiac vagal control. In older adults there exists a paucity of studies examining the effects of antidepressants on HRV, despite the high prevalence of CVD and greater applicability in this age group. In addition, most existing studies have used small, clinical samples limiting extrapolation to the general population. To our knowledge, this is the first study to examine the effects of individual antidepressant classes on HRV using a large representative population sample of older adults.

Co-morbid anxiety or lifestyle factors did not explain our results. Relative to controls, participants taking antidepressants (with or without depression) had significantly lower measures of HRV whereas no significant differences were observed between controls and depressed individuals not taking antidepressants. This suggests that antidepressants and not depression are responsible for the lower measures of HRV observed in our participants. If depression was responsible, we would have expected the remitted group to
have superior measures of HRV compared to participants who were currently depressed but not taking antidepressants, particularly given some evidence that suggests antidepressants may reverse reductions in HRV associated with depression [270, 271]. This is not what we observed, in fact, the remitted group had the lowest measures of HRV (relative to control subjects) observed in our study. Of course it must be acknowledged that some participants in our remitted group may have been taking antidepressants for conditions other than depression and this could have influenced our findings (anxiety, sleep problems, pain). Nevertheless, our data does imply that antidepressants are associated with lower HRV in older adults and may partially explain why expected reductions in cardiovascular morbidity and mortality are not observed in depressed patients who successfully respond to antidepressant treatment.

In our study, we compared measures of HRV between controls and participants who were only taking one class of psychoactive medication. This allowed us to examine the effect of individual medication classes on HRV. Overall, we found that participants on antidepressants (SSRI, TCA's, SNRI's) had significantly lower measures of HRV relative to controls; and those exclusively on SNRI's had the lowest measures of HRV recorded in our study. In general, previous research has shown that TCAs are associated with a large decrease in HRV but the data for SSRIs and other antidepressants is not clear [57, 149]. Some researchers [70, 149] have argued that the literature has not shown a reduction in HRV associated with SSRIs, and they suggest that SSRIs may in fact increase vagal modulation of heart rate. While our findings
suggest that participants on SSRI’s have better indices of HRV compared to other antidepressants (TCA’s and SNRI’s), their measures were still significantly lower that controls on SDNN (p=.051) and LF (p=.007). The difference was non-significant (p=0.251) for the HF (parasympathetic) measure of HRV. In SSRI users, low HRV was not accompanied by increased HR, providing support for the proposition [153] that SSRI’s may have a beneficial effects on sympathetic activity that could counter their negative effects on parasympathetic activity and protect against CVD [153].

Our results imply that HRV is not reduced in depression. In univariate analysis depression was associated with significantly lower HRV; however, the association lost significance once antidepressant medications were considered in the model. As a result, the hypothesis that reductions in HRV observed in depression are driven by the effects of antidepressants [152, 153] is supported by our findings. Specifically, in the fully adjusted multivariate analysis SSRI’s and SNRI’s were associated with lower measures of SDNN and LF and only SNRI’s were associated with lower HF (parasympathetic). Importantly, after controlling for baseline HR; TCA’s were no longer associated with lower HRV. For this reason, we conclude that in older adults SSRI’s and SNRI’s have a direct effect on HRV independent of HR, whereas the effect of TCA’s is mediated by their impact on HR. This is important to our understanding of the precise mechanism by which antidepressants may impair HRV. It is not clear from available literature whether previous studies have controlled for baseline HR.
The mechanisms through which antidepressants exert their effects on sympathetic/parasympathetic control over the heart remain incompletely understood. Increases in HR and decreases in HRV are believed to be due, at least in part, to the degree of anticholinergic (i.e., antimuscarinic) activity associated with different antidepressant medications leading to diminished cardiac vagal tone [270]. At the brainstem level, serotonin reuptake inhibition may influence various relay nuclei of the parasympathetic nervous system [272, 273]. The antivagal effects of TCAs and SNRIs are believed to occur largely in the heart itself. Both types of antidepressants inhibit the reuptake of norepinephrine, causing a major increase in norepinephrine in the synaptic cleft [274]. The effects of this on the sinoatrial adrenoceptors may not only increase HR directly [274] but also decrease acetylcholinergic effects on the pacemaker cells by the principles of accentuated antagonism [275, 276].

Although our findings suggest that depression is not associated with impaired HRV we must acknowledge that our measure of depression was not a formal diagnosis of MDD and this may have influenced our findings. Antidepressant use may be a marker of disease severity; therefore depression and not the antidepressants could have caused the reductions in HRV observed in our study. However, depression is known to be under-diagnosed and under-treated in older adults and estimates suggest that less than 20% of cases are detected or treated in the community [13]. We therefore would expect the group representing participants who were classified as depressed by the CES-D but who were not taking antidepressants to have included individuals with undiagnosed depression (especially given the fact that mean CES-D score is
similarly high in both depression groups). If the disorder and not the antidepressants were responsible for impaired HRV we might have expected to observe lower HRV in this group, relative to control subjects. However, this was not the case; depressed participants not taking antidepressants had measures of HRV that were in general, similar to controls. A further consideration is that our analysis assumes that depressed individuals not taking antidepressants are similar to depressed individuals who take antidepressants and this may not be correct. Prior to treatment, depression severity could have been greater in those taking antidepressants, making it difficult to speculate as to whether the observed effects are due to some intrinsic effects of this severe depression, a vulnerability, or an antidepressant effect. Defining depression using cut-off scores may also have impacted our findings since both HR and HRV have been shown to be related to the severity of depression in previous studies [149]. We therefore repeated the analysis using the CES-D as a continuous measure which resulted in a similar pattern of findings.

The main strengths of this study are the large population representative sample and comprehensive health assessment. Short-term recording of HRV (5 minute) are believed to hold an advantage over long recording times (24 hour) since the shorter duration makes it possible to create physiologically fixed or stationary states [277]. Additionally, our paced breathing condition controlled for respiration rate, indicating that the relationships we observed are independent of variations in respiratory sinus arrhythmia driven by respiration. Limitations include that the data was analysed cross-sectionally
and thus causal inferences cannot be made. Although many relevant risk factors were assessed and statistically controlled for in the analysis, the possibility of residual confounding cannot be ruled out. Participants were not requested to refrain from eating, smoking, alcohol, caffeine, exercise, or medications prior to assessment, and time of day for assessment was not restricted, based on practicality of delivering health assessments to participants from all over the country [278]. These factors may affect reproducibility of results [123], however time of day and food ingestion did not influence orthostatic blood pressure behaviour (another marker of autonomic function) in a previous TILDA pilot study [242].

In summary, this study provides an important clarification of the impact of depression and antidepressant medication on HRV. Our findings indicate that while SSRI’s have less impact on HRV than other antidepressants with anticholinergic effects; they are still associated with lower measures of HRV. In older adults the use of SNRI’s poses a particular risk to the cardiovascular system since they are associated with the lowest measures of HRV observed in our study. Given that antidepressants such as SSRIs are now prescribed not only for depression, but also for a wide range of conditions; this issue has relevance to the general population. Longitudinal data is required to determine whether observed effects of antidepressants on HRV translate into CVD morbidity and mortality in depressed older adults.
7 General discussion

The overarching purpose of this thesis was to investigate the role of autonomic function/dysfunction in the relationship between depression and CVD. Specific objectives were: to estimate the prevalence of depression in older adults; to examine associations between OH and depression and to examine associations between depression and HRV. In the present chapter, the main findings of this thesis will be summarised and discussed within the framework of outcomes of previous studies. Next, methodological issues, relevant for this thesis, will be addressed and possible clinical implications of our findings will be given. Finally, some topics for future research are identified.

7.1 Main Findings

Prevalence of Depression

Paper 1 presented the prevalence of depression in a nationally representative sample of older Irish adults. The estimated weighted prevalence was 10% for adults aged 50 years and over. The prevalence was highest in adults aged 50–64 years (11%; 95% CI: 10–12%) and lowest in those aged 75 years and older (9%; 95% CI: 7-11%). Overall, women reported more depression than men (12.5%; 95% CI: 11–14% vs. 7.2%, 95% CI: 6–8% p<.0001). This prevalence is within the range reported by other studies [5, 6, 19, 255] and is very similar to the 12% reported by the EURODEP study [9] for a sample of older adults resident in Dublin. Our findings are based on the CES-D scale; a self-report instrument that has good sensitivity and specificity for the detection
of MDD in older adults [110, 248]. Most recently, a study by Head et al (2013) using participants from the Whitehall II Study, concluded that the CES-D had good criterion validity in older adults as a measure of MDD against the interviewer-administered Clinical Interview Schedule [279], (commonly used to diagnose depression).

Orthostatic Hypotension and Depression

Paper 2 examined the prevalence and severity of OH in older adults using continuous beat-to-beat blood pressure monitoring and explored the relationship between OH and depression. Depressed participants had a higher prevalence of symptomatic OH and initial OH relative to non-depressed controls. In multivariate analysis, sustained symptomatic OH was associated with greater odds of being depressed.

Emerging evidence suggests that hypoperfusion may be an important factor in the development of late life vascular depression [56]. OH can lead to cerebral auto-dysregulation [252] which can impair CBF [117]. Mild CBF reduction may impair cognitive and affective processes, while greater CBF reduction in the context of autoregulatory deficits may cause ischemic injury and WMHs [56]. To date, two studies [173, 201] have shown that the burden of OH is greater in LLD relative to non-depressed controls and one study [67] has shown an association between orthostatic SBP drop and WMH volume in depressed older adults. Our findings support the limited literature in this area; and demonstrate that the association between OH and depression extends to the
general older population. We are not aware of any studies that have investigated the direct effect of OH on cerebral perfusion in older adults with depression. A limited number of studies have demonstrated changes in CBF in older individuals with depression, but there are considerable inconsistencies between studies [280-283]. Most recently, a study by Colloby and colleagues showed increased blood flow in the white matter of patients with LLD. They postulated that this represented a response to white matter pathological change or alternatively could be a marker of those who respond to antidepressant treatment [284].

Paper 3 examined the relationship between OH and depression using an oscillometric measure of blood pressure to detect OH. Importantly, this investigation facilitated the inclusion of participants who were unable or unwilling to attend a health assessment centre. We previously demonstrated that participants who selected a home assessment were older and had poorer physical health with higher levels of depression [91]. Using this extended sample, we found that participants with symptomatic OH had higher levels of depression relative to participants with asymptomatic OH or participants without OH. Linear regression analysis showed that symptomatic OH was associated with higher CES-D scores compared to participants without OH. In both studies, the relationship between OH and depression was dependant on the presence of symptoms of hypoperfusion. Participants with symptomatic OH may have more extreme changes in CBF resulting in orthostatic symptoms. In contrast, those with asymptomatic OH may have better preserved auto
regulation centrally and therefore no symptoms of hypoperfusion from impaired CBF, despite clinically significant drops in BP during orthostasis.

In summary, the association between SOH and depression was consistent across both studies, regardless of the measures used to determine OH. The hypothesis that OH may directly contribute to depression by reducing cerebral perfusion in the areas of the brain associated with depression is thus broadly supported by our findings. Longitudinal evidence is required to determine if OH predicts individuals who might develop depression. This would support the study of interventions that improve cerebral perfusion and may improve depression outcomes in older adults. Already, two studies have shown that augmentation of antidepressant medication with Nimodipine (a calcium channel blocker used to treat hemorrhage-induced vasospasm) in the treatment of vascular depression led to a greater and more rapid improvement in depressive symptomatology, lower rates of recurrence, and a higher rate of full remission when compared to those patients on antidepressant medication alone [285, 286]. In addition, a pilot study for a randomised control trial is underway in the US, to determine if improving cerebral perfusion with angiotensin receptor blockers, improves depression outcomes in older adults.

**Depression and HRV**

Paper 4 examined the associations between depression and HRV and explored the influence of lifestyle, anxiety and antidepressants on these associations. We found no relationship between depression and reductions in HRV; however, we did find that antidepressants have an unfavourable effect on autonomic
activity. All antidepressants had a lowering effect on HRV with SSRI’s showing the better HRV profile relative to TCA’s and SNRI’s respectively.

HRV in depression is now an important issue since both depression and decreased HRV have been shown to be predictors of cardiac morbidity and mortality [269]. As a result, there has been substantial interest in the relationship between HRV and depression and the role, if any, of antidepressant medications. Some cross-sectional studies have shown a reduction in HRV in un-medicated, physically healthy individuals [149, 150] while others have demonstrated that the relationship between depression and HRV is driven by antidepressant use [152]. The only longitudinal evidence available supports the latter hypothesis [153]. In our study, depression was associated with reduced HRV, but not heart rate, when antidepressants were not considered in the analysis. However, once antidepressants were introduced as a confounder, all significant associations with HRV were eliminated. Our results show that SSRI’s and SNRI’s have a direct effect on HRV independent of HR, whereas the effect of TCA’s on HRV is mediated by their impact on HR. This information furthers our understanding of the mechanism by which antidepressants impair HRV.

There exists a paucity of studies examining the effects of antidepressants on HRV in older adults, despite the high prevalence of CVD and greater applicability in this age group. To our knowledge, this is the first study to examine the effects of individual antidepressant classes on HRV, using a large representative population sample of older adults. While our findings suggest that antidepressants have negative effect on autonomic activity; it is as yet
unknown whether this translates into unfavourable CVD outcomes. Recent data from the Scottish Health Survey (2011) have confirmed that TCA users have increased risk of incident CVD [287].

The mechanism by which antidepressants influence cardiac autonomic function is complex and as yet not fully understood. There is evidence that TCA’s mainly inhibit NE re-uptake increasing circulating levels of NE. By a process of accentuated antagonism, NE has a blocking effect on muscarinic receptors and TCAs are also believed to have intrinsic anticholinergic effects that may further decrease parasympathetic activity [274, 288-290]. Similar to TCAs, SNRIs inhibit NE re-uptake which increases SNS activity and through accentuated antagonism they also decrease PNS activity. Finally, SSRIs act primarily by inhibiting serotonin (5-HT) re-uptake; activation of 5-HT receptors may inhibit muscarinic receptors while increasing NE clearance, causing decreased PNS and SNS activity [272, 291-293].

In summary, our evidence suggests that dysregulation of the ANS may mediate the relationship between depression and CVD; but not directly by the intrinsic effects of the depression but indirectly, through the use of antidepressants medications prescribed for the disorder. Moreover, inflammation is under the control of the central nervous system and increased SNS and decreased PNS activity has been associated with increased cytokine production [294-296]. Therefore antidepressant effects on ANS functions could also lead to the development of CVD through inflammatory processes. Data
from the Scottish Health Survey also demonstrated that the use of TCAs was associated with systemic inflammation [287]

7.2 Clinical Implications

Findings from this thesis are relevant for clinical practice including, but not limited, to cardiology, psychiatry and general practice. Firstly, our findings suggest that OH may be an important factor in the development of depression in older adults. OH is particularly common in older adults and similar to depression shows increasing prevalence moving from community to primary care and to long term care and hospital settings. OH is a treatable condition and therefore a potentially modifiable risk factor for depression. Non-pharmacologic treatments include avoidance of potentially hypotensive medications, use of physical counter manoeuvres, hydration and sodium supplementation. If these non-pharmacologic measures prove inadequate, various pharmacotherapeutic agents, including fludrocortisone, midodrine, and nonsteroidal anti-inflammatory drugs can be considered [250].

Secondly, depression and CVD are highly prevalent disorders in older adults so clinicians need to be aware of the autonomic effects of antidepressant medications. SSRIs do not increase heart rate but they do have a negative impact on HRV; although considerably less than other classes of antidepressants. Careful consideration should be given to the prescription of TCAs and SNRIs in older adults, particularly those with existing CVD. In patients with severe CVD other kinds of therapy may be deemed more
appropriate; however, this will need to be considered in the context of depression severity and the associated risk of social isolation, functional impairment and potentially suicide [5, 297]. Ultimately, clinicians need to consider whether the cardiovascular risk associated with lower HRV outweighs the beneficial effects of antidepressant treatment in older adults with depression. Given that antidepressants such as SSRIs are now prescribed not only for depression, but also for a wide range of conditions; this issue has relevance to the general population.

7.3 Methodological Considerations

Possible limitations of the present study have been addressed in individual papers but the most important considerations with respect to the validity of our observations are (re)considered below.

Firstly, our measure of depression was not a formal diagnosis of MDD and this may have influenced our findings. Structured diagnostic interviews (based on the DSM-IV) are expensive and often impractical for use in large, epidemiological studies. Large surveys have therefore often relied on self-administered instruments to identify psychiatric illness and morbidity and these have been shown to be sensitive for the detection of depression in older adults [110, 248]. The prevalence of MDD in community samples of older adults ranges from 1-5%, with the majority of studies reporting prevalence in the lower end of the range [5, 6, 213, 255]. It is therefore likely that the CES-D overestimated the prevalence of MDD and our prevalence represents both major and subthreshold depression.
There has been growing evidence for the clinical significance of subthreshold depressive symptoms [18-20] and for the view that subthreshold depression falls on a continuum with full threshold depression [298, 299]. The continuum view is supported by research indicating that subthreshold depression is associated with impairment that is comparable to major depression [18-20] and in particular, there is evidence that subthreshold depression is associated with increased risk for coronary events and CHD-related mortality in older adults [21, 300, 301]. So although our measure of depression was not a formal diagnosis of MDD; this was balanced by the large representative sample that provided good statistical power and enabled extrapolation to the general population. Moreover, the CES-D reflects the current emphasis on dimensional aspects of psychopathology in its measurement of depression; by including subthreshold depression which is more prevalent in older adults and associated with negative health, social and functional consequences similar to MDD.

In the context of the results presented in this thesis, the lack of a significant relationship between depression and HRV could have been due to our measure of depression. A formal classification of MDD may have revealed an association between depression and HRV which persisted after controlling for antidepressant use. Previous evidence showing a negative association between depression severity and HRV, such that the more severe the depression, the lower the HRV provides support for this possibility [149]. Subsequent waves of the TILDA study include the DSM-IV based Composite International Diagnostic Interview –short form (CIDI-SF, [302]), which will allow us to test
the validity of the findings compared with a gold standard diagnosis of depression [16].

An additional limitation of our study is that we were not able to determine whether participants had late onset or early onset depression. The study of late-onset depression has generated mechanistic hypotheses on the role of ageing-related and disease-related changes in the development of depression; however, methodological and conceptual concerns limit their importance. For example onset of depression is difficult to identify, especially when mild and neurological changes could contribute to a late-life episode irrespective of other depressive episodes in early life. Moreover, early-onset depression might be a risk factor for late-life depression by contributing to brain abnormalities that predispose to depression (dysfunction of HPA axis). So as pointed out by Alexopoulous (2005), even if there is a special late onset form of depression, it may also arise in an older patient who had depression earlier in life. Thus, characteristics that define late onset depression might be found as well in some older patients who report a previous episode of depression. Since we did not distinguish age of onset in our study, our measure of LLD encompasses both late-onset cases as well as early-onset cases that recur or continue into later years [31] and existing literature supports this definition of LLD [6, 28, 31]. In relation to our findings, our ability to identify a relationship between OH and depression may have been reduced by the inclusion of participants with both early- and late-onset depressive disorder but we do not feel it impacts the validity of the associations we presented here.
The cross-sectional design of the current thesis allows associations to be established but limits inferences on causality. Although many relevant risk factors were assessed and statistically controlled for in the analysis, the possibility of residual confounding cannot be ruled out. TILDA is a prospective study; so the potential exists to examine all of the cross-sectional associations presented in this thesis, once the collection of the next wave of health data is completed in early 2015. Our results, particularly in relation to antidepressant use are of an observational nature, in contrast to results obtained in a randomized controlled trial of antidepressant use. Although a pseudo-experimental setup was created (comparing 3 different depression group to a control group) and important covariates were considered (lifestyle, co-morbidity, anxiety), the observational design of the study along with the cross-sectional nature of the current analysis does not allow a definite statement on causality. Moreover, it has yet to be determined whether reductions in HRV associated with antidepressant use are of the magnitude to translate into an increased risk of CVD. Longitudinal studies are needed to address this important issue and the temporal relationship between OH and depression.

Our measures of OH and HRV were only performed once and without standardisation for time of day, medications, meals and lifestyle factors (e.g. smoking, caffeine, alcohol), based on practicality of delivering health assessments to participants from all over the country [278]. These factors may affect reproducibility of results [123], however time of day and food ingestion did not influence orthostatic blood pressure in a previous TILDA pilot study [242]. Variability in measures of autonomic function can be considerable.
and this could have led to the misclassification of disease states in our study; but equally, there is evidence to suggest that reproducibility is not always an issue in older adults [305, 306].

In summary, despite these limitations there are several strengths of our study. Firstly it was based on a large nationally representative sample that measured a variety of factors relevant to the health of older adults. Reliable and valid objective assessments tools were used to measure autonomic function and depression and data collection was extensive which allowed for good control of confounders in statistical analysis.

7.4 Future Research

This thesis aimed to provide insight into the links between autonomic function/dysfunction and depression. Possible associations of interest for future investigation, with regard to the focus of this thesis are now discussed. Firstly the causal relationship between hypotensive-induced cerebral hypoperfusion and WMHs in older adults with depression has yet to be established. A first step is to examine whether orthostatic hypotension actually leads to reduced CBF in depressed older adults. Common modalities (CT, PET, and MRI) for monitoring CBF are often limited by practical and technological hurdles in large cohort and community studies. Noninvasive measures are best suited to prospective studies and include transcranial Doppler (TCD) ultrasonography. However, TCD ultrasonography is limited to observations of large vessel flow velocities, which do not necessarily reflect microvascular perfusion in patients with cerebrovascular disease, and importantly lack
sensitivity for assessing CBF during active stand (signal is lost due to movement). Near-infrared diffuse optical spectroscopy (NIRS) is currently being piloted for inclusion in wave 3 of TILDA since it purports to offer a non-invasive, rapid, portable and low-cost alternative for direct monitoring of cerebral tissue oxygenation in microvasculature [307, 308]. Inclusion of this device will facilitate much needed research on the magnitude of CBF reductions associated with OH and provide insights into the autoregulatory decline associated with ageing. Furthermore, TILDA plans to introduce MRI scanning into wave 3 pending funding. This will afford the opportunity to compare density and location of WMHs in older adults with depression.

Secondly, the occurrence of CVD can be compared longitudinally between individuals with depression who are using and not using antidepressants, to confirm whether the relationship between antidepressant use and reduced HRV is truly a risk factor for cardiovascular morbidity and morbidity. Moreover, functional MRI could be used to specify the brain areas associated with autonomic dysfunction in antidepressant users. If future research confirms our findings, it may facilitate the development of new and novel treatment options to reduce the causes and consequences of depression in older adults.
8 Bibliography


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121. Reed MJ, Robertson CE, Addison PS. Heart rate variability measurements and the prediction of ventricular arrhythmias. QJM. 2005 Feb;98(2):87-95.


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## Appendix 1

**Center for Epidemiologic Studies Depression Scale (CES-D), NIMH**

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

<table>
<thead>
<tr>
<th>Week</th>
<th>During the Past</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarely or none of the time (less than 1 day)</td>
<td>Some or a little of the time (1-2 days)</td>
</tr>
<tr>
<td>1. I was bothered by things that usually don't bother me.</td>
<td>□</td>
</tr>
<tr>
<td>2. I did not feel like eating, my appetite was poor.</td>
<td>□</td>
</tr>
<tr>
<td>3. I felt that I could not shake off the blues even with help from my family or friends.</td>
<td>□</td>
</tr>
<tr>
<td>4. I felt I was just as good as other people.</td>
<td>□</td>
</tr>
<tr>
<td>5. I had trouble keeping my mind on what I was doing.</td>
<td>□</td>
</tr>
<tr>
<td>6. I felt depressed.</td>
<td>□</td>
</tr>
<tr>
<td>7. I felt that everything I did was an effort.</td>
<td>□</td>
</tr>
<tr>
<td>8. I felt hopeful about the future.</td>
<td>□</td>
</tr>
<tr>
<td>9. I thought my life had been a failure.</td>
<td>□</td>
</tr>
<tr>
<td>10. I felt fearful.</td>
<td>□</td>
</tr>
<tr>
<td>11. My sleep was restless.</td>
<td>□</td>
</tr>
<tr>
<td>12. I was happy.</td>
<td>□</td>
</tr>
<tr>
<td>13. I talked less than usual.</td>
<td>□</td>
</tr>
<tr>
<td>15. People were unfriendly.</td>
<td>□</td>
</tr>
<tr>
<td>16. I enjoyed life.</td>
<td>□</td>
</tr>
<tr>
<td>17. I had crying spells.</td>
<td>□</td>
</tr>
<tr>
<td>18. I felt sad.</td>
<td>□</td>
</tr>
<tr>
<td>19. I felt that people dislike me.</td>
<td>□</td>
</tr>
<tr>
<td>20. I could not get &quot;going.&quot;</td>
<td>□</td>
</tr>
</tbody>
</table>

**SCORING:** 0 for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.
## Appendix 2

### Appendix 2. Summary of measurements from TILDA health assessment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Health Centre</th>
<th>Home</th>
<th>No. of measurements</th>
<th>Equipment Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>Yes</td>
<td>Yes</td>
<td>Once</td>
<td>SECA 240 wall mounted measuring rod</td>
</tr>
<tr>
<td>Weight</td>
<td>Yes</td>
<td>Yes</td>
<td>Once</td>
<td>SECA electronic floor scales</td>
</tr>
<tr>
<td>Waist size a</td>
<td>Yes</td>
<td>Yes</td>
<td>Two</td>
<td>Standard tape measure</td>
</tr>
<tr>
<td>Hip size b</td>
<td>Yes</td>
<td>Yes</td>
<td>Two</td>
<td>Standard tape measure</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Yes</td>
<td>Yes</td>
<td>Three - 2 seated &amp; 1 standing</td>
<td>OMRON^™ digital automatic blood pressure monitor</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Yes</td>
<td>Yes</td>
<td>Three</td>
<td>OMRON^™ digital automatic blood pressure monitor</td>
</tr>
<tr>
<td>Grip Strength</td>
<td>Yes</td>
<td>Yes</td>
<td>Two - 2 readings on each hand</td>
<td>Baseline Hydraulic Hand dynamometer</td>
</tr>
<tr>
<td>Global cognition</td>
<td>Yes</td>
<td>Yes</td>
<td>Two</td>
<td>1. Montreal Cognitive Assessment (MOCA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Mini Mental State examination (MMSE)</td>
</tr>
<tr>
<td>Attention</td>
<td>Yes</td>
<td>Yes</td>
<td>Once</td>
<td>Sustained Attention Response Time</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>Yes</td>
<td>Yes</td>
<td>Once</td>
<td>CAMDEX Memory Test (Acquisition, Free recall, Recognition)</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>Yes</td>
<td>Yes</td>
<td>Once</td>
<td>Choice reaction time test</td>
</tr>
<tr>
<td>Executive function</td>
<td>Yes</td>
<td>Yes</td>
<td>Three</td>
<td>Timed Colour Trails 1 &amp; 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Visual reasoning – CES-D - 8 Item</td>
</tr>
<tr>
<td>Mood</td>
<td>Yes</td>
<td>Yes</td>
<td>one</td>
<td></td>
</tr>
<tr>
<td>Timed Up &amp; Go</td>
<td>Yes</td>
<td>Yes</td>
<td>Once</td>
<td>Standard tape measure/Chair/tape</td>
</tr>
<tr>
<td>Phasic Blood Pressure</td>
<td>Yes</td>
<td>No</td>
<td>Eight – 1 at baseline and 7 recording after active stand</td>
<td>Finometer MIDI</td>
</tr>
<tr>
<td>Pulse Wave Velocity</td>
<td>Yes</td>
<td>No</td>
<td>Twice</td>
<td>Vicorder</td>
</tr>
<tr>
<td>Heart Rate Variability</td>
<td>Yes</td>
<td>No</td>
<td>One 10 minute recording</td>
<td>Medilog Darwin AR12</td>
</tr>
<tr>
<td>Visual Acuity</td>
<td>Yes</td>
<td>No</td>
<td>Two – left &amp; right eye</td>
<td>Logmar chart</td>
</tr>
<tr>
<td>Contrast Sensitivity</td>
<td>Yes</td>
<td>No</td>
<td>Three - left &amp; right eye &amp; both eyes together</td>
<td>Functional visual analyzer</td>
</tr>
<tr>
<td>Retinal Photograph</td>
<td>Yes</td>
<td>No</td>
<td>Two – left &amp; right eye</td>
<td>NIDEX - Non-Mydriatic Auto-Fundus Camera</td>
</tr>
<tr>
<td>Macular Pigment Optical Density</td>
<td>Yes</td>
<td>No</td>
<td>Twelve – 6 measurements per eye</td>
<td>Macular Metrics Dietisometer™</td>
</tr>
<tr>
<td>Bone density</td>
<td>Yes</td>
<td>No</td>
<td>Once – non dominant foot</td>
<td>Achilles Insight Heel</td>
</tr>
<tr>
<td>Assessment of Gait</td>
<td>Yes</td>
<td>No</td>
<td>Four – one normal walk – simple cognitive task – Manual task</td>
<td>GAITRite sensored mat</td>
</tr>
<tr>
<td>Venous blood sample</td>
<td>Yes</td>
<td>Yes</td>
<td>25mls</td>
<td>Standard blood taking materials</td>
</tr>
</tbody>
</table>