A Prospective Evaluation of the Long-term Clinical Associations of Neurocardiovascular Instability in Older People

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Abstract

Introduction

Neurocardiovascular instability (NCVI) describes a group of disorders characterised by orthostatic hypotension (OH), carotid sinus hypersensitivity (CSH) and autonomic dysfunction.

In cross-sectional studies, NCVI has been associated with cognitive impairment, depression and falls. It is suggested that episodic hypotension causes cerebral hypoperfusion, which in turn causes anoxic brain damage. White matter hyperintensities (WMH) on MRI are thought to represent ischaemic damage due to hypoperfusion and are also associated with cognitive impairment, depression, and falls.

Despite these observations, the long-term clinical significance of NCVI remains unclear, particularly in asymptomatic individuals

Aims

- To examine the associations between NCVI and cognition, depression and falls over a ten-year follow-up
- To examine the association between NCVI and WMH volume on MRI
- To examine the association between NCVI and ten-year all-cause mortality.

Methods

Participants were recruited from an established cohort of people aged ≥65 years in 2002. Baseline evaluation of neurocardiovascular function in 2002 included heart rate variability, autonomic function tests and carotid sinus massage. Neuropsychological assessment was performed at baseline and at follow-up. MRI was performed at follow-up (but not at baseline). WMH volume was calculated using FLAIR MRI. Cox regression analysis was used to examine the association between NCVI and mortality.

Results

In 2002 1000 individuals aged ≥65 years were selected at random from a single GP practice and invited to participate in the study. 353 consented to enrolment in the

baseline study. Of whom 104 individuals [median age 79 years (range 74-92)] participated in the year 10 follow-up.

Asymptomatic NCVI was not associated with cognition, depression, falls or WMH volume at follow-up. Symptomatic OH was associated with greater decline in CAMCOG memory score [B =1.19, P<0.05] and symptomatic CSH was independently associated with increased WMH volume [P<0.01].

NCVI defined according to standard criteria was not associated with ten-year mortality. However, at baseline it had been identified that the 95^{th} percentile for systolic vasodepression was 76.6 mmHg and the 95^{th} percentile for RR interval post CSM was 7.3 seconds. These thresholds were used to define CSH modified criteria. CSH defined according to modified criteria, derived from the baseline populations' response to CSM, was associated with increased mortality [HR2.37, P=0.02].

Conclusions

NCVI is not associated with adverse outcomes at ten years in asymptomatic older people but symptomatic NCVI is associated with decline in memory and greater WMH volume, suggesting symptoms are of prognostic significance. Modified CSH criteria are better predictors of ten-year mortality than current criteria.

Funding Organisations

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Abbreviations

A&E	Accident and Emergency Department
AAN	American Academy of Neurology
ABP	Ambulatory Blood Pressure
ABPM	Ambulatory Blood Pressure Monitor
ACE	Angiotensin Converting Enzyme
ACH	Acetylcholine
AD	Alzheimer's Disease
ADH	Anti-diuretic Hormone
ADL	Activity of daily living
AFT	Autonomic Function Test
ANS	Autonomic Nervous System
BMI	Body Mass Index
BP	Blood Pressure
CAMCOG	Cambridge Cognitive Assessment (Revised Version Used)
CAMDEX-R	Cambridge Mental Disorders of the Elderly Examination – Revised
CCF	Congestive Cardiac Failure
CDR	Computerised Drug Research Battery
CED-S	Centre for Epidemiology Depression Scores
CI	Confidence Interval
CNS	Central Nervous System
Cog RT	Cognitive Reaction Time
COMPASS	Computerised Mental Performance System
CRT	Choice Reaction Time
CSH	Carotid Sinus Hypersensitivity
CSM	Carotid sinus massage
CSS	Carotid Sinus Syndrome
CT	X-ray Computed Tomography
CVD	Cerebrovascular Disease
DBP	Diastolic Blood Pressure
DLB	Dementia of Lewy Bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders

ECG	Electrocardiogram
FLAIR	Fluid Attenuated Inversion Recovery
GP	General Practice
HADS	Hospital Anxiety and Depression Scale
HF	High Frequency
HF/LF	High Frequency / Low Frequency Ratio
HR	Hazard Ratio
HRV	Heart rate variability
ICD	International Statistical Classification of Diseases and Related Health Problems
IHD	Ischaemic Heart Disease
IQR	Inter Quartile Range
IRR	Incident Rate Ratio
LF	Low Frequency
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NCVI	Neurocardiovascular Instability
NICE	National Institute of Clinical Excellence
NRES	National Research Ethics Committee Service
OH	Orthostatic Hypotension
ONS	Office For National Statistics
OR	Odds Ratio
PD	Parkinson’s Disease
PMH	Past Medical History
POA	Power of Attention
POMA	Performance Orientated Mobility Assessment
RAAS	Renin Angiotensin Aldosterone System
RCI	Reliable Change Indices
SA	Sino Atrial Node
SBP	Systolic Blood Pressure
SD	Standard Deviation
SD (DBP)	Diastolic Blood Pressure Variability
SD (SBP)	Systolic Blood Pressure Variability

SDRR	Standard Deviation of Successive Normal RR Intervals
SMR	Standardised Mortality Rate
SPSS	Statistical Package of Social Science
SRT	Simple Reaction Time
SSRI	Selective Serotonin Reuptake Inhibitors
UK	United Kingdom
USA	United States of America
VD	Vascular Dementia
VigRT	Digit Vigilance Reaction Time
VLF	Very Low Frequency
WHO	World Health Organisation
WMH	White Matter Hyperintensities

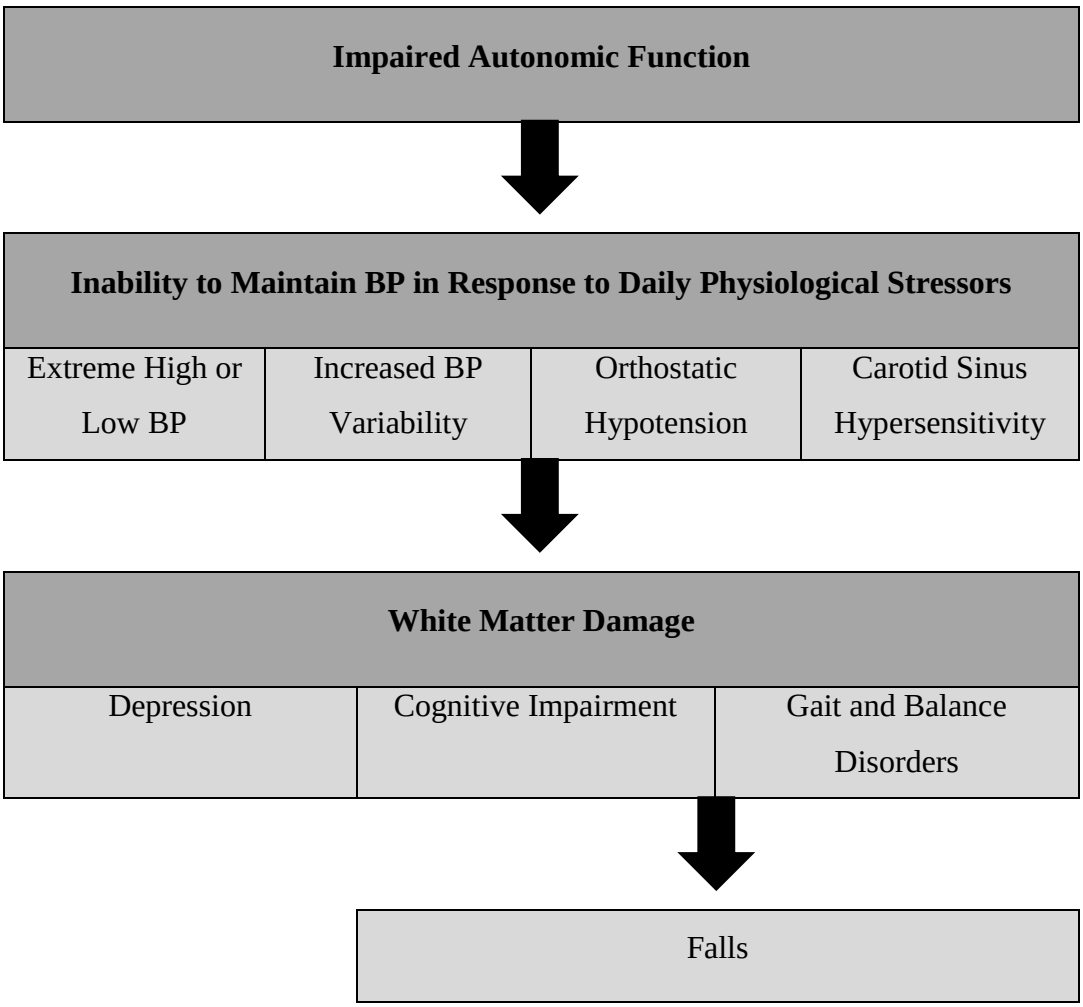
Rationale for the Study

Cognitive impairment, gait and balance disorders, falls and depression are common in older people (World Health Organization and Life Course, 2008, Luppa et al., 2012, Ferri et al., 2005, Axer et al., 2010). Loss of cognitive and physical independence is feared by individuals and, in societies with an ageing population, present significant social and economic challenges (Luengo-Fernandez et al., 2011, Jeon et al., 2006). This combination of cognitive and motor dysfunction is so frequently encountered by geriatricians and older patients that it is sometimes referred to as a "geriatric syndrome". Small vessel cerebrovascular disease, seen as white matter hyperintensities on magnetic resonance imaging (MRI), has been proposed as one possible underlying pathological mechanism for this syndrome (Sonohara et al., 2008, Kuo and Lipsitz, 2004).

White matter hyperintensities are common in older people and have been associated with cognitive impairment, gait and balance abnormalities, and late-life depression (Sonohara et al., 2008, Kuo and Lipsitz, 2004, The et al., 2011). They occur close to the cerebral ventricles, in an arterial "watershed" and are thought to represent ischaemic damage resulting from chronic or recurrent hypoperfusion (Pantoni, 2002). Cerebral autoregulation maintains cerebral perfusion over a range of systemic BP, typically 60-150 mmHg (Panerai, 2008). Falls in systemic blood pressure (BP), below the lower limit of cerebral autoregulation, result in cerebral hypoperfusion. The neurocardiovascular mechanisms responsible for maintaining systemic BP become impaired with age, making older people vulnerable to sporadic hypotensive episodes and cerebral hypoperfusion (Kenny et al., 2002). This thesis explores the longitudinal association between systemic blood pressure control, white matter hyperintensities on MRI and common clinical features of the geriatric syndrome, namely; cognitive impairment, depression, gait and balance impairment, and falls.

The overarching hypothesis is that age-related changes in cardiovascular and autonomic nervous system function lead to impaired homeostasis of systemic BP, causing recurrent hypotensive episodes. These hypotensive episodes in turn result in cerebral hypoperfusion and white matter damage, causing cognitive impairment, gait and balance disorders, depression and falls. Figure 0-1 displays the proposed mechanism.

Figure 0-1 Proposed Mechanism of Association between Neurocardiovascular Instability, White Matter Hyperintensities, Cognitive Impairment and Gait Disorders



The following introduction describes the epidemiology of cognitive impairment, falls and depression in the context of an ageing population and reviews the published literature examining the associations between blood pressure control, white matter hyperintensities and the clinical correlates of white matter hyperintensities.

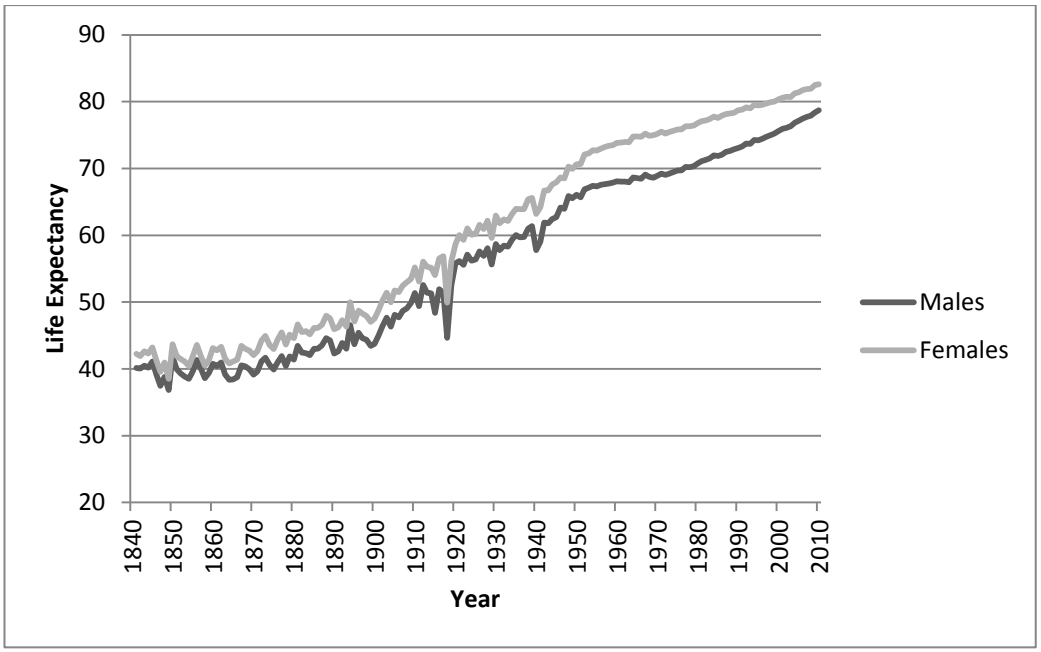
Chapter 1 Introduction and Summary of Existing Literature

1.1 Ageing Population

1.1.1 Demographic Changes

The worldwide population is ageing. Over the last century, life expectancy in Europe, USA and Canada has increased by approximately 30 years (Christensen et al., 2009). Figure 1-1 shows the steady increase in life expectancy at birth observed in the UK between 1841 and 2010 (ONS, 2012a).

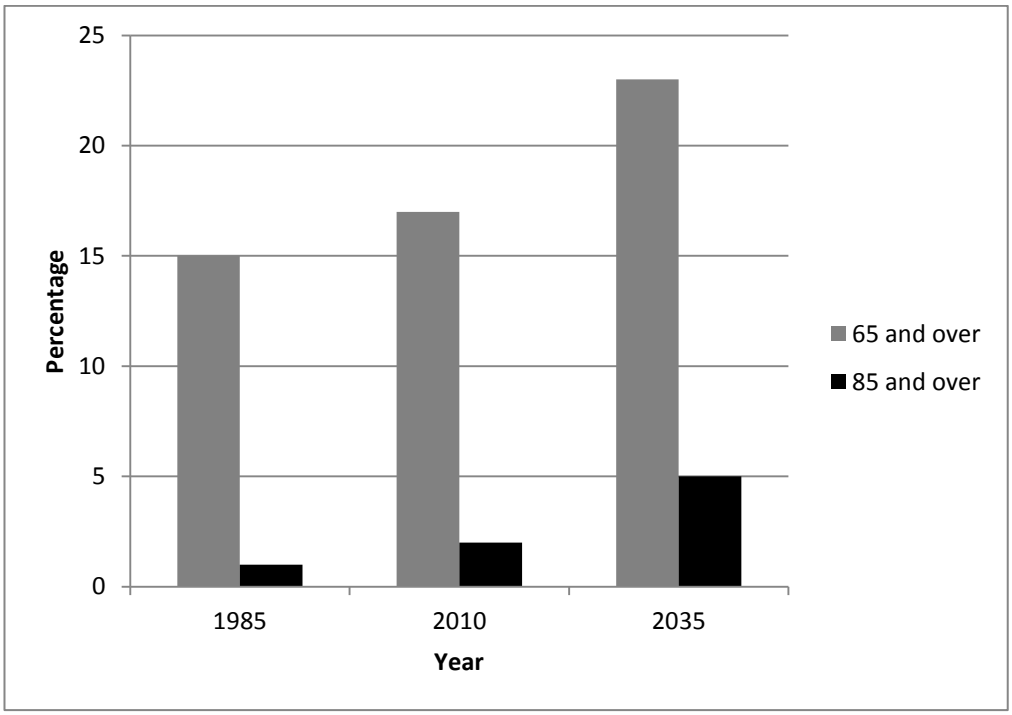
Figure 1-1 Life expectancy at birth in the UK 1841 to 2010 (*reproduced from Office of National Statistics Report Population Ageing in the United Kingdom its constituent countries and the European Union – Permission granted under free use licence)*



Initial increases in life expectancy were a result of decreases in infant and childhood mortality but since the 1970s increases have been due to decreases in old age mortality, resulting in an ageing population (Spijker and MacInnes, 2013). Figure 1-2 shows that in the UK the percentage of persons aged 65 and over increased from 15% in 1985 to 17% in 2010, an increase of 1.7 million people. The oldest old (people aged >85) are the most rapidly increasing segment of the population. Between 1985-2010 the number of people in the UK aged 85 and over more than doubled to 1.4 million (ONS, 2012b). By

2035 people aged 65 and over are predicted to account for over 20% of the population and people aged 85 years and over for 5%.

Figure 1-2 Percentage of older people in the UK, 1985, 2010 and 2035 (*reproduced from Office of National Statistics Report Population Ageing in the United Kingdom its constituent countries and the European Union – Permission granted under free use license)*



These demographic changes have significant implications for medicine and society. Older people, particularly those over 70, are at high risk of disease and disability (Christensen et al., 2009). With increasing age, cognitive and physical impairments become greater threats to functional independence (Reynish, 2009, Bischkopf et al., 2002, Wolfson, 2001). Understanding and addressing underlying risk factors for cognitive and motor decline in later life is essential in order to ensure increases in longevity are not accompanied by unacceptable increases in morbidity and disability.

1.2 Cognition, Depression and Physical Function in the Ageing Population

1.2.1 Cognition and Ageing

1.2.1.1 Dementia and Ageing

Prevalence of dementia increases significantly with age. In Europe, dementia affects 1.5% of people aged 65-70 compared to 24.8% of people aged 85 and over (Ferri et al., 2005). For woman aged 95 and older studies have found prevalence as high as 50% (Reynish, 2009).

Incidence studies report a positive association between age and incidence rates of dementia. However, the trend of association with age is not clear. A meta-analysis by Goa et al indicated that the increase in the incidence rate of dementia slows down with increasing age, although the incidence rates themselves do not decline(Gao et al., 1998). They reported, for every five-year increase in age, dementia incidence rates triple before age 64, double before age 75, and increase 1.5 times around age 85 (Gao et al., 1998). In contrast, two meta-analysis have found that the incidence of dementia and AD increase with age (Jorm and Jolley, 1998, Launer et al., 1999). Corrada et al found incident rates continued to increase even in individuals aged 90 and older, with estimates of incidence as high as 41% per year in centenarians (Corrada et al., 2010).

1.2.1.2 Mild Cognitive Impairment

It is recognised that milder forms of cognitive impairment, insufficiently severe for the diagnosis of dementia, also occur commonly among older people (Morris et al., 2001a, Petersen et al., 2001). Several names have been used to describe this state between normal cognition and dementia. The term currently most in use is mild cognitive impairment (MCI). MCI is considered a pathological entity. Petersen(Petersen et al., 1997), originally, defined the diagnostic criteria as;

1. Normal functional abilities with activities of daily living
2. The absence of dementia
3. Abnormal cognitive function in memory domains
4. Normal function in other cognitive domains.
5. Self-reported subjective memory loss.

The last point, self-reported subjective memory loss, is intended to ensure there has been a change in cognitive performance rather than life long cognitive impairment (Luck et al., 2010b, Petersen et al., 1997).

More recently, the definition of MCI has broadened. MCI no longer refers to isolated memory loss. Where memory and at least one other cognitive domain are impaired, it is termed multi-domain amnesic MCI. Non- amnesic forms of MCI are also recognised and can be single or multi-domain (Luck et al., 2010b, Petersen, 2004, Bischkopf et al., 2002) . Reported incidences vary widely. In a thorough meta-analysis of studies reporting the prevalence and incidence of MCI, Ward et al reported an incidence ranging from 21.5-71.3 per 1,000 person-years for MCI – all types and 8.5-25.9 per 1,000 person years for amnesic MCI (Ward et al., 2012). Reported prevalence for MCI-all types ranged from 3%-42% (Ward et al., 2012). Prevalence of MCI increased with age after 65 years but appeared to plateau after the age of 85(Bischkopf et al., 2002). Variations in reported prevalence and incidence in these studies resulted from variations in the operational definitions used to describe MCI variations in the population characteristics of study samples.

Identifying risk factors for MCI is important as MCI is associated with increased risk of Alzheimer's disease and vascular dementia. Reported annual rates of conversion from MCI to dementia range from five to 65% (Katz et al., 2009, Palmer et al., 2008).

1.2.2 **Depression and Ageing**

Cognitive deterioration among older people is commonly associated with late-life depression (Weisenbach et al., 2012). Luppa et al performed a meta-analysis, examining the prevalence of depression among older people (Luppa et al., 2012). They grouped studies into two categories: (1) studies using classification systems such as ICD-10 and DSM, which they called "categorical studies"; and (2) studies using rating scales to diagnose clinically significant depression called "dimensional diagnostics." Meta-analysis of categorical studies indicated a point prevalence of major depression of 4.6% -9.5% for people aged 75 years and over, and 2.1%-11.1% for people aged 85 years and over. Analysis of studies using depression rating scales showed prevalence rates between 4.5% and 37.4% for people aged 75 years and older (Luppa et al., 2012). Age of onset of psychiatric symptoms is important as early and late-life depression are

thought to have different aetiology, prognosis and presentation. Over half of older people with depression experience their first episode after the age 60 (Fiske et al., 2009). Depression in late-life has been associated with dementia, cerebrovascular disease, and white matter disease. This has led authors to hypothesise that depression in later life is secondary to cerebral small vessel disease (Jellinger, 2013).

1.2.3 **Physical Function and Ageing**

1.2.3.1 Mobility and Ageing

Mobility is impaired in 14% of people aged 65-74 and 50% of people aged 85 years and over (Wolfson, 2001). A survey of older people found that half limit their daily activity in some way due to concerns about their mobility (Sudarsky, 1990)

1.2.3.2 Gait, Balance and Walking

It is estimated that 15% of people aged 60 and 82% of people aged 85 have a gait disorder (Axer et al., 2010). Gait speed remains stable up to the seventh decade then decreases at a rate of 15% per decade (Wolfson, 2001). Normal gait velocity for a person aged 80 is about 1.0 -1.2 m/s. A cohort study of 79 year olds in Goteborg, Sweden, found none could comfortably walk at 1.4 m/s, a pace considered by the Swedish government to be the norm for pedestrian crossings (Sudarsky, 1990). After the seventh decade, sway when standing still increases, and single leg stance time decreases. Gait broadens and more time is spent with both feet on the ground. One in four people over age 79 walked with a walking aid (Sudarsky, 1990). Ability to compensate for trips and pushes becomes impaired with age and older people become more reliant on sensory input for multiple modalities to remain stable (Wolfson, 2001). These changes are important since impaired gait and balance are major risk factors for falls (Voermans et al., 2007).

1.2.3.3 Ageing and Falls

Thirty-five to forty per cent of community-dwelling people aged 65 years and older will fall once in a year (Blake et al., 1988, Rubenstein, 2006, Campbell et al., 1989). Rates increase with age, 50% of adults aged 85 and older, and 60% of adults aged 90 and over report falling in a year (Fleming et al., 2008, Iinattiniemi et al., 2009). Falling is particularly dangerous in the elderly because of their high susceptibility to injury (Axer et al., 2010). Of people aged 65 and older, 1 in 40 will be hospitalised due to a fall (Rubenstein, 2006). Accidental injury due to falls is a cause of death in 20% of older

Americans (Sudarsky, 1990). Falls also result in decreased confidence, loss of independence and isolation (Scheffer et al., 2008).

Cognitive impairment, late-life depression, impaired mobility and falls commonly co-occur in older people and are sometimes referred to as geriatric syndromes. Traditionally the term *syndrome* is used to describe a collection of symptoms or signs resulting from a single pathogenic pathway. In older peoples' medicine the term geriatric syndrome is used to describe a collection of symptoms highly prevalent in the older population resulting from multiple disease and risk factors (Rikkert et al., 2003). Although the causes of geriatric syndromes are multifactorial, growing attention has turned to the association between small vessel cerebrovascular disease common geriatric syndromes including cognitive and motor decline in later life. Other terms such as "geriatric phenotype" have also been proposed however phenotype is generally considered to describe observable characteristics determined by genotype(Inouye et al., 2007). While genetic and environmental factors both undoubtedly contribute to the diseases underlying geriatric syndromes there is limited understanding of the association between genotype and frailty. The term Geriatric Syndrome therefore appears more appropriate in this context

1.3 White Matter Hyperintensities and Selected Geriatric Syndromes

Cerebral white matter hyperintensities (WMH) are thought to represent small vessel cerebrovascular disease and are common in older patients. Seen as symmetrical patchy or diffuse areas of hyperintensity on dual echo or FLAIR MRI, white matter hyperintensities are found in 27 – 86 % of patients over 65 (Kuo and Lipsitz, 2004). Previously dismissed as benign age-related changes, studies have suggested associations between WMH and cognitive impairment, depression, reduced mobility and falls (Sonohara et al., 2008, Kuo and Lipsitz, 2004, The et al., 2011). Severe WMH have been shown to predict global functional decline (Inzitari et al., 2009, Briley et al., 2000).

1.3.1 White Matter Hyperintensities and Cognition

Cross-sectional population-based studies have demonstrated an association between greater white matter hyperintensity volume and poorer performance on tests of cognitive function (Longstreth et al., 1996, Au et al., 2006, de Groot et al., 2000,

Geerlings et al., 2009). Longitudinal studies show that progression of white matter hyperintensities parallels decline in cognitive function (Longstreth et al., 2005, Schmidt et al., 2005, Van Den Heuvel et al., 2006). Extensive WMH volume has been associated with incident dementia and MCI independent of other vascular risk factors and in patients with dementia the presence and severity of white matter hyperintensities associates with degree of cognitive impairment and functional status (Debette et al., 2010).

The impact of lesion location on cognitive function remains controversial. Lesions are classified as periventricular white matter lesions (PVWMH) if WMHs adjoin the margins of the lateral ventricle and deep white matter lesions (DWMH) if they are separate from it (Kim et al., 2008). Two meta-analyses have examined association between lesion location and different cognitive outcomes. Gunning-Dixon et al concluded that there was insufficient evidence to conclude reliably that lesion location affects global functioning, speed, fluid intelligence or executive functioning (Gunning-Dixon and Raz, 2000). Bolandzadeh et al found that a greater number of studies reported an association between periventricular WMHs and executive function/processing speed than deep WMHs (Bolandzadeh et al., 2012). However, they also concluded that it remains unclear whether WMHs in different brain regions have a differential effect on cognitive function (Bolandzadeh et al., 2012).

Studies investigating the association between WMH and performance on specific cognitive domains have used different cognitive tests, making direct comparison between studies difficult. Gunning-Dixon et al aimed to establish if WMH are associated with deficits in specific cognitive domains (Gunning-Dixon and Raz, 2000). They concluded greater WMH volume was associated with poorer performance on tests of global cognitive functioning, speed of processing, immediate-recent memory, delayed memory, and executive functioning. The group went onto assess whether any of the cognitive domains related to WMH were differentially sensitive to WMH. Tests of executive function and speed of process appeared to be more strongly associated with WMH than tests of memory (Gunning-Dixon and Raz, 2000). Subsequently Parks et al have suggested that executive function mediates the effect of WMH on memory (Parks et al., 2011)

1.3.2 **White Matter Hyperintensities and Depression**

Evidence also suggests that white matter disease may be associated with depression in older people (Chen et al., 2006, de Groot et al., 2000, Firbank et al., 2005, Godin et al., 2008, Firbank et al., 2004). In the largest studies, patients with severe white matter disease were 3-5 times more likely to have depressive symptoms than those with mild or no WMH and individuals with greater white matter volumes at baseline were at increased risk of developing depression (de Groot et al., 2000). Longitudinal studies have shown an association between progression of WMH and incident depression (Firbank et al., 2012b). The underlying mechanism for this association remains unclear. Proponents of the vascular depression hypothesis suggest WMH are indicative of vascular disease changes to the brain, predisposing individuals to the development of depression by disrupting fibre tracts in the frontostriatal cortex (Firbank et al., 2012b) (Teodorczuk et al., 2009). Alternatively, the association between white matter hyperintensities and depression may reflect the recognised associations between greater WMH volume and increased disability as a result of cognitive and motor decline. Some studies controlling for functional ability found white matter disease no longer predicted depressive symptoms (Steffens et al., 1999).

1.3.3 **White Matter Hyperintensities, Gait, Balance and Falls**

Several studies have shown associations between WMH, lower limb dysfunction and falls (Baezner et al., 2008, Soumaré et al., 2009, Blahak et al., 2009, Tell et al., 1998, Starr et al., 2003, Baloh et al., 2003, Rosano et al., 2005, Whitman et al., 2001). The LADIS study showed that more severe WMH were associated with slower walking speed and poorer performance on assessments of gait (Baezner et al., 2008, Soumaré et al., 2009). Severity of WMH has been shown to be significantly associated with balance (Blahak et al., 2009, Tell et al., 1998, Starr et al., 2003) and greater WMH load has been shown to predict future decline in gait and walking speed (Baloh et al., 2003, Soumaré et al., 2009). Incident self-reported physical impairment is more common in patients with moderate grades of WMH compared to those with minimal WMH and longitudinal studies show decline in gait and balance parallels increases in WMH(Rosano et al., 2005, Whitman et al., 2001). Periventricular WMH appear particularly associated with gait disturbances and falls, possibly reflecting involvement of descending and ascending pathways serving the lower extremities (Longstreth et al., 1996, Blahak et al., 2009, Soumaré et al., 2009, Onen et al., 2008). Patients with white

matter disease report increased falls in retrospective studies and greater WMH volume has been associated with incident falls (Zheng et al., 2012, Srikanth et al., 2009, Blahak et al., 2009).

1.3.4 **Pathophysiology of White Matter Hyperintensities**

Given the associations observed between white matter hyperintensities, cognition, depression, gait, balance and falls, growing attention has turned to identifying and understanding the risk factors associated with the development of WMHs.

The most well studied modifiable risk factor for the development of WMH is hypertension (Park et al., 2005, Skoog, 1998, van Dijk et al., 2004, de Leeuw et al., 2002, Dufouil et al., 2001, Liao et al., 1997). Studies show that hypertension is a risk factor for the development of WMH and that the severity and progression of white matter disease is associated with the severity and duration of hypertension (Basile et al., 2006, de Leeuw et al., 2002, Dufouil et al., 2001, Goldstein et al., 2005, Liao et al., 1997, Veldink et al., 1998). Similarly, smoking (Basile et al., 2006, Jeerakathil et al., 2004, Longstreth et al., 2005) dyslipidemia (Bokura et al., 2008, Park et al., 2007) and diabetes (Harten et al., 2006) have been identified as risk factors for the development and progression of WMH. Patients with white matter disease are at significantly increased risk of stroke, particularly lacunar infarcts, and myocardial infarction (Gerdes et al., 2006).

The association between WMH, vascular risk factors and cardiovascular disease has led to the widely held belief that WMH represents cerebral small vessel disease. Arteries close to WMH show: concentric hyaline thickening, a reduction in the ratio of arterial lumen to external diameter and atherosclerosis (O'Sullivan, 2008). Histopathology studies of WMH show a range of changes including; myelin pallor, axonal loss, mild reactive gliosis and dilated perivascular spaces (Brun and Englund, 1986, Chimowitz et al., 1992, Fazekas et al., 1998, Grafton et al., 1991, van Swieten et al., 1991). However, as frank infarction is not seen it has been suggested that that these changes represent ischaemic damage resulting from hypoperfusion, termed “incomplete infarction”(Bowler, 2003).

Cerebral white matter is particularly vulnerable to hypoperfusion. Blood supply to the periventricular area is via long, penetrating arteries, originating from the pial network on the surface of the brain and ending some distance from the ventricular wall (Pantoni and Garcia, 1997). The region closest to the ventricle wall is supplied by the ventriculofugal vessels arising from subependymal arteries. These systems do not anastomose or form collaterals, resulting in an arterial "watershed", within the periventricular white matter (O'Sullivan, 2008, Pantoni and Garcia, 1997). The low perfusion pressure in this vulnerable region means that any reduction in cerebral perfusion may result in ischaemic damage.

Under normal conditions, cerebral perfusion is maintained by cerebral autoregulation. For healthy adults, cerebral autoregulation ensures that stable cerebral blood flow can be adequately sustained over a systemic systolic blood pressure ranging from 60 mmHg – 150mmHg. Systemic BP below this lower limit is associated with cerebral hypoperfusion.

Older people are at greater risk of cerebral perfusion pressure falling below the lower limit of cerebral autoregulation for two reasons:

1. The limits of cerebral autoregulation are not fixed. Chronic hypertension shifts the autoregulation curve to the right (Strandgaard and Paulson, 1984). This protects the brain from elevated BP, but raises the lower limit of autoregulation. Falls in BP below the lower limit of autoregulation result in precipitous reduction in cerebral perfusion. Although studies suggest that cerebral autoregulation, itself does not change in healthy older people, conditions associated with shifts in the autoregulation curve, particularly hypertension, increase in prevalence with age such that the lower limit of cerebral autoregulation is elevated in many older people making them vulnerable to cerebral hypoperfusion at systemic systolic BP well above 60 mmHg (van Beek et al., 2008).
2. In addition to changes in the lower limits of cerebral autoregulation, increasing age and hypertension are associated with impaired autonomic control of systemic blood pressure and heart rate, resulting in greater BP variability (Parati et al., 2006). Hypotensive syndromes, associated with sudden drops in systemic BP, such as orthostatic hypotension, postprandial hypotension and carotid sinus

hypersensitivity become more common in older adults (Low, 2008, Humm and Mathias, 2006, Luciano et al., 2010) .

Thus, older people are at risk of episodic hypotension and, as a result of altered cerebral autoregulation, may be at greater risk of cerebral hypoperfusion. It is hypothesised that episodic hypotension among older people may result in WMH secondary to cerebral hypoperfusion and anoxic damage.

1.4 Blood Pressure Regulation and Ageing

This section will briefly describe blood pressure control in healthy individuals, the changes in blood pressure regulation associated with ageing and some of the common clinical syndromes associated abnormal blood pressure control encountered in older people.

1.4.1 Regulation of Blood Pressure in Healthy Individuals

Blood pressure homeostasis involves multiple interrelated self-regulating mechanisms, principally the autonomic nervous system, central nervous system and hormonal control.

1.4.1.1 The autonomic nervous system

The autonomic nervous system (ANS) controls blood pressure via the sympathetic and parasympathetic branches. Baroreceptors and mechano-receptors monitor blood pressure, feeding information to the central nervous system, which in turn adjusts heart rate and blood pressure via efferent pathways of the ANS. Of all the cardiovascular reflexes, the baroreflex is the most important (Sun, 1995). Baroreceptors in the aortic arch and carotid sinus respond to stretch in the vessel wall. Rises in blood pressure cause increased stretch, triggering baroreceptor discharge. These changes result in increased vagal activity and decreased sympathetic activity which in turn causes a reduction in heart rate and a decrease in peripheral vascular resistance.

Mechano-receptors are also present in the large veins, pulmonary circulation and atria. These primarily detect changes in circulating volume. Reduced venous return results in increased sympathetic and decreased vagal activity, in turn causing an increase in heart rate and peripheral vasoconstriction (Izzo and Taylor, 1999). Increases in efferent

sympathetic activity also cause renal vasoconstriction, decreased diuresis and increased circulating volume.

1.4.1.2 Endocrine System

The renin angiotensin aldosterone system (RAAS) regulates blood volume and is directly affected by and affects the autonomic nervous system. Renin is produced in response to falls in arterial blood pressure, reduced plasma sodium and increased sympathetic activity(Sunhaeswaran, 1998). Renin converts angiotensinogen to angiotensin1, which in turn is converted to angiotensin II. Angiotensin II causes an increase in blood pressure by stimulating the aldosterone secretion from the adrenal cortex and, at high concentrations, causing noradrenaline release from sympathetic nerve terminals in vascular smooth muscle(Sunhaeswaran, 1998).

Antidiuretic Hormone (ADH) is produced by the hypothalamus by rises in plasma osmolality, and to a much lesser extent, by a fall in blood pressure. ADH causes increased water retention by the kidney and peripheral vasoconstriction(Sunhaeswaran, 1998).

1.4.1.3 The central nervous system

The central nervous system has a complex role in the processing of signals from the peripheral autonomic nervous system and the cerebral cortex. Most studies examining the central control of the peripheral autonomic nervous system have been conducted in anesthetised animals. Information from the baroreceptors is received by the nucleus tractus solitarius and is relayed to the hypothalamus (Sunhaeswaran, 1998, Dampney et al., 2002). The rostral ventral lateral medulla and ambiguous nucleus are responsible for the sympathetic and parasympathetic outflow respectively. Higher frontal and temporal cortical centres are also believed to be able to exert central control over the cardiovascular response via the brain stem (Dampney et al., 2002).

1.4.2 **Blood Pressure Regulation and Ageing**

Several age-related changes have been noted in these homeostatic mechanisms (Kaye and Esler, 2008, Izzo and Taylor, 1999, Monahan, 2007, Ferrari et al., 2003, Diz, 2008). Sympathetic activity increases with age (Kaye and Esler, 2008). Plasma norepinephrine levels become elevated, even when blood pressure is raised**,** resulting in increased vascular resistance (Kaye and Esler, 2008, Izzo and Taylor, 1999). Decreased clearance

of catecholamines has been demonstrated among older people (Kaye and Esler, 2008, Izzo and Taylor, 1999)**.**

Numerous studies have demonstrated an age-related decrease in the success of baroreflex to control BP (Monahan, 2007, Ferrari et al., 2003). Alterations in any part of the reflex arc may result in a diminished ability to respond to changes in blood pressure. Baroreceptors in the aorta and carotid sinus respond to stretch of the arterial wall. With age vessels become less compliant, resulting in reduced dispensability. The range of stretch of the mechanoreceptors is decreased and baroreflex sensitivity is reduced (Monahan, 2007, Ferrari et al., 2003, Izzo and Taylor, 1999). Studies also suggest there may be decreased baroreceptor neural discharge in older people(Ferrari et al., 2003).

In animals, electrophysiological studies and pharmacological studies designed to increase acetylcholine (ACH) at the sinoatrial node (SA) found that older animals had a much greater bradycardic response to increased ACH (Ferrari et al., 2003). It is hypothesized that age related impaired parasympathetic drive causes sinus nodal muscarinic receptor up regulation (Ferrari et al., 2003).

Hormonal controls of BP also diminish with age. Renin release from the kidney decreases with age. This is a result of decreased renin in juxtaglomerular cells, decreased renin release in response to challenges and decreased plasma renin and angiotensin II (Diz et al., 2008) .

1.5 Assessment of Autonomic Function and Blood Pressure Control and Age-related Changes

Several techniques have been developed to access cardiovascular autonomic function. Two of the most commonly used are heart rate variability and the Ewing and Clark battery.

1.5.1 Heart Rate Variability

Heart rate variability is a, non-invasive method used to assess sympathovagal balance. ECG recordings are made at rest under controlled conditions (5 minute recording) or during activity using an ambulatory monitor (24-hour recordings).

Time and frequency domain indices of heart rate variability have been developed (Camm et al., 1996). Time domain indices measure the variation in successive normal RR intervals. Several measures have been developed including: standard deviation of successive normal RR intervals (SDRR), standard deviation of the average RR interval calculated over 5 minutes (SDARR), the square root of the mean square differences between successive intervals (RMSSD), the number of interval differences of successive normal RR interval greater than 50ms (NN50) and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) (Camm et al., 1996).

Power spectral analysis (most commonly using a fast Fourier transform) provides the basic information of how power (variance) distributes as a function of frequency (Camm et al., 1996, Ori et al., 1992). Three main components are present in the spectrum recorded from short (5 minute) recordings; high frequency fluctuations (0.15-0.40 Hz), low frequency fluctuations (0.04-0.15) and very low frequency fluctuations (<0.04) (Xhyheri et al., 2012). High frequency (HF) fluctuations are abolished by atropine and are thought to represent parasympathetic activity. Low frequency (LF) fluctuations are abolished by both beta blockers and atropine suggesting the LF fluctuations are under both parasympathetic and sympathetic influences (Kleiger et al., 2005). The significance of very low frequency (VLF) fluctuations remains poorly understood. LF:HF ratio gives some information about the relevant balance of the sympathetic and parasysmpathetic branches of ANS.

Ageing is associated with a reduction in heart rate variability; however the pattern of change is measure dependent (Umetani et al., 1998, Jensen-Urstad et al., 1997). Umetani et al reported a 40% reduction in SDRR between the second and tenth decade compared to a 75% reduction in P50NN between the second and sixth decade (Umetani et al., 1998). Similarly LF, HF and VLF power are negatively associated with age where as HF:LF ratio does not appear to associate with age (Jensen-Urstad et al., 1997).

1.5.2 **Ewing and Clark Autonomic Function Tests**

HRV only allows autonomic control of heart rate to be measured. Other batteries of autonomic function tests have been developed that monitor both HR and BP response physiological stressors (Ewing and Clarke, 1982). The Ewing and Clark battery consists

of six components (three tests of parasympathetic function and three tests of sympathetic function) (Table 1-1)(Ewing and Clarke, 1982).

Table 1-1 Components Ewing and Clark Battery

Test of Parasympathetic Function	Tests of Sympathetic Function
Heart rate response to standing	Systolic BP response to Standing
Heart rate response to deep breathing	Diastolic BP response to hand grip
Heart rate response to Valsalva manoeuvre	Blood pressure response to Valsalva manoeuvre

Cut-offs for normal, borderline and abnormal response to each test have been defined (Ewing et al., 1985). Results from this battery of tests are grouped into one of five categories;

- Normal: all tests are normal or borderline
- Early autonomic dysfunction: one of the three heart rate tests are abnormal or two borderline
- Definite autonomic dysfunction: two or more of the heart rate tests abnormal
- Severe autonomic dysfunction involvement: two or more of the heart rate tests abnormal plus one or both of the blood pressure tests abnormal, or both borderline
- Atypical: any other combination of abnormal tests.

As with HRV, response to these autonomic function tests is associated with age (Ewing et al., 1985, Gautschy et al., 1986). Ewing et al examined response to autonomic function tests in a cohort of healthy individuals aged 16-69 years and found heart rate response to standing deep breathing decreased with increasing ageing but that Valsalva ratio, BP response to standing and BP response to hand grip were unaffected by age (Ewing et al., 1985). Gautschy et al examined the association between age and response to autonomic function tests in an older cohort (aged 22 – 92 years) and found that reduced response to all tests except BP response to hand grip was associated with increasing age (Gautschy et al., 1986). The Ewing and Clark battery only uses one normal range regardless of age making it vulnerable to generating false positive results in older people (Ryder and Hardisty, 1990). Confidence in tests of autonomic function may be increased by using age related normal ranges and many centres have developed

there own normal ranges for people age 65 years and over (Kenny, 2008). The high number of abnormal autnomic function tests found in apparently healthy older people has lead some authors to adapted Ewing classification when applying them to older populations. Collins et al defined autonomic dysfunction as having ≥ 2 autonomic function tests as abnormal (Collins et al., 2012). Where as Kenny et al uses more stringent criteria for those over 65, requiring ≥3 abnormal tests before the diagnosis of autonomic dysfunction is made (Kenny, 2008). To date no formal assessment has been made of the specificity and sensitivity of the modified criteria.

1.5.3 Ambulatory Blood Pressure Monitoring and Age-related Blood Pressure Changes

Age-related changes in sympathetic / parasympathetic balance as noted on HRV and autonomic function testing contribute to increases in blood pressure with advancing age. Systolic BP rises from age 20 to 75 before plateauing and then declining in old age (>80 years) (Bobrie and Potter, 2002, Bots et al., 1991). Diastolic BP rises up to age 50 or 60 years and then levels off or slightly decreases (Pestana, 2001).

Individual BP readings are affected by time of day, eating, fullness of bladder, temperature, and white coat hypertension. Ambulatory BP monitoring (ABPM) allows these changes to be recorded. An appropriate blood pressure cuff and recording device can be worn for up to 48 hours and BP measurements taken at predefined intervals (usually every 15-60 minutes). ABPM allows calculation of mean BP and BP variability for the full 24-hour monitoring period and separately for daytime and night-time.

Mean BP is a better predictor of cardiovascular and renal disease than casual office BP, particularly among older people in whom white coat hypertension is common (Minutolo et al., 2011, O'Brien, 2011). Recent National Institute for Health and Care Excellence guidelines define hypertension as a mean daytime BP >135/80 on 24-hour ABPM (NICE, 2011).

Blood pressure variability is usually defined as SD of the blood pressure recordings or by the variation co-efficient (SD/ mean ambulatory BP) (Floras et al., 1988a, Ramirez et al., 1985). BP variability reflects fluctuations in BP caused by sleep, eating, physical activity and medication. It provides information on individuals' ability to maintain BP

homeostasis. Cross-sectional studies, have shown increased blood pressure variability in older age groups (Imai et al., 1997, Jaquet et al., 1998, Mancia et al., 1985) and a positive correlation between blood pressure variability and age (Imai et al., 1997, Pringle et al., 2003).

Increased ambulatory blood pressure variability is associated with decreased baroreflex sensitivity both during beat-to-beat monitoring and over longer periods (Mancia et al., 1985, Mancia et al., 1986, Floras et al., 1988b). In humans, blood pressure variability is not affected by either α or β adrenergic receptor blockade. In dogs, atropine increases blood pressure variability. These observations suggest that regulation by the parasympathetic nervous system is the principal determinant of blood pressure variability (Floras et al., 1988b, Di Rienzo et al., 1985, Mancia et al., 1986, Parati et al., 1995, Mancia et al., 1995).

1.6 Neurocardiovascular Instability

Neurocardiovascular instability (NCVI) describes a group of disorders associated with intermittent hypotension and bradycardia resulting from these age-related changes in blood pressure and heart rate control (Kenny et al., 2002). The commonest clinical manifestations of NCVI in older people are; orthostatic hypotension and carotid sinus hypersensitivity. The following section will define these disorders and describe how they are diagnosed.

1.6.1 Orthostatic Hypotension

On standing, gravity causes 300- 800 ml of blood to pool in the lower limbs and splanchnic circulation (Freeman et al., 2011). There is a resulting decrease in venous return to the heart and reduction in cardiac output. Under normal conditions, neurocardiovascular mechanisms cause increased sympathetic outflow to the heart and peripheral circulation and decreased vagal activity. These adjustments increase vascular tone, increase heart rate and cardiac contractility, maintaining blood pressure on standing (Freeman et al., 2011). As previously described, these mechanisms become impaired with advancing age, making older adults vulnerable to sudden drops in blood pressure on orthostasis (Gupta and Lipsitz, 2007).

Classical orthostatic hypotension (OH) is a marked fall in blood pressure on standing or being tilted upright. The American Autonomic Society and the American Academy of Neurology (AAN) have defined classical OH as a systolic blood pressure decrease of at least 20 mmHg or a diastolic blood pressure decrease of at least 10 mmHg within three minutes of standing or being tilted to 60 degrees (Freeman et al., 2011).

It should be noted that the definition does not state how long individuals should rest supine before lying BP is recorded, how BP should be recorded, how often BP readings should be taken during the three minute stand, or if the patient should be symptomatic. This makes comparison of studies problematic.

There are two approaches used to record BP during active stand. Firstly, and most commonly, BP is recorded at predefined intervals throughout the stand using a standard sphygmomanometer. Intervals between measurements vary between protocols. Alternatively, continuous beat-to-beat BP recordings can be chronicled using digital photoplethysmography. Continuous beat-to-beat monitoring allows all drops in BP to be captured and a calculation of the true nadir to be made. Intermittent readings potentially miss short-lived drops in BP and are unlikely to capture the true nadir.

The reported prevalence for OH varies considerably depending on method used to detect change in BP. In a review of studies, using intermittent BP recordings, Low et al, reported a prevalence of OH of 5-35%, with prevalence increasing with increasing age (Low, 2008). Newer studies that have used beat-to-beat BP monitoring to record postural change in BP report a prevalence of OH ranging from 59% -94% among adults aged ≥65 years (Cooke et al., 2013, Romero-Ortuno et al., 2011a, Kerr, 2009).

1.6.2 **Carotid Sinus Hypersensitivity**

CSH is diagnosed if there is ≥50 mmHg drop in systolic BP or ≥3 seconds asystole or both in response to carotid sinus massage (CSM). CSH is an age-related phenomenon. Rarely seen below 40 years of age, the prevalence of CSH increases with advancing age. Among patients referred to an autonomic centre the reported prevalence ranged from 2.4% among adults aged 50-59 years to 40.4% among adults aged ≥ 80 (Humm and Mathias, 2006).Kerr et al reported a prevalence of CSH of 39% among community-

dwelling older people aged ≥65 years in whom CSM was performed using beat-to-beat monitoring (Kerr et al., 2006).

It is clear from these studies, that neurocardiovascular instability (in the form of OH and / or CSH) is common among older people, particularly when beat-to-beat monitoring is used to make the diagnosis. Symptomatic patients often present to clinical services with falls, dizziness or syncope, but many patients remain asymptomatic despite changes in BP or heart rate in keeping with diagnostic criteria for CSH or OH (Kerr et al., 2006, Romero-Ortuno et al., 2013). The long-term consequences of recurrent hypotension and intermittent bradycardia are not fully understood. As discussed above there is evidence to suggest that systemic hypotension may contribute to the formation of white matter hyperintensities in older people. The following sections will review the association between BP control and white matter hyperintensities and between BP control and the clinical associates of white matter hyperintensities namely; cognition, depression, gait, balance and falls

1.7 Blood Pressure Control and White Matter Hyperintensities

Age aside hypertension is one of the strongest risk factors for the development of white matter hyperintensities. But studies also suggest increased variation in blood pressure and low blood pressure may be associated with WMH.

1.7.1 Blood Pressure Variability and White Matter Hyperintensities

Several approaches have been used to investigate the question of whether there is an association between BP variability and WMH volume. Visit-to-visit blood pressure variability records the variation in BP recorded in clinic using a sphygmomanometer. Intervals between visits vary from days to years depending on study protocol (Rothwell et al., 2010). Short-term BP variability looks at the variation in BP measured with either a sphygmomanometer or continuous beat-to-beat monitoring record over a shorter period, usually 30 minutes to two hours, at rest under controlled conditions. Ambulatory BP monitors usually report BP variability for one of three time periods; 24-hours, daytime and / or night-time. A number of indices are commonly recorded;

- BP variability (the within-subject standard deviation of all readings over a defined period),
- Coefficient of variability (variability of BP/mean BP)

- The maximal variation of BP (difference between the maximum and minimum BP over a defined period).

A number of studies have investigated the question of whether BP variability is associated with WMH volume (Puisieux et al., 2001, Goldstein et al., 2005, Marti-Fabregas et al., 2001, Gomez-Angelats et al., 2004, Tartaro et al., 1999). Results have been mixed. Puisieux retrospectively examined the CT scans and 24-hour ambulatory BP recordings of 79 older people (Puisieux et al., 2001). Higher white matter scores were associated with higher maximal variation of SBP, greater variability of SBP during 24-hour, daytime and nocturnal periods and greater coefficient of variability of SBP during sleep (Puisieux et al., 2001). Tataro et al compared BP variability among older healthy individuals with and without WMH (n=45 and n=21 respectively) (Tartaro et al., 1999). Individuals with WMH had significantly greater nocturnal systolic and diastolic BP variability. Daytime and 24 hour BP variability did not significantly differ between groups. These findings are in contast to those of Marti-Fabregas et al who found no association between blood pressure variability and severity of white matter disease (Marti-Fabregas et al., 2001). However the latter paper included only 25 individuals and all were recruited from a tertiary neurology clinic where they were being treated for symptomatic small vessel disease (Marti-Fabregas et al., 2001)

Three groups have attempted to examine the longitudinal association between BP variability and WMH progression (Goldstein et al., 2005) (White et al., 2011, Yamaguchi et al., 2014) Goldstein et al examined if if BP variability predicts severity of white matter disease 5 years later in a cohort of 155 older healthy individuals (Goldstein et al., 2005). Greater daytime systolic BP standard deviation at baseline was significantly associated with more severe white matter disease at 5 year follow-up(Goldstein et al., 2005). A more recent study examined the association between BP variability and small vessel cerebrovascular disease in a cohort of 210 Japanese people aged 70-72 years. BP variability, MRI and cognitive function were recorded at baseline and repeated 4 years later. Systolic and diastolic coefficient of variation but not BP standard deviation were associated with progression of small vessel disease independent of other risk factors. Similalry, White et al examined 72 subjects aged 75-89 to establish if vascular risk factors were associated with white matter disease progression. Ambulatory BP monitoring and MRI were performed at baseline and 24 months later.

Mean BP but not BP variability (measured as SD) was associated with WMH progression. This group did not measure coefficient of variation.

Gomez et al examined BP variability using both conventional intermittent ambulatory 24-hour BP monitoring in the community and beat-to-beat monitoring in hospital for 24-hours (Gomez-Angelats et al., 2004). Data from ABPM showed that 24-hours systolic BP variability was greater among people with white matter disease than those without. Daytime and night-time BP variability recorded by ABPM did not differ between white matter groups. Similarly long-term beat-to-beat monitoring showed that systolic BP variability but not diastolic BP variability was greater in the group with white matter disease. Shorter-term BP variability (recorded over 30 minutes) was not associated with white matter disease. Gunstad et al have also examined the association between resting short-term BP variability and white matter disease. BP was recorded with sphygmomanometer every ten minutes for 2 hours (Gunstad et al., 2005). Systolic variability and the coefficient of systolic variability were associated with total white matter load and neocortical white matter disease. There was no association with periventricular disease. Diastolic variability was not associated with white matter disease.

Three groups have examined the association between visit-to-visit variation in office BP and white matter disease (Havlik et al., 2002) (Liu et al., 2012, Brickman et al., 2010). As part of the Honolulu heart study, 575 participants underwent three assessments of office BP between 1965 and 1974 and an MRI scan between 1991 and 1993 (Havlik et al., 2002). The cohort was divided into quintiles according to BP variability in mid-life (1965 -1977). Compared with those in the lowest quintile, those in the upper three quintiles of SBP variability were at an elevated risk of WMHs. There was no relationship with diastolic BP variability. The Inwood Columbia Ageing Project included 686 non demented older adults. BP measurements were recuorded during 3 study visits over 24. MRI scans were performed at the final visit. WMH volume was highest in patients in the highest quartile of mean BP and the highest quartile of BP variability (Brickman et al., 2010).In a study of 584 stroke patients, Liu et al recorded BP every 30 days for 12 – 18 months and MRI scans were performed at baseline and at the end of the study (Liu et al., 2012). BP variability, BP co-efferent and successive variation in BP were calculated. Participants with WMH at baseline had significantly

greater systolic BP standard deviation but other variables did not differ between groups. BP variability was not associated with white matter disease progression.

1.7.2 **Orthostatic Hypotension and White Matter Hyperintensities**

Raiha et al were the first to examine the potential association between orthostatic hypotension and white matter hyperintensities (Raiha et al., 1993). A review of the case notes of 204 patients who had undergone CT brain scans found that hypotension, congestive cardiac failure (CCF) and orthostatic hypotension were more common among patients with WMH. Logistic regression showed age, history of CCF and SBP <130, but not OH predicted WMH. Four studies have examined the association between OH and WMH in community-dwelling populations, all used a standard sphygmomanometer to record postural change in BP (Matsubayashi et al., 1997, Longstreth et al., 1996, Havlik et al., 2002, Gottesman et al., 2011). Matsubayashi et al found that people with postural hypotension (n= 20) had more advanced white matter hyperintensities than those with a normal response to standing (n=285) (Matsubayashi et al., 1997). The group also found that postural hypertension (defined as a 20mmHg rise in systolic BP or 10 mmHg rise diastolic BP on standing) was associated with more advanced WMH. In a population-based study of 3301 people, Longstregth et al found higher white matter grade was associated with presence of OH independent of age, sex and SBP(Longstreth et al., 1996). The association however was not significant after adjusting for presence of silent cerebral infarct. The Honolulu heart study recorded postural drop in 3734 men in 1991. OH was defined according to standard criteria. MRI scans were performed in a subset of 575 men between1993–1996. OH status was not associated with white matter load (Havlik et al., 2002). Finally a recent abstract published from the ARIC study found that presence of OH did not predict white matter hyperintensity progression but severity of OH (i.e. degree of postural drop) did predict WMH progression (Gottesman et al., 2011).

Colloby et al examined the association between white matter volume and BP response to standing using beat-to-beat monitoring in 38 individuals with late-life depression and 30 age-matched controls (Colloby et al., 2011). An association between systolic vasodepression and white matter volume in the temporal and parietal was found for the depressed group, but not for the controls.

1.7.3 Carotid Sinus Hypersensitivity and White Matter Hyperintensities

Few studies have examined the association between CSH and WMH. Kenny et al examined the association between CSH and white matter disease in 23 patients with Lewy body dementia, 22 with Alzheimer's disease. There was a correlation between magnitude of fall in SBP during CSM and severity of deep white matter changes among the Lewy body dementia group, but not for the Alzheimer's disease or control group (Kenny et al., 2004). A similar study including 17 patients with Lewy body dementia and 13 Alzheimer's patients found that vasodepression ≥30mmHg in response to CSM or active stand was associated with more severe WMH on MRI.

1.8 Blood Pressure Control and the Clinical Correlates of White Matter Hyperintensities

Section 1.7 shows that there is some evidence to support an association between episodic hypotension and increased WMH volume in later life. If hypotensive episodes are a risk factor for WMHs it would be anticipated that they are also a risk factor for the clinical presentations associated with white matter damage. The following section will review the existing literature examining the association between BP control and the clinical correlates of WMH, specifically; cognitive impairment, depression and falls.

1.8.1 Blood Pressure Homeostasis and Cognition

1.8.1.1 Hypertension and Cognition

Alzheimer's disease and vascular dementia are the most common forms of dementia, together accounting for 80% of all dementia cases (Collins and Kenny, 2007). Once thought of as two separate diseases it is now acknowledged that there is overlap between the condition (Viswanathan and Sudarsky, 2012, Roman and Kalaria, 2006). Cerebral infarctions, multiple lacunar infarctions, and ischaemic periventricular WMH (typical of vascular dementia) are common in both vascular dementia and Alzheimer's disease (Langa et al., 2004).

Age aside, hypertesntion is the most commonly recognised risk factor for WMH. There has been extensive research investigating the association between hypertension and dementia. Results have been conflicting, but several reviews have tried to summarise these data (Daviglus et al., 2011, Purnell et al., 2009, Power et al., 2011, Sharp et al., 2011). Daviglus et al reported conclusions of a recent National Institutes of Health

State-of-the-Science Conference (Daviglus et al., 2011). An independent panel reviewed the evidence for association between multiple vascular risk factors and Alzheimer's disease. The group described ten studies but did not perform a meta- analysis. They were unable to identify a consistent relationship between self-reported hypertension or recorded hypertension and Alzheimer's disease. The group concluded that hypertension is not a risk factor for Alzheimer's. Power et al performed a systematic review and meta-analysis of 18 prospective studies examining the associations between hypertension and Alzheimer's disease (Power et al., 2011). They concluded there was insufficient evidence to prove a causal relationship between hypertension and Alzheimer's disease. Similarly a systematic review by Purnell et al failed to show a significant relationship between hypertension and incident AD (Purnell et al., 2009).

In contrast with Alzheimer's disease, vascular dementia does appear to be associated with hypertension. Sharp et al reviewed six longitudinal studies assessing the association between hypertension and vascular dementia. A meta-analysis showed that hypertension was significantly associated with increased risk of incident vascular dementia (odds ratio: 1.59, 95% CI: 1.29-1.95, $p < 0.0001$) (Sharp et al., 2011).

Results from longitudinal studies examining the association between hypertension and cognitive decline have also been conflicting. Verdlho, Knopman. Reitz and Luck et al have shown an association between hypertension and cognitive decline (Luck et al., 2010c, Knopman et al., 2001, Luck et al., 2010b, Knopman et al., 2009, Verdelho et al., 2007). However, the cognitive domains affected have differed between studies. Reitz found elevated BP was associated with increased risk of all cause MCI and non-amnesic MCI, but not amnesic MCI (Reitz et al., 2007), whereas Luck et al found hypertension was associated with increased risk of amnesic MCI in the AgeCoDe study, but showed no association between blood pressure and incident MCI in the Leipzig Longitudinal Study of the Aged (Luck et al., 2010c, Luck et al., 2010a). Oveisgharan and Verdelho found hypertension to be associated with decline in executive function (although Oveisgharan did not find this to be the case when executive dysfunction was impaired in combination with memory impairment) (Verdelho et al., 2007, Oveisgharan and Hachinski, 2010). A systematic review of 11 longitudinal studies, Birns et al found most studies showed a relationship between hypertension and cognitive decline (Birns and Kalra, 2009). Similarly, in an earlier review, Eftekhari concluded long standing

sustained hypertension was associated with cognitive dysfunction (Eftekhari et al., 2007).

1.8.1.2 Essential Hypotension and Cognition

Interestingly, in addition to studies demonstrating an association between impaired cognitive function and hypertension, there are several studies suggesting a U or J shaped relationship between BP and cognitive function (Power et al., 2011, Guo et al., 1996, Morris et al., 2000, Hestad et al., 2005, Richmond et al., 2011). Power et al found a suggestion of an inverse association between late-life hypertension and Alzheimer disease (Power et al., 2011). Cross-sectional studies have shown increased prevalence of dementia (both AD and VD) among older people with relatively low systolic or diastolic blood pressure (Guo et al., 1996, Morris et al., 2000). Guo et al found significantly elevated odds ratio for dementia among older people with systolic pressure ≤140 mm Hg or diastolic pressure ≤75 mm Hg. The associations were stronger in those with a longer duration of disease and those with more severe dementia (Guo et al., 1996) . Similarly in the CHAP study Morris et al found Alzheimer's disease to be significantly more prevalent among individuals with relatively low systolic blood pressure (BP <130) (Morris et al., 2000). In a later cross-sectional study involving 5,816 participants aged ≥ 65 years, Morris et al found a curvilinear relationship between blood pressure and cognitive performance independent of age, sex and race (Morris et al., 2002). Hestad et al studied 207 community-dwelling older people aged ≥80 years(Hestad et al., 2005). Blood pressure was significantly lower in participants with MMSE <24. Low diastolic pressure was the best predictor of cognitive impairment as measured by the MMSE, followed by low systolic BP. Likewise, an analysis by Richmond et al studying the oldest cohort (142 participants, mean age 101.1) found low systolic BP was positively associated with MMSE [r=0.37 (P=0.001)] (Richmond et al., 2011).

Prospective studies also report associations between chronic hypotension and incident dementia (Verghese et al., 2003, Guo et al., 1999, Euser et al., 2009). Between 1980 and 1983, 488 individuals aged 75 and older enrolled in The Bronx Ageing Study (Verghese et al., 2003). Subjects were assessed at 12–18 month intervals. Follow-up lasted up to 21 years, mean follow-up 6.6 years. Four hundred and six individuals attended at least one follow-up of which, 122 developed dementia. Increased risk of incident dementia was associated with low diastolic pressure. Risk of incident dementia was higher in

subjects with persistently low BP. The Kungsholmen study included 1270 participants (aged 75 – 101). The authors found that high systolic BP (>180 mmHg) and low diastolic BP (<70 mmHg) were associated with increased risk of Alzheimer's disease (Guo et al., 1999). Low systolic BP and high diastolic BP were not associated with cognitive impairment. Euser et al. found for persons aged 65 to 74, higher baseline SBP and DBP were related to worse cognitive function 11 years later. In contrast, in older age (≥75), higher SBP and DBP seemed to be related to better cognitive function at the end of follow-up. This effect appeared strongest in the highest age group (aged 85) (Euser et al., 2009).

1.8.1.3 Blood Pressure Variability and Cognition

Several studies have shown a cross-sectional association between greater 24-hour (or daytime) BP variability and poorer cognitive function (Goldstein et al., 1998, Kanemaru et al., 2001, Bellelli et al., 2002, Sakakura et al., 2007). In contrast, studies examining the association between short-term BP variability measured over two hours found a significant positive relationship between a function of BP variability (standard deviation of systolic BP divided by the average diastolic BP) and cognitive function (Keary et al., 2007). Okonkwo et al examined the long-term association between short-term (two-hour) BP variability and cognitive decline (Okonkwo et al., 2011). Using random effects modelling, the group demonstrated that reduced variability in systolic BP and increased variability in diastolic BP were associated with a faster rate of decline in Attention-Executive-Psychomotor function (Okonkwo et al., 2011). There are no published studies examining the long-term association between 24-hour ambulatory BP variability and incident cognitive impairment / dementia or the impact of 24-hour BP variability on cognitive decline.

Two studies report the association between long-term BP variability and cognition (Nagai et al., 2012, Alperovitch et al., 2013). Nagai et al recorded 12 BP readings at one-month interval in 201 older people (Nagai et al., 2012). Exaggerated visit-to-visit BP fluctuations were significant indicators for cognitive impairment. In the largest study to examine the association between BP variability and cognition, Alperovitch et al examined the association between the variation in BP recorded on three occasions over three years and incident dementia (Alperovitch et al., 2013). During the 40,151 person-years of follow-up, 474 participants developed dementia. In the fully adjusted Cox model, the hazard ratio of dementia for those in the highest decile of the coefficient of

variation of systolic blood pressure was 1.77 (1.17–2.69) compared with the lowest decile (Alperovitch et al., 2013).

ABPM also provides information on diurnal variation. Loss of normal, nocturnal, dipping pattern also appears to be associated with cognition in cross-sectional studies. Non-dipping, extreme-dipping and reverse-dipping have been associated with poorer cognitive function in most studies (Guo et al., 2009, Yano et al., 2011, Yamamoto et al., 2005). Similarly, non-dipping has been associated with incident dementia over a mean follow-up of 8.9 years (Yamamoto et al., 2002).

1.8.1.4 Orthostatic Hypotension and Cognition

The reported association between chronic hypotension and cognitive impairment/ dementia led authors to investigate the relationship between cognitive function and episodic low blood pressure associated with NCVI

Two studies have examined the prevalence of OH in dementia compared to controls (Andersson et al., 2008, Mehrabian et al., 2010). Mehrabian performed sitting and standing BP on 495 patients attending a memory clinic (Mehrabian et al., 2010). Orthostatic hypotension was significantly more common among patients with dementia compared with non-demented patients (OH was present in 22% of vascular dementia patients, 15% of AD, 4% normal controls; $P<0.001$) (Mehrabian et al., 2010). Similarly, Anderson et al investigated 235 Alzheimer's dementia patients, 52 with patients with Lewy body dementia and 60 controls. OH was more common among individuals with Alzheimer's disease or Lewy body dementia than age-matched controls (Andersson et al., 2008).

Mehrabian et al also found OH was more common among individuals with MCI than controls and that after adjustment for age, education level, systolic BP, diastolic BP, weight, and antihypertensive drugs, subjects with OH performed significantly more poorly on the Cognitive Efficacy Profile than those without OH (Mehrabian et al., 2010). In keeping with these findings, Collins et al demonstrated that people with MCI show greater changes in SBP on orthostasis, compared to controls, and patients with MCI have poorer BP recovery (Collins et al., 2010). Failure of BP to return to baseline by 40 seconds was associated with impaired executive function (Collins et al., 2010).

In a large community study Yap et al examined 2,321 community-living older adults, in China (Yap et al., 2008). OH was not associated with cognitive impairment overall. However, among hypotensive participants, OH was associated with increased risk of cognitive impairment while hypertensive participants with OH showed reduced risk of cognitive impairment (Yap et al., 2008).

In a smaller community-dwelling cohort, Matsubayashi et al found patients with postural dysregulation (participants with >20mmHg drop in systolic BP or >20mmHg rise in systolic BP on standing) performed more poorly on cognitive tests compared to participants with normal BP regulation (Matsubayashi et al., 1997). Similarly, among participants recruited from primary care and hospital general medical wards, Czarjkowska found both orthostatic hypotension and orthostatic hypertension to be associated with poorer cognitive function (Czajkowska et al., 2010).

Four studies have examined the association between OH and cognitive decline (Rose et al., 2010, Yap et al., 2008 Viramo et al., 1999 Elmstahl and Rosen, 1997). Rose et al examined 12702 individuals. At baseline, participants with OH were more likely to be in the lowest quartile of cognitive tests scores than were those without OH. Similarly, at follow-up, OH was associated with increased odds of being in the greatest quintile of decline in cognitive test scores. After adjustment for socio-demographic and cardiovascular risk factors, these associations were no longer significant (Rose et al., 2010). It should be noted that this group defined BP change as the difference between the average of the standing and supine BP measurements rather than the difference between the lying BP and standing nadir and that they excluded the first standing measurement. This potentially will have resulted in an underestimation of the prevalence of OH and will have missed initial OH. In keeping with the findings of Rose et al, and in contrast to their cross-sectional findings, Yap et al did not find any association between OH and cognitive decline among (Yap et al., 2008). Viramo et al followed-up 651 community-dwelling people aged ≥70 years and found neither systolic or diastolic OH predicted cognitive decline at a 2.5 year follow-up (Viramo et al., 1999). Similarly, despite finding a cross-sectional association between OH and cognitive impairment Yap et al found no association between OH and cognitive decline over a one year follow-up period among a large cohort of Chinese older people (Yap et al., 2008). Only one longitudinal study has found an association OH and cognition. The

study was small with just 33 healthy woman, but with a longer follow-up period (5 years). Women who developed cognitive decline had significantly greater orthostatic fall in BP at baseline (Elmstahl and Rosen, 1997).

1.8.1.5 Carotid Sinus Hypersensitivity and Cognition

Carotid sinus hypersensitivity is more common in people with dementia. Kenny et al showed that prevalence of cardioinhibitory CSH was significantly higher among patients with Lewy body dementia than controls (Kenny et al., 2004). Kerr et al compared CAMCOG scores and performance on computerised drug research battery among community dwelling older people with and without CSH and found there were no differences in cognitive function.

1.8.2 **Blood Pressure Homeostasis and Depression**

In addition to the concept of vascular cognitive impairment, the model of vascular depression has been developed (Sneed and Culang-Reinlieb, 2011). It has long been recognised that there is a bidirectional association between vascular disease and depression, particularly depression starting in later life (Newberg et al., 2006). Depression is more common among patients with myocardial infarction and stroke than matched controls and has been found to be more strongly associated with vascular dementia than Alzheimer's disease (Frasure-Smith and Lespérance, 2010, Diniz et al., 2013, Newberg et al., 2006). Conversely depression has been identified as a risk factor for stroke (Dong et al., 2012).

1.8.2.1 Hypertension and Depression

These observations and the previously described associations between depression and white matter hyperintensities led to researchers to examine the association between vascular risk factors as depression in late-life. A recent meta-analysis aimed to quantify the extent to which hypertension might be associated with depression in late-life (Valkanova and Ebmeier, 2013). The study reviewed 14 papers examining the prevalence or incidence of late-life depression among people with and without hypertension. In total 20197 participants were included in the studies. After pooling the 14 studies the OR of depression was > 1 but statistically non-significant (OR: 1.14; 95% CI: 0 .94–1.40; P=0.19). The authors suggested that the failure to identify an association between hypertension and late-life depression may be because only individuals who

develop the most severe cerebrovascular disease develop clinical disease, i.e. that there is a threshold effect rather than a linear association between blood pressure and risk of developing depression. Other authors have argued that the failure to show an association between late-life depression and conventional cardiovascular risk factors in community cohorts, despite histopathological evidence of ischaemia in WMH, suggests non-conventional risk factors, associated with cerebral hypoperfusion, may be important in the pathogenesis of late-life depression (Vasudev et al., 2012). If this were true, aspects of cardiovascular autonomic control such as neurocardiovascular instability and BP and heart rate variability may be of importance. A small number of studies have investigated if depression is associated with NCVI .

1.8.2.2 Blood Pressure Variability and Depression

Kayano et al recently examined the association between anxiety (defined as a score >10 on the Hospital Anxiety and Depression Scale (HADS)) and diurnal variation among 120 hypertensive Japanese patients, mean age 67 years (Kayano et al., 2012). The group found that nocturnal and early morning BP were significantly higher in the anxiety group than in the control group. Odds of an existing anxiety disorder were significantly higher in the nocturnal risers than in the dippers. Furthermore, daytime and night-time BP variability were significantly greater in the anxiety group. Sunbul et al also found an association between dipping status and anxiety / depression scores (Sunbul et al., 2013). Hypertensive patients with a normal nocturnal BP dipping pattern had significantly lower HADS scores than non- dippers.

Kario examined the association between depression, anxiety and ABPM recordings in men and woman of working age (Kario et al., 2001). Depression was associated with a diminished diurnal variation in BP in men, but not in women. Interestingly this finding was independent of daytime activity or nocturnal sleep quality. In an older cohort, Scuteri et al found that after controlling for age, sex, and traditional cardiovascular risk factors, subjects with depressive symptoms (diagnosed on the Geriatric Depression Scale) had a significantly lower night-time SBP fall than non-depressed ones with a significantly higher occurrence of non-dipper status (Scuteri et al., 2009).

As all these studies are cross-sectional, it is currently impossible to establish conclusively the direction of association. Altered BP control may contribute to subsequent depression through cerebral small vessel disease, as hypothesised.

Alternatively, depression may result in altered mood, disturbed sleep and altered behaviour in turn causing changes in BP control.

1.8.2.3 Neurocardiovascular Instability and Depression

Two small cross-sectional studies have examined the association between orthostatic hypotension and depression (Vasudev et al., 2012, Colloby et al., 2011). Both studies showed greater systolic vasodepression on standing in older people diagnosed with depression than in age and sex matched controls. The depressed groups in both cases were recruited from a secondary care psychiatric service and had a history of current or previous major depressive episode.

It should be noted that cross-sectional studies examining the association between OH and depression are complicated by the use of medication. Anti-depressants, particularly tricyclic medication and selective serotonin reuptake inhibitors (SSRI) are recognised as having effects on the autonomic nervous system. Tricyclic anti-depressants have been associated with increased prevalence of OH and SSRIs are used as a treatment for disorders of the autonomic nervous system including OH.

A more recent population-based study compared Centre for Epidemiology Depression Scores (CED-S) among participants with symptomatic OH, asymptomatic OH and no OH. Participants with symptomatic OH had significantly higher CED-S than participants with asymptomatic OH or no OH (Regan et al., 2013). Participants in this study were not taking antidepressant medication. These findings suggest that symptoms suggestive of cerebral hypoperfusion are associated with depression.

Fewer studies have examined the association between carotid sinus hypersensitivity (CSH) and depression. In one study of 315 CSH patients, total Cornell score was significantly higher in participants with CSH than controls (Pearce, 2007). Similarly, the proportion of participants scoring 10 or more on the Cornell score (indicative of probable depression) was significantly greater in the CSH group.

To my knowledge there are no longitudinal studies examining the association between depression and OH or CSH.

1.8.2.4 Measures of Autonomic Function and Depression

Heart rate variability has been the most commonly used measure of autonomic function in studies examining the association between depression and cardiovascular autonomic nervous system function. Several studies have shown that heart rate variability is reduced in patients with depression, particularly low frequency heart rate variability, indicating withdrawal of parasympathetic control (Carney et al., 2001, Dauphinot et al., 2012, Koschke et al., 2009, Robinson et al., 2008, Vasudev et al., 2011).

Studies examining the association between HRV and depression are often complicated by confounding factors such as use of medications known to affect mood and the autonomic nervous system e.g. beta-blockers, SSRIs and the inclusion of participants with medical conditions associated with altered cardiovascular autonomic function and depression, e.g. myocardial infarction. Rotenberg et al performed a meta-analysis to establish the effect of depression on cardiovagal control (Rottenberg, 2007). Studies included in the primary analysis excluded patients who had health conditions that compromise vagal control or who took medications known to or likely to affect the autonomic nervous system, including antidepressants. The group concluded that depression is associated with reduced cardiovagal control, but that the effect is small. A more recent meta-analysis reviewing 19 studies including 673 depressed participants and 407 healthy comparison found that participants with depression had lower HRV than healthy control subjects, and depression severity was negatively correlated with HRV(Kemp et al., 2010).

Despite cross-sectional evidence for association between HRV and depression there is an absence of studies examining the longitudinal associations between cardiovascular autonomic function and mood. It is currently impossible to know if depression causes changes in HRV or alternatively if impaired HRV predates depression.

1.8.3 **Blood Pressure Homeostasis and Gait, Balance and Falls**

Impaired blood pressure control and NCVI are a frequently cited in guidelines as risk factors for falls in older people (NICE, 2013, Panel on Prevention of Falls in Older Persons and British Geriatrics, 2011, Beauchet et al., 2011). There are a number of plausible physiological mechanisms that may explain this association;

1. Sudden reduction in systemic BP may result in sufficient drops in cerebral hypoperfusion to induce syncope. It is recognised that over 20% of non-demented older people with syncope are amnesic to loss of consciousness (Shaw and Kenny, 1997). If no eyewitness history is available, these cases may be attributed incorrectly to falls rather than syncope.
2. Cerebral hypoperfusion insufficient to impair consciousness may be enough to result in a transient loss of coordination. In individuals with multiple risk factors for fall this may be sufficient to result in loss of balance.
3. As previously discussed, repetitive episodes of hypoperfusion are thought to contribute to the development of WMH (Pantoni and Garcia, 1997). Greater WMH volume is associated with impaired gait, balance and cognition (Willey et al., 2013, Kreisel et al., 2013, Callisaya et al., 2013, Soumaré et al., 2009, DeCarli, 2013). Impairment of gait and cognition are among the strongest risk factors for falls (Frith and Davison, 2013).

This final section of the introduction will review the association between blood pressure homeostasis, gait, balance and falls.

1.8.3.1 Blood Pressure Variability, Gait, Balance and Falls

Ambulatory blood pressure monitoring is often used in clinical practice to identify people whose fall may have been a result of chronic hypotension or recurrent drops in BP. Surprisingly, only a few studies have examined the association between ABPM profile and falls (Puisieux et al., 2000, Jonsson et al., 1990). Puisieux compared ABPM records in three groups; older patients with syncope, older patients with falls and an age-mated control group (Puisieux et al., 2000). There were no significant differences in BP variability or diurnal variation between groups. This is interesting as greater BP variability in response to common daily activities such as eating and standing has been associated with falls among nursing home residents (Jonsson et al., 1990). It should be noted that Jonsson et al included response to nitro-glycerine in their analysis.

1.8.3.2 Neurocardiovascular Instability, Gait, Balance and Falls

More attention has been paid to the association between NCVI and falls. Several prospective studies have examined the association between OH and falls. Results have been inconsistent (Tromp et al., 2001, Ooi et al., 2000, Campbell et al., 1989, Gangavati et al., 2011). Campbell et al found that OH was more common in female fallers than

non-fallers, but, after adjusting for age the association between OH and falls was no longer statistically significant (Campbell et al., 1989). Similarly, Tromp et al failed show an association between OH and falls in 1285 community-dwelling older people (Tromp et al., 2001). In a study of 844 nursing home residents, OH was not associated with falls among the total cohort. However, among individuals who had fallen in the prior 6 months, OH was associated with increased risk of falling (Ooi et al., 2000). The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study examined the association between OH and recurrent falls (>2 falls in 12 months). The study showed that OH by itself was not an independent risk factor for recurrent falls. However, OH at one minute in uncontrolled hypertensive people was a risk factor for falling (Gangavati et al., 2011).

A number of literature reviews have aimed to summarise risk factors for falls. Not surprisingly results have been inconsistent with some concluding OH is a risk factor for falls while others have not (Rubenstein, 2006, Ganz et al., 2007). McCarthy et al reviewed 16 studies examining the association between OH and falls in older people (McCarthy et al., 2010). Only four of the studies showed an association. The authors concluded the evidence for OH as a risk factor for falls is weak.

The discrepancies in these results in part reflect the vagaries of the current definition of OH. Studies have not consistently used the same methods of recording BP or recorded BP at the same intervals during the active stand. Studies using beat-to-beat monitoring instead of a sphygmomanometer find OH to be highly prevalent among the general population and have not shown an association between OH defined according to conventional criteria and falls (Romero-Ortuno et al., 2011a, Kerr, 2009). Romero-Ortuno et al did however show an association between initial OH (defined as a transient BP decrease, within 15 seconds after standing, of more than 40mmHg in SBP or more than 20mmHg in DBP, with symptoms of cerebral hypoperfusion) and falls(Romero-Ortuno et al., 2011a). Van Der Velde et al examined which time average of continuous-finger-blood-pressure measurement showed the best association between orthostatic hypotension and falls (Van Der Velde et al., 2007). Drops averaged over 5 seconds showed the strongest association. In their study, the odds ratio of a fall according to orthostatic hypotension using the 5 second average was 2.54 (95% CI: 1.37 - 4.71).

Symptoms may also be of clinical importance in defining the association between OH and falls. Graafmans et al showed that a history of dizziness on standing was associated with increased risk of falls (OR 2.1, 95% CI: 1.2 – 3.7) and recurrent falls (OR 2.1, 95% CI: 1.1 -4.2) even though orthostatic hypotension itself was not associated with falling (Graafmans et al., 1996). It should be noted that the definition of initial OH (found to be associated with falls) used by Romero-Ortuno included a requirement that participants had symptoms of cerebral hypoperfusion (Romero-Ortuno et al., 2011a). Similarly symptoms of cerebral hypoperfusion during active, stand rather than degree of vasodepression, have been shown to be associated with fall in cross sectional studies (McDonald, 2013).

Fewer studies have examined the association between carotid sinus hypersensitivity and falls. CSH and CSS are more common among individuals presenting to A&E with non-accidental falls than controls (Davies et al., 2001). Sachpekidis et al compared prevalence of CSH among controls, accidental fallers and individuals with unexplained falls presenting with fractured neck of femur and reported rates of 18.2%, 17.6% and 66.7% respectively (Sachpekidis et al., 2009). Ward et al reported a prevalence of CSH of 36% among individuals presenting with fractured neck of femur compared to 13% among individuals admitted for elective hip replacement (Ward et al., 1999). To date there have been no prospective studies examining the incidence of falls in people with CSH compared to controls. Studies examining the role of permanent pacing as a treatment to reduce falls in patients of carotid sinus syndrome have shown mixed results (Parry and Matthews, 2013). Un-blinded studies in younger cohorts suggest a possible benefit to pacing. However the only double blinded study in older individuals failed to show any benefit in the paced group, although this was underpowered(Parry et al., 2009).

The association between neurocardiovascular instability and gait and balance is poorly understood. Cross-sectional studies have shown that older fallers with OH spend more time in the stance phase than controls, but that gait variability does not differ between groups (Barrett et al., 2008). OH has been associated with poor performance on the Berg balance scale in diabetic individuals, and increased postural sway in patients with Parkinson's disease (Matinolli et al., 2009, Cordeiro et al., 2009). These studies are

small and there are no longitudinal studies examining the association between NCVI and future gait and balance problems.

1.9 **Summary and Aims**

In summary, impaired blood pressure and heart rate control have been associated with cognitive impairment, depression and falls in older adults. These clinical presentations have in turn also been associated with greater white matter hyperintensity volume in older people. There is histopathological evidence suggesting that these WMH may result from cerebral hypoperfusion. Most studies have been cross-sectional and there is an absence of comprehensive prospective studies simultaneously examining the long-term clinical and radiological associations of NCVI. Furthermore, beat-to-beat monitoring of BP and heart rate changes during tests of neurocardiovascular function are now routinely used in clinical practice. However, as most studies examining the long-term consequences of NCVI have used a sphygmomanometere the long-term consequences of disorders diagnosed using beat-to-beat techniques is not known.

The aim of this study is to establish the long-term relationship between neurocardiovascular function in later life and cognition, depression, falls and white matter damage. The thesis reports data from the ten year follow-up of a community cohort in whom cardiovascular autonomic function and the prevalence of NCVI was well characterised in 2002, using beat-to-beat monitoring. The cohort has undergone comprehensive follow-up in terms of repeat cognitive testing, assessment of mood, gait and balance and documentation of falls. Brain MRI has been used to quantify WMH volume. The association between baseline autonomic and neurocardiovascular function and each of these variables is discussed in separate chapters. A brief description of key methodological points is summarised at the beginning of each results chapter and supplements the methods described in chapter two. At the end of each chapter the key results are discussed and interpreted in the context of existing literature. In order to examine if loss to follow-up due to mortality has been associated with autonomic function and NCVI at baseline, a final section examines the association between cardiovascular autonomic function, and ten-year all-cause mortality in the entire baseline cohort.

Chapter 2 Methods

This is a longitudinal follow-up of a cohort initially recruited in 2002. The description of baseline methods is as described in Dr Simon Kerr's Thesis (Kerr, 2009).

2.1 Recruitment

Participants were first recruited in April 2002 from a single General Practice (GP) in the North East of England. Details of all patients registered with the practice are held on the GP electronic database. In order to participate in the study, individuals had to be aged 65 years or over at time of sampling and living independently in the community. Individuals living in nursing or residential care were excluded prior to sampling. At sampling 1517 individuals met these criteria. The sample population was sub-stratified by age and sex into four groups.

- Male aged <75
- Female aged <75
- Male aged ≥ 75
- Female aged ≥75

Computer generated random samples of 250 individuals were drawn from each group. Selected participants were sent a letter outlining the purpose of the study. Included with the letter was a response card and a prepaid envelope. Participants were given three options: 1) indication of interest in the study, 2) unwillingness to take part in the study, but consent to review of their G.P notes, 3) unwillingness to participate in the study. Where subjects failed to respond to the initial letter, a second invitation was sent. Subjects failing to respond to the second invitation were not re-contacted.

Three hundred and fifty two individuals participated in the study at baseline in 2002 / 2003 (35% of those invited). Between the initial assessment and the current study participants were invited to take part in two further assessments at two and five years follow-up. Participants who did not take part in these assessments were considered to have withdrawn from the study. Two hundred and nine individuals took part in the 2008 follow-up and were eligible participate in this study.

2.2 Baseline Clinical Assessment

2.2.1 History of Falls, Dizziness or Syncope

The number of falls, and/or episodes loss of consciousness in the preceding 12 months were recorded. Information regarding the cause of a fall or episode of loss of consciousness was sought and whether it had resulted in injury, attendance at an Accident and Emergency department or hospital admission.

2.2.2 Past Medical History

Past medical history was obtained by direct interview of the subject or subject and friend or relative if the participant was accompanied when they attended the assessment. Particular attention was paid to the presence or absence of cardiovascular and cerebrovascular disease and risk factors. Where possible, participants' answers were recorded as categorical "yes" or "no" responses. If participants were unsure of their past medical history, GP medical notes were reviewed.

Ischaemic heart disease was defined as a clinical history of angina or myocardial infarction. Participants were designated as having "cardiac disease" if they had any ischaemic heart disease, cardiac failure, an arrhythmia or previous rheumatic fever.

2.2.3 Social History

Smoking and alcohol history were recorded. For smokers and ex-smokers, pack years were recorded. A pack year is calculated by multiplying the number of packs of 20 cigarettes smoked per day by the number of years the person has smoked. For ex-smokers, the number of years since cessation was also recorded. The number of units of alcohol consumed per week was recorded. Age on leaving education and the number of years in education were noted.

2.2.4 Medication Use

Participants were asked to bring a list of all of their prescribed and over-the-counter medications with them to the baseline assessment. Medication history was recorded. Three composite variables were derived.

- *Cardioactive Medication*: participants were defined as taking a cardioactive medication if they were taking any antihypertensive medication, diuretic medication, antianginal, antiarrythmic, fludrocortiosone or midodrine

- *Anti-hypertensive medication*: participants were defined as taking an anti-hypertensive medication if they were taking any angiotensin converting enzyme (ACE) inhibitors, alpha blockers, beta blockers, calcium channel blockers, angiotensin type 2 receptor blockers and thiazides

- *Psychoactive medication*: participants were defined as taking a psychoactive medication if they were taking any typical neuroleptic, atypical neuroleptic, anti-cholinergic, cholinesterase inhibitor, tricyclic antidepressant, selective serotonin reuptake inhibitor, other antidepressant, anti-Parkinson's or other psychotropic medication.

2.2.5 **Physical Examination**

Height and weight were recorded and body mass index calculated. Pulse rate, rhythm and character were recorded. Heart sounds were auscultated and presence or absence of signs of peripheral or pulmonary oedema noted. Blood pressure was recorded in the semi-supine position after a period of rest using a standard sphygmomanometer.

2.2.6 **Gait and Balance Assessment**

Gait and balance were assessed using the Tinetti Performance Orientated Mobility Assessment (POMA) (Tinetti, 1986). Gait and balance are assessed separately. Subjects are asked to perform manoeuvres frequently encountered in normal day-to-day activities. There are several versions of the instrument reported in the literature with variation in items and scoring (Kopke and Meyer, 2006). The gait assessment used in this study was made up of nine manoeuvres. Each component was scored one point if it was "normal" and zero if it was abnormal or the subject was unable to complete the manoeuvre.

The balance scale was made up of 13 manoeuvres that assessed balance in the sitting and standing positions. The subjects' performance on each task was scored zero, one or

two depending on whether their ability was considered abnormal, adaptive or normal respectively.

2.3 **Baseline Neurocardiovascular Assessment**

All tests were carried out between 09.00 and 13.00 at a local day hospital. Participants were asked to refrain from coffee or nicotine from the previous evening and to have only a light breakfast prior to attending for the tests.

Autonomic function tests were carried out in a single bed treatment room to ensure a quiet environment. A three lead electrocardiogram (ECG) was used to monitor cardiac response to the test. Continuous beat-to-beat blood pressure was recorded from the hand using digital photoplethysmography (Portapress, TNO- Biomedical, Amsterdam). The subject's hand was supported at heart level during throughout all measurements.

Standard tests of autonomic function followed on directly from tests of heart rate variability. A minimum of two minutes rest occurred between each test to allow for recovery and explanation of the next test.

2.3.1 **Short-term (five minute) Heart Rate Variability**

Blood pressure and ECG data were recorded continuously while participants rested supine for ten minutes. The first five minutes of the data were discarded. The remaining data was digitised and stored on a laptop computer.

Two locally developed software packages were used to examine the recordings (CRISP 1.1 and Alpha 1.0). The programs identified a fixed point on the R wave, the fiducial point. Where there was unexpected variation in the R wave interval (>30%) the program automatically inserts an interpolated R wave based on the variation recorded in the preceding four R waves. Recordings were manually reviewed and any incorrectly identified R waves or incorrectly interpolated beats removed. The total number of beats was calculated and only recordings where ≤ 10% of the beats were interpolated or ectopic were included in the analysis.

Once recordings were reviewed and cleaned, mean RR interval and standard deviation of RR intervals were calculated for each recording. Power spectral analysis using a fast

Fourier transform calculated total power and divided RR intervals into characteristic frequencies; high frequency fluctuations (0.15-0.40 Hz), low frequency fluctuations (0.04-0.15 Hz) and very low frequency fluctuations (<0.04 Hz). The HF:LF ratio was also calculated.

2.3.2 **Heart Rate and Blood Pressure Response to Standing (Active Stand)**

After resting in the supine position subjects were asked to assume a standing position as quickly as possible and without assistance and maintain this position for 3 minutes or as long as possible. The recorded heart rate and blood pressure response to standing included the time assuming the upright position.

The heart rate response was defined as the 30:15 ratio (the ratio of the longest RR interval around the thirtieth beat to the shortest RR interval around the fifteenth beat after standing)

The blood pressure response was defined as the earliest sustained drop in systolic and diastolic pressure. The time to reach the nadir and time to recover to baseline were recorded for each blood pressure response.

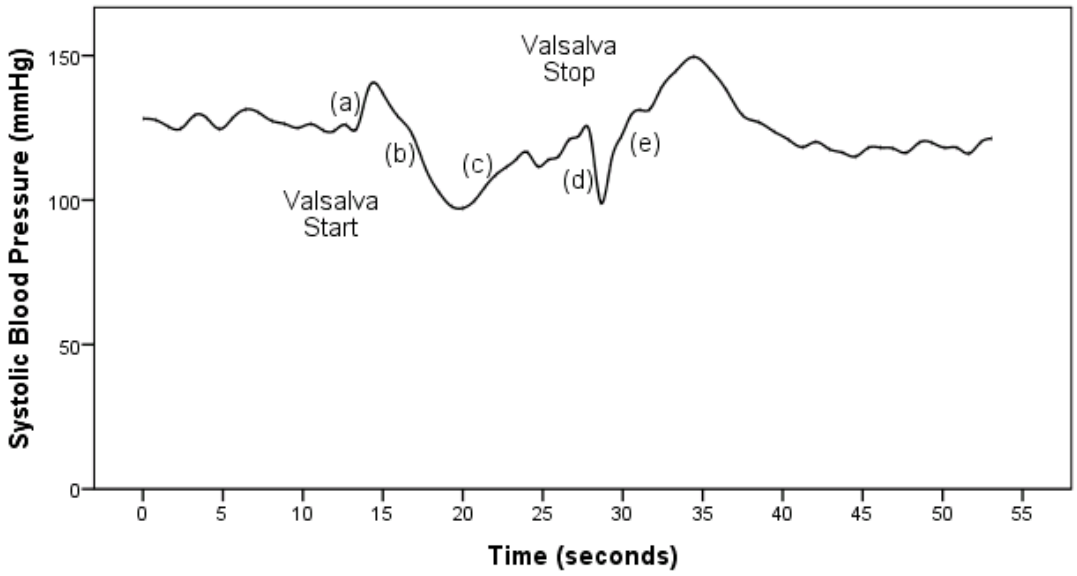
2.3.3 **Isometric Exercise**

Participants rose to a sitting position (with legs supported on the bed) from a supine position. They were instructed to maintain the positions for three minutes or as long as they could manage. Blood pressure response was taken as the difference between the average diastolic BP in the 20 beats before the procedure and the average diastolic BP in the 20 beats after the procedure

2.3.4 **Valsalva Manoeuvre**

Participants sat quietly on the edge of the bed then blow into a disposable mouthpiece to a pressure of 40mmHg for 15 seconds. A bar scale and digital clock, shown on the laptop screen, gave visual feedback and helped aid participants to maintain the necessary pressure for the required duration. After the test, participants were instructed to sit quietly for the next 30 seconds to avoid contaminating the reflex. The manoeuvre was repeated three times.

Figure 2-1 Systolic Blood Pressure Response to Valsalva Manoeuvre (adapted from data provided Dr James Frith (Frith, 2011))



The Valsalva manoeuvre has 4 phases:

- *Phase I*: Blood is expelled from the thoracic vessels by the increase in intrathoracic pressure (a).
- *Phase II:*
    - *Early*: The increase in intrathoracic pressure causes a reduction of venous return, lowering the preload and BP (b).
    - *Late*: The baroreceptor reflex is activated, causing vasoconstriction and a tachycardia, raising BP towards normal (c).
- *Phase III*: As intrathoracic pressure suddenly drops there is pooling of blood in the pulmonary vessels, causing a further drop in BP (d).
- *Phase IV*: With venous return restored there is an overshoot, as compensatory mechanisms continue to operate (e).

The ratio of the longest RR interval in the first 30 seconds after the manoeuvre (phase IV) to the shortest RR interval during the manoeuvre (phase III) was then measured.

Blood pressure response was the difference between the phase II trough and the phase IV overshoot. The best BP response and largest Valsalva ratio were used for the analysis.

2.3.5 **Cold Pressor**

While seated, participants were instructed to fully submerge their hand in a bowl containing a mixture of ice and water. They were asked to keep their hand submerged for a maximum of one minute, or as long as they could tolerate. They were asked to keep their hand still with the palm open.

Blood pressure response was the difference the mean DBP in the 20 beats before placing their hand in water and the mean DBP in 20 beats immediately afterwards.

2.3.6 **Heart Rate Response to Deep Breathing**

Subjects lay supine on the couch and were instructed to breathe deeply and evenly at a rate of six breaths per minute. To help the subject maintain the correct breathing rate, the researcher counted the five seconds inspiration and expiration for each cycle.

The maximum and minimum heart rates during each breathing cycle were measured. The mean of the differences for six breathing cycles was calculated

2.3.7 **Defining Normal Ranges for Autonomic Function Tests**

Autonomic function for each participant was categorised according to Ewing criteria. Two modifications were made to these criteria. Firstly, blood pressure response to isometric exercise was measured using the active sit as a stimulus rather than sustained handgrip as described by Ewing and Clark. Secondly age-appropriate normal ranges were used to define abnormal, borderline and normal response.

The normal ranges for response to autonomic function tests defined by Ewing and Clark were developed in individuals aged 16 -65 years. As previously discussed, response to autonomic function tests are highly correlated with age (Ewing et al., 1985). As participants in this study were aged 65 years and over at baseline, age-appropriate normal ranges were defined at baseline based on response to autonomic function tests observed in a normal subsample. The normal subgroup was defined by excluding all subjects with a documented history of cardiovascular disease, diabetes, cerebrovascular disease, Parkinson's disease, dementia, or using cardiac or psychoactive medication. The fifth and ninety-fifth percentiles from the normal subgroup were used to quantify abnormal, borderline, and normal responses for each autonomic tests.

Overall function was then categorised in accordance with Ewing Criteria. Autonomic function was considered normal if all tests were normal or abnormal if one or more tests were abnormal.

2.3.8 **Carotid Sinus Massage**

Carotid sinus massage (CSM) was performed in consenting participants without contraindication. Contraindications included myocardial infarction, stroke or transient ischaemic attack in the preceding three months, history of significant carotid stenosis, carotid bruit or clinical suspicion of carotid stenosis.

Participants underwent CSM at the end of the neurocardiovascular assessment. Subjects rested supine for five minutes before CSM. CSM was performed by the same doctor in every case. The point of maximum pulsation over the carotid artery, between the angle of the mandible and thyroid cartilage was identified. Firm longitudinal massage was applied for five seconds. Heart rate and BP were recorded continuously as described above. CSM was stopped before five seconds if >3 seconds asystole was recorded. CSM was first performed on the right hand side in the supine position, followed by the left hand side in a 70 degree head-up tilt, then right standing and finally left head-up tilt position. One minute rest was allowed between each period of massage.

After each episode, participants were asked to report dizziness, light-headedness, or symptoms suggestive of pre syncope and the examiner noted any syncopal episodes. A maximum of 4 periods of CSM were performed. However, if syncope was observed in conjunction with a hypersensitive response, further CSM was not performed.

Carotid sinus hypersensitivity was defined according to standard criteria

- Cardio inhibitory: ≥ 3 seconds asystole
- Vasodepressive : ≥ 50 mmHg drop in systolic BP
- Mixed: both of the above

2.4 **Twenty-four Hour Ambulatory Blood Pressure Monitoring**

Consenting participants were fitted with a twenty-four hour blood pressure monitor (Spacelabs 90207 – Spacelabs Medical Inc, Redmond, Washington USA). An

appropriate sized cuff was fitted to the non-dominant arm. Subjects were instructed to relax their arm where possible when the cuff was inflating and during the one-two minutes while the reading was calculated. A test reading was taken at the time of monitor reading. Monitors were programmed to take a BP recording every 30 minutes during the day (7 am to 10 pm) and every hour overnight (10 pm to 7 am). If the monitor failed to obtain a BP recording on the first attempt, it would automatically retry the measurement 1-2 minutes later.

Three time periods were examined: daytime (10 am -8 pm), night-time (midnight – 6 am) and the full 24-hour period. Only studies with at least 16 recordings within 24-hours were included in the analysis. Studies with 10 or more daytime recordings were deemed suitable for daytime analysis and studies with five or more night-time recordings were deemed suitable for nocturnal analysis.

Minimum, mean and maximum (with standard deviations) systolic and diastolic blood pressure were calculated for each time period as were mean arterial pressure and heart rate. Blood pressure variability was calculated using the standard deviation of the mean systolic and diastolic blood pressures for each time period. Diurnal variation was calculated by the difference between day and night-time mean BP (i.e. day mean BP minus night mean BP) expressed as a percentage of the day mean.

Hypertension was defined according to NICE guidelines as mean daytime BP >135/58 mmHg. In some studies, participants taking antihypertensive medication or who report a past medical history of hypertension are also classed as hypertensive. We chose not apply these methods in this study because self reported history of hypertension may be inaccurate in older people and many medications with antihypertensive properties are frequently prescribed to normotensive patients for other indications for example diuretics and beta blockers(Bush et al., 1989).

2.5 Assessment of Activities of Daily Living

2.5.1 Nottingham Activities of Daily Living Scale

The Nottingham Activities of Daily Living Scale is a widely used self-assessment of functional independence. It includes 22 activities relevant to daily living divided across

four sections: kitchen, mobility, domestic and leisure activities. Subjects are asked which activities they have "actually" done over the preceding week (not which activities they think they could do). Four possible responses can be given; "on my own", "on my own with difficulty", "help", "not done". A score of one is assigned if they have done the activity on their own or on their own but with difficulty. A score of 0 is assigned if they have needed help or not done the activity (Nouri and Lincoln, 1987, Lincoln and Gladman, 1992). Scores can be derived for subsections or summed to give an overall score.

2.5.2 **Bristol Activities of Daily Living Scale**

The Bristol activity of daily living scale has been validated for use in patients with cognitive impairment. The assessment is an informant rated questionnaire covering 20 daily activities. Items are rated on a four-point scale from totally independent (0) to totally dependent (3), with an additional "not applicable" option. The scale has a minimum score of 0 indicating total independence and a maximum score of 60, indicating total dependence (Bucks et al., 1996).

2.6 **Baseline Assessment of Cognitive Function**

Baseline cognitive assessment was performed in participants' homes by a trained nurse.

2.6.1 **MMSE**

The Mini Mental State Examination is a 17 item cognitive assessment covering various cognitive domains (including orientation, memory, attention and language) (Tombaugh and McIntyre, 1992, Folstein et al.). Maximum score achievable is 30. Higher scores indicate better cognitive function. Deterioration in cognitive function is indicated by decreasing scores over repeated tests (Folstein et al.). A score of 23 or less is generally thought to indicate cognitive impairment although cut offs are influenced by age and education (Tombaugh and McIntyre, 1992).

2.6.2 **CAMCOG-R**

The CAMCOG-R is part of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Roth et al., 1999). It comprises 67 items of which 59 contribute to the total score. Items contribute between one and six points to the total score. The maximum potential total score is 105. The test assesses orientation,

language, memory, attention, praxis, abstract thinking, perception and calculation. Two composite subscores can be obtained: the memory subscore (the combined remote, recent and learning memory scores) and an executive subscore (which includes two additional questions added when the CAMCOG was revised to form the CAMCOG-R). The maximum, attainable memory and executive subscores are 27 and 28 respectively.

2.6.3 **Computerised Drug Research Battery (CDR)**

The Cognitive Drug Research (CDR) Battery is a computerised test designed to test components of executive function including cognitive process speed, attention and concentration. Each test was carried out using a laptop computer and response pad with two buttons "yes" and "no". Instructions were given to participants in a standard manner and each session was preceded by a standardised training period. Participants completed three tests;

- Simple reaction time
  Subjects were instructed to place their finger over the "yes" button and instructed to press the button as quickly as possible every time the word yes appeared on the screen. There were 30 stimuli.
- Digit vigilance
  A fixed number was presented on the right hand side of the screen. A series of numbers appeared one after another on the left of the screen. Participants were instructed to press the "yes" button as quickly as possible each time the two numbers on the screen matched.
- Choice reaction time.
  The words "yes" or "no" appeared individually on the screen at random intervals. Subjects were instructed to press the matching word on the response pad as quickly as possible each time "yes" or "no" appeared on the screen.

All data was processed centrally by CDR, Reading, Berkshire, England.
In addition to the raw scores, two derived measures were calculated

- Cognitive reaction time: the choice reaction time minus the simple reaction time
- Power of attention: the sum of the simple reaction time, choice reaction time and the digit vigilance reaction time.

2.6.4 **Cornell Depression Scale**

The Cornell depression scale was designed to assess depression in people with cognitive impairment. A semi-structured interview is conducted with the study participants and separately with a relative or friend who has regular contact with the participant. The scale enquires about symptoms in the two weeks preceding the interview. Nineteen symptoms are reviewed. Each item is scored for its severity (zero if not a problem, one if it is a mild or intermittent problem, two if it is a severe or constant problem). The final score on the scale represents the interviewer's clinical impression rather than the response of the informant or the participants. A score of 10 indicates probable depression. Scores of less than six are unlikely to be associated with depression.

2.7 **Recruitment of 2011 Follow-up Cohort**

To examine the long-term associations of neurocardiovascular instability, participants were reviewed in 2011 /2012. The general practice computer database was reviewed to identify if participants were alive and still registered with the participating GP. If a study participant had died, the date of their death, as documented in the GP notes, was recorded. All surviving individuals, who had participated in year 5 follow-up and were still registered with the participating General Practice, were invited to participate in this phase of the study. Participants who had previously withdrawn from the study were not contacted.

Potential participants were sent a letter outlining the purpose of this phase of the study. The letter included a patient information sheet describing the study and a copy of the consent form they would be asked to sign. The letter explained that a member of the research team would contact them in the next few weeks to answer any questions the participant may have and to establish if they would be interested in taking part in this follow-up.

Letters were sent out in a staggered fashion. Forty participants were contacted at a time, grouped by postcode. Two weeks after the letters had been posted a member of the team contacted potential participants by phone, explained the study, answered questions and booked an appointment to meet with individuals who wished to take part.

2.8 Consent to Participation in Follow-up Study

To obtain participants' consent the researcher visited all potential participants in their own home. The interviewer confirmed that the participant had received and read the participant information sheet and consent form. The researcher repeated the explanation of the study that had been given over the phone and individuals were given a further opportunity to ask questions about the study.

In order to ensure participants had capacity to consent to the study a, "consent pathway" was followed. Potential participants were first asked if they were happy to take part in the study. If they agreed to take part they were asked three further questions

- "In a few words, can you tell me what the study is about?"
- "Can you tell me what would happen to you if you agreed to take part in this study?"
- "What will you do if you change your mind and decide you no longer wish to participate in the study"

Patients who had understood the study were asked to give written informed consent.

If the researcher felt the participant had not fully understood the study, the researcher explained it again, offered the participant an opportunity to ask further questions and rechecked their understanding. Where the researcher remained concerned that the participant did not fully understand the study and lacked capacity, a personal consultee was consulted. A personal consultee could be a relative or close friend of the participant. In order to act as a personal consultee they needed to be able to advise the researcher about the participants likely wishes and feelings in relation to the study.

If a personal consultee was required, an additional information sheet explaining the role of a personal consultee was provided. Personal consultees were asked to sign a declaration stating that, as far as they were aware, the participant would not object to participating in the study.

2.9 Follow-up Clinical Assessment

The follow-up study consisted of two home visits. At the first visit a clinical history and examination were carried out in accordance with baseline protocol (section 2.2, page 40). Neurocardiovascular assessment was not carried out at follow-up with the

exception of ambulatory blood pressure monitoring which was carried out as described in section 2.4, page 46.

2.10 **Follow-up Cognitive Assessment**

The second visit was conducted in participant's homes. Where possible, friends and family members were asked to leave the room during testing to avoid distractions. In accordance with baseline assessments, MMSE, CAMCOG, and Cornell Depression Score were repeated (see section 2.6 Assessment of Cognitive Function, Page 48).

The Cognitive Drug Research Battery was unavailable at ten year follow-up as the manufacturer was no longer supporting analysis of the data. Simple reaction time, choice reaction time and digit vigilance reaction time were assessed using The Computerised Mental Performance Assessment System (COMPASS) (Northumbria University, Newcastle, UK). Data using the two programs are not directly comparable. The Cognitive Drug Research Battery cleans long responses (≥2.5 standard deviation away from the mean for an individual participant). As a result, reaction times, obtained using COMPASS, generally show wider variability than those obtained using CDR. Consequently, change in reaction times over the follow-up period, could not be accessed in this study.

Participants' ability with activities of daily living at ten years were assessed using the Nottingham and Bristol ADL scales (2.5 Assessment of Activities of Daily Living, page 47).

2.11 **Magnetic Resonance Imaging**

At the 2011/ 2012 examination all participants without contraindications were invited to undergo magnetic resonance scan of the brain. Participants who agreed to MRI were asked if they had any of the following; cardiac pacemaker, aneurysm clips, stents, heart valve replacement, cochlear implant, shunts, spinal stimulation wire or other implants. Where a participant answered yes, their relevant medical notes were reviewed to find the make and model of the device. MRI compatibility of the device was checked with the manufacturer. If T3 MRI compatibility could not be confirmed, or if it was found to be unsafe the participant was excluded from the MRI portion of the study. Participants were also excluded from this phase of the study if they reported previous injury with metal fragments such as shrapnel or shot. Relevant contraindication to inclusion in the

MRI portion of the study included claustrophobia and inability to lie flat for 40 minutes due to either pain or breathing difficulties. Participants were required to complete a safety questionnaire immediately before the MRI scan to ensure there had been no changes to their health.

All scans were performed in the same T3 MRI scanner (Intera Achieva scanner; Philips, Eindhoven, the Netherlands) at the Newcastle Magnetic Resonance Centre, Newcastle University, UK.

Images acquired included a T1-weighted volumetric sequence covering the whole brain (MPRAGE, sagittal acquisition, slice thickness = 1.2 mm, voxel size = 1.15 × 1.15 mm; repetition time = 9.6ms; echo time=4.6ms; flip angle = 8 degrees; SENSE factor = 2) and FLAIR (TR = 11,000ms; TE = 125ms; inversion time = 2,800ms; SENSE factor = 1.5; voxel size = 1.02 × 1.02; 50 slice thickness = 3 mm).

Volumetric estimates of global, periventricular, and regional WMHs were obtained for each subject. First, statistical parametric mapping was used to partition T1 scan of the subjects into grey, white, and cerebrospinal fluid images. From the segmentations, the total brain volume of each subject was calculated from grey matter plus white matter. Second, each subject's FLAIR scan was co-registered to its corresponding T1 image in native space, and WMHs were identified using a validated automated segmentation method (Firbank et al., 2004).

Each scan was visually checked for accuracy by two trained raters, blinded to the participants' clinical characteristics. Total volume of white matter hyperintensities and volume of periventricular white matter hyperintensities were calculated. In addition, volumes of hyperintensities in each lobe were calculated.

2.12 **Summary of Study Time Table**

The table below highlights the key stages of the study and the individuals responsible for data collection and analysis.

Figure 2-2 Summary of Study Time Table and Personnel Responsible for Assessment and Analysis

Year	Assessment	Personnel
2002-2004	Clinical Assessment	Simon Kerr
	Autonomic Function Test and Test of NCVI	Simon Kerr
	Cognitive Testing	Michelle Widdrington
	Baseline Analysis	Simon Kerr
2005 Follow-up	Cognitive Testing	Michelle Widdrington
2007 Follow-up	Cognitive Testing	Michelle Widdrington
2011 Follow-up	Clinical Assessment	Claire McDonald
	Cognitive Testing	Claire McDonald
	Magnetic Resonance Imaging and Processing	Newcastle Magnetic Resonance Centre
	Visual inspection of Magnetic resonance scans	Claire McDonald Ieuan Lewis
	Follow-up Analysis	Claire McDonald

2.13 **Statistical Methods**

The long-term associations of NCVI and autonomic dysfunction are the focus of this thesis; consequently, only follow-up data from the year 10 assessments will be analysed here.

Statistical methods relevant to all results chapters are described here. More detailed descriptions of statistics relevant to individual chapters are given at the beginning of each chapter.

All data was analysed using Statistical Package for Social Science (SPSS) version 19. For all tests the level of statistical significance was set at <0.05.

2.13.1 **Responses to active stand, carotid sinus massage and autonomic function tests have been classified as a categorical or continuous hemodynamic response. For example the response to active stand may be categorical if it is calcified according to the presence or OH or absence OH defined according to standard criteria. The term continuous haemodynamic response is used when BP or HR respone to a stimulus has been used as a continuous variable in the analysis e.g. in the case of active stand where the size of the systolic BP response is used as an explanatory variable or covariate. All BP and HR measurments recorded in this study were recorded using beat to beat recordings. Distribution of Data**

Frequency distributions of continuous data were examined to assess if data were normally distributed. In addition the Kolmogorov Smirnov statistic and associated P value were used assess if data were normally distributed.

Normally distributed data are described using the mean and standard deviation. Non-parametric data are described using the median and inter quartile. In some rare cases data was skewed such that 25^{th}, 50^{th} and 75^{th} percentile were identical, in these cases range has been used in place of interquartile range.

2.13.2 **Comparison of Data between Samples**

2.13.2.1 Categorical data

Chi square test was used to test for differences in distribution of categorical observations between two groups. For small samples that violated the assumptions of the Chi square test Fisher's exact test was used.

2.13.2.2 Continuous data from two independent groups

Normally distributed data were analysed using the independent t-test

Non-parametric data were assessed using Mann- Whitney U test.

2.13.2.3 Continuous data from two related samples

Normally distributed data were analysed using paired t-test

Non-parametric data were assessed using Wilcoxon Signed Ranks test.

2.13.2.4 Association between two continuous variables

The associations between two continuous variables were initially assessed using correlation. Where data were normally distributed Pearson's correlation co-efficient was used. If data were not normally distributed Spearman's correlation co-efficient was used to assess the significance of the correlation.

2.13.2.5 Association between categorical dependent variables and linear explanatory variable.

Binary logistic regression was used to assess the association between linear explanatory variables and categorical dependent variables.

2.13.2.6 Association between multiple explanatory variables and a dependent variable

Where the dependent variable was continuous, multi-linear regression was used to assess the association between multiple linear and categorical explanatory variables and a single continuous dependent variable. Where the dependent variable was categorical binary logistic regression with multiple explanatory variables was used.

2.14 **Ethical Approval**

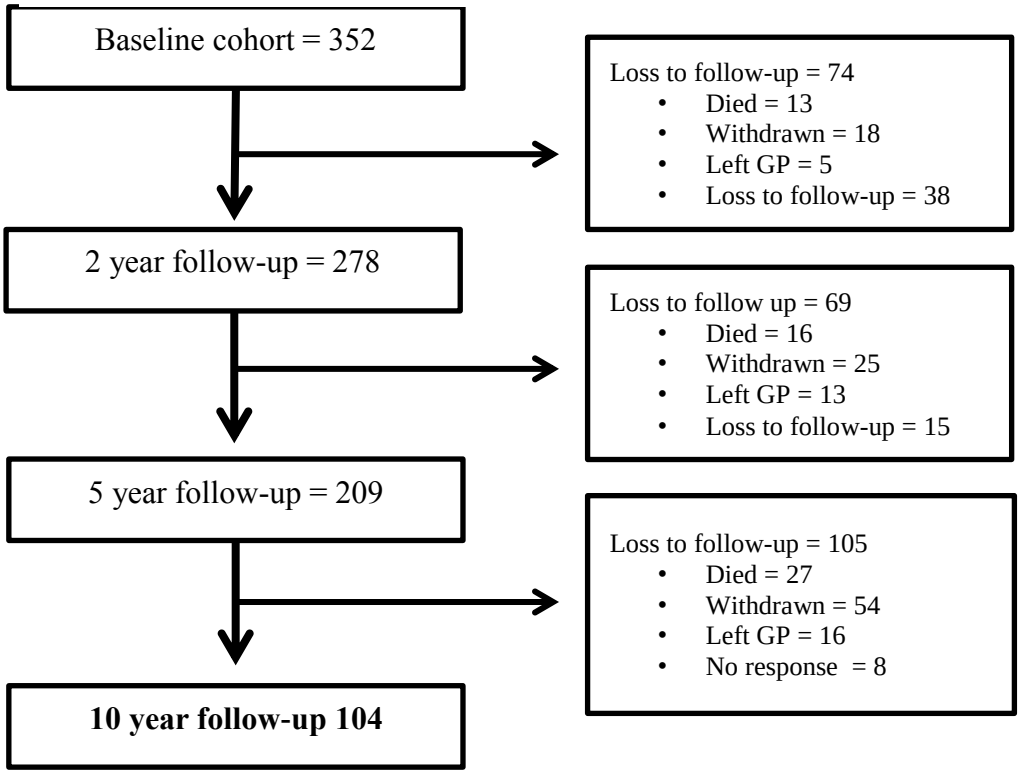
Ethical approval for the baseline study was provided by the County Durham and Darlington Local Research Ethics Committee in February 2002. Ethical Approval for the Follow-up study was granted by the Nation Research Ethics Service Committee North East- Newcastle and North Tyneside one in August 2011.

Chapter 3 Description of the Cohort Participating in Ten Year Follow-up

3.1 Recruitment to Ten Year Follow-up

Review of GP medical records in October 2011 revealed that of the 209 individuals who participated in five-follow-up, 27 had died and 16 were no longer registered with the general practice. Of the remaining 166 individuals, 54 declined to participate in this phase of the study and eight could not be contacted, despite two letters and three phone calls. Thus 104 individuals consented to participate in this follow-up phase (Figure 3-1 Flow Chart of Patient Recruitment and Follow-up). Follow-up participants' median age was 79 (range 74-92) and 55% were male.

Figure 3-1 Flow Chart of Patient Recruitment and Follow-up



3.2 Comparison of Ten Year Follow-up Participants and Participants Lost to Follow-up

3.2.1 Comparison of Demographics and Baseline Clinical Characteristics

Data from the baseline study was used to compare baseline characteristic of the 104 individuals participating in this follow-up with the 248 individuals lost to follow-up. Follow-up participants were significantly younger than non-participants [median age at baseline 70 years (range 65, 83) versus 74 years (65, 93) respectively ($P < 0.001$)].

Baseline clinical characteristics and cardiovascular risk factors for the two groups are shown in Table 3-1. The groups were well matched in terms of sex, smoking status and alcohol use. There were no significant differences in the proportion of participants reporting a past medical history of hypertension, diabetes, ischaemic heart disease (IHD), cerebrovascular disease (CVD), peripheral vascular disease and hyperlipidaemia at baseline. Use of antihypertensive medication, cardioactive medication and psychoactive medication were similar between the two groups at baseline.

Table 3-1 Baseline Characteristics for Individuals Participating in the Ten Year Follow-up and Non-participants.

Variable	Participants N = 104	Non- participants N = 248	P
	Frequency (%)	Frequency (%)	
Sex (male)	57 (55)	143 (58)	0.62
Smoker at baseline	8 (7.7)	21 (8.4)	0.81
Ex-smoker at baseline	65 (63)	147 (59)	0.57
Alcohol use at baseline	73 (61)	164 (66)	0.40
Past Medical History at Baseline			
Ischaemic heart disease	22 (21)	68 (27)	0.22
Hypertension	33 (32)	89 (39)	0.46
Diabetes	4 (3.8)	19 (7.6)	0.24
Cerebrovascular disease	8 (7.6)	31 (13)	0.19
Peripheral vascular disease	6 (5.7)	31 (13)	0.06
Hyperlipidaemia	36 (34)	74 (30)	0.38
Pacemaker	0 (0)	3 (1.2)	0.56
Medication Use at Baseline			
Any antihypertensive medication	48 (46)	113 (46)	0.92
Any cardioactive medication	51 (49)	134 (45)	0.39
Any psychoactive medication	15 (14)	46 (19)	0.35

3.2.2 **Comparison of Baseline Falls History**

Baseline characteristics in terms of history of falls, recurrent falls and injurious falls did not significantly differ between year ten participants and participants lost to follow-up (Table 3-2).

Table 3-2: Prior Symptoms of Falls, Syncope and Dizziness at Baseline for Year 10 Follow-up Participants and Non-Participants

Variable	**Follow-up Participants N = 104**	**Non- participants N = 248**	**P**
	Frequency (%)	**Frequency (%)**	
Faller	45 (43)	116 (47)	0.55
Recurrent Falls	10 (9.6)	31 (13)	0.59
Injurious Falls	20 (19)	50 (20)	0.89
	Median (range)	**Median (range)**	
Number of falls in 12 months	0 (0 -100)	0 (0-50)	0.96

3.2.3 **Comparison of Baseline Tinetti Gait and Balance Scores**

At baseline, compared to follow-up participants, participants lost to follow-up performed more poorly on Tinetti assessments of balance (Table 3-3). Although the median Tinetti gait scores at baseline for the two groups were similar the range of Tinetti scores was significantly wider for the group of individuals not participating in follow-up assessment.

Table 3-3: Baseline Tinetti scores for Year 10 Participants and Non-Participants

	Year 10 Participants N=104	**Non- participants N = 248**	**P**
	Median (range)	**Median (range)**	
Tinetti Balance	25 (12, 26)	24 (3, 26)	0.001
Tinetti Gait	9 (6, 9)	9 (0, 9)	0.002

3.2.4 **Comparison of Baseline Activity of Daily Living Scores**

Similarly, although the median ADL scores at baseline were similar for the two groups, individuals not participating in the follow-up examination had a significantly wider distribution of scores (Table 3-4).

Table 3-4 Comparison of Baseline ADL scores for Year 10 Follow-up Participants and Non-Participants

	Follow-up Participants N=104	**Non- participants N = 248**	**P**
	Median (range)	**Median (range)**	
Bristol ADL	0 (0, 6)	0 (0, 26)	<0.001
Nottingham ADL	22 (15, 22)	21 (8, 22)	<0.001

3.2.5 **Comparison of Baseline Cognitive Function**

Three hundred and thirteen individuals underwent cognitive testing at baseline. All ten year follow-up study participants had undergone full cognitive testing at baseline. Median ages on leaving education and median years in education were the same for participants and non-participants; however, distribution of data differed significantly, with greater numbers of non-participants leaving school at an earlier age, with fewer years in education (Table 3-5).

Compared with participants lost to follow-up, follow-up participants performed significantly better on MMSE and CAMCOG assessments at baseline. Comparing CDR results for follow-up participants and non-participants revealed that non-participants had significantly longer reaction times on the choice reaction time tests, digit vigilance reaction time test and tests of power of attention, indicating poorer cognition. Simple reaction times and cognitive reaction times at baseline did not differ significantly between follow-up participants and non-participants. Baseline Cornell depression scores did not differ between follow-up participants and non-participants (Table 3-5).

Table 3-5: Baseline Cognitive Function for Year 10 Follow-up Participants and Non-participants

Variable	Year 10 Participants N = 104	Non- participants N = 209	P
	Median (range)	**Median (range)**	
Age on leaving education	15 (14, 26)	15 (11, 25)	**<0.01**
Years in education	10 (9, 21)	10 (6, 20)	**<0.01**
MMSE	29 (25, 30)	28 (20, 30)	**<0.01**
CAMCOG Total Score	97 (92,103)	94 (64, 104)	**<0.01**
CAMCOG Memory Score	24 (18, 27)	23 (7, 27)	**<0.01**
CAMCOG Executive Score	22 (14, 28)	19 (8, 27)	**<0.01**
Simple Reaction Time (ms)	332 (219, 987)	351 (221, 1611)	**0.05**
Choice Reaction Time (ms)	511 (371, 801)	537 (374, 1125)	**<0.01**
Digit Vigilance (ms)	446 (339, 707)	474 (357, 746)	**<0.01**
Power of attention (ms)	1298 (1046, 2270)	1367 (1020, 2786)	**<0.01**
Cognitive Reaction Time (ms)	161 (-341, 348)	180 (-913, 629)	0.14
Cornell depression scale	2 (0, 26)	3 (0, 13)	0.74
	Frequency (%)	**Frequency (%)**	
Cornell depression scale >10	8 (8)	15 (7)	0.86
MMSE ≤24	0	6 (3)	0.18
CAMCOG ≤80	0	15 (7)	**<0.01**

3.2.6 **Comparison of Baseline Ambulatory Blood Pressure Recordings.**

Three hundred and forty six participants underwent 24-hour ambulatory blood pressure monitoring (ABPM) at baseline. Of these, 338 had a minimum of 16 recordings over the 24-hour period, 333 had ten or more daytime recordings, and 311 had five or more nocturnal recordings.

Incidence of hypertension on ABPM, at baseline as defined by NICE (BP>135/85) did not significantly differ between follow-up participants and non-participant (45% versus 48% respectively, P=0.51). Mean daytime systolic BP was lower for follow-up participants than non-participants, but this did not quite reach statistical significance

(P=0.07) (Table 3-6). Daytime systolic and diastolic variability however were significantly greater for non-participants than participants (Table 3-6). Mean nocturnal mean systolic BP was significantly lower for follow-up participants versus non-participants (Table 3-7). Mean 24-hour mean systolic BP was lower in follow-up participants than non-participants (Table 3-8).

Table 3-6: Baseline Daytime ABPM results for Ten Year Follow-up Participants and Non -participants

Variable	**Follow-up Participants**	**Non-participants**	**P**
	Mean (SD)	**Mean (SD)**	
DAY	**N=101**	**N=231**	
Mean SBP (mmHg)	132 (15.8)	135 (14.4)	0.07
Mean DBP (mmHg)	76 (8.0)	76 (10)	0.60
SD SBP (mmHg)	11 (3.4)	13 (4.2)	**0.02**
SD DBP (mmHg)	7.8 (2.3)	8.4 (2.4)	**0.04**

Table 3-7 Baseline nocturnal ABPM results for Ten Year Follow-up Participants and Non-participants

Variable	**Follow-up Participants**	**Non-participants**	**P**
	Mean (SD)	**Mean (SD)**	
Night	**N=91**	**N=220**	
Mean SBP (mmHg)	116 (13.1)	120 (16.3)	**0.01**
Mean DBP (mmHg)	63 (8.2)	64 (8.4)	0.38
SD SBP (mmHg)	9 (3.7)	9 (3.9)	0.68
SD DBP (mmHg)	7 (2.9)	7 (3.0)	0.87

Table 3-8 Baseline 24-hour ABPM results for Ten Year Follow-up Participants and Non-participants

Variable	Follow-up Participants	Non-participants	P
	Mean (SD)	**Mean (SD)**	
24-hour	**N = 103**	**N = 235**	
Mean SBP (mmHg)	127 (14.1)	130 (14.1)	**0.04**
Mean DBP (mmHg)	72 (8.9)	72 (7.5)	0.92
SD SBP (mmHg)	13 (3.3)	14. (3.8)	0.08
SD DBP(mmHg)	9.5 (2.3)	9.7 (2.3)	0.46

Comparing participants with non-participants did not reveal any statistically significant differences in systolic or diastolic diurnal variation between groups (Table 3-9).

Table 3-9 Diurnal Variation at Baseline for Year 10 Follow-up Participants and Non-Participants

Variable	Follow-up Participants	Non-participants	P
	Mean (SD)	**Mean (SD)**	
Diurnal variation	**N=89**	**N=213**	
Systolic %	0.11 (0.08)	0.11 (0.09)	0.93
Diastolic %	0.16 (0.09)	0.15 (0.08)	0.48

3.2.7 **Comparison of Response to Active Stand at Baseline**

Active stand was performed in 318 participants at baseline. Of the 104 participants who underwent follow-up examination at ten years, 98 had results available from baseline active stand. Prevalence of OH as defined by the American Academy of Neurology and subtypes of OH did not significantly differ between those participating in the follow-up and those not participating. Similarly, systolic or diastolic; baseline blood pressure, nadir reached during stand or degree of vasodepression did not significantly differ between the groups (Table 3-10).

Table 3-10: Response to Active Stand at Baseline for Year 10 Participants versus Non-Participants

Variable	**Follow-up Participants N = 98**	**Non- participants N = 220**	**P**
	Frequency (%)	**Frequency (%)**	
OH Positive	80 (82)	181 (82)	0.89
Systolic OH Positive	63 (64)	146 (66)	0.72
Diastolic OH Positive	71 (72)	154 (70)	0.66
	Mean (SD)	**Mean (SD)**	
Systolic Nadir (mmHg)	113 (27.3)	118 (20.1)	0.12
Diastolic Nadir (mmHg)	47 (14.1)	47 (13.0)	0.91
Systolic Vasodepression (mmHg)	28 (18.0)	25 (17.4)	0.18
Diastolic Vasodepression (mmHg)	15 (9.5)	28 (18.1)	0.93

3.2.8 **Comparison of Response to Carotid Sinus Massage (CSM) at Baseline.**

Two hundred and seventy two individuals consented to carotid sinus massage at baseline. Of the 104 assessed at ten year follow-up, 90 consented to CSM at baseline. There was no significant difference in incidence of CSH or CSH subtypes between follow-up participants and non-participants. Maximum RR interval post CSM and maximum delta RR were lower in follow-up participants than non-participants. Vasodepression and systolic nadir post CSM did not differ significantly between groups (Table 3-11).

Table 3-11: Comparison of Response to CSM at Baseline at Baseline for Ten Year Follow-up Participants and Non-participants

Variable	**Year 10 Participants N = 90**	**Non- participants N = 182**	**P**
	Frequency (%)	**Frequency (%)**	
CSH	28 (31)	78 (43)	0.06
Cardioinhibitory CSH	2 (2)	4 (2)	1
Vasodepressive CSH	12 (13)	30 (16)	0.50
Mixed CSH	14 (15)	44 (24)	0.10
	Median (IQ range)	**Median (IQ range)**	
Maximum RR interval (ms)	1481 (1156, 2391)	1816 (1304, 3345)	**0.03**
Maximum delta RR (ms)	549 (232, 1372)	866 (63, 2286)	**0.04**
SBP Vasodepression (mmHg)	43 (30, 53)	46 (32, 60)	0.13
SBP Nadir (mmHg)	81 (68, 101)	79 (63, 98)	0.18

3.2.9 **Comparison of Response to Autonomic Function Tests at Baseline**

Ninety of the follow-up participants and 190 of the non-participants completed sufficient autonomic function tests to define autonomic function as normal or abnormal according to Modified Ewing criteria at baseline. There were no significant differences in the incidence of abnormal autonomic function between groups (non-participants =33.6% v follow-up participants =32.2%, P=0.89).

Continuous response to individual autonomic function tests was compared for follow-up participants versus non participants. Non-participants had a significantly larger systolic BP overshoot in response to Valsalva manoeuvre. There was a trend towards greater heart response to deep breathing and greater Valsalva ratio in participants but this did not quite reach statistical significance (P=0.08 in both cases) (Table 3-12).

Table 3-12 Comparison of Response to Autonomic Function Tests at Baseline for Ten Year Follow-up Participants and Non-participants

	Non-Participants	**Participants**	**P**
	Median (IQR)	**Median (IQR)**	
30:15 ratio	1.34 (1.08, 1.20)	1.13 (1.05, 1.21)	0.64
Diastolic BP response to Isometric exercise (mmHg)	13.0 (4.00, 19.0)	12.0 (5.0, 19.8)	0.97
Diastolic BP response to cold pressor test	8.5 (3.0, 15.0)	9.0 (3.0, 15.0)	0.67
Heart rate response to deep breathing	6.6 (4.2, 9.9)	7.8 (5.0, 11.5)	0.08
Systolic BP over shoot in response to Valsalva	21.5 (6.8, 37.5)	25.5 (11.8, 53.0)	0.04
Valsalva ratio	1.4 (1.3, 1.6)	1.5 (1.3, 1.7)	0.08

3.2.10 **Comparison of Heart Rate Variability at Baseline**

Two hundred and ninety five individuals had heart rate variability recordings performed at baseline. Of these 280 had studies where $\leq$10% of beats were interpolated or edited. Eighty-three individuals participated in the follow-up study and had baseline HRV recordings suitable for analysis. Baseline HRV parameters did not differ significantly between individuals participating in the follow-up study and those lost to follow-up (Table 3-13).

Table 3-13: Baseline Heart Rate Variability for Ten Year Follow-up Participants and Non-participants

Variable	**Year 10 Participants N = 83**	**Non- participants N = 197**	**P**
	Median (range)	**Median (range)**	
RRSD	27.4 (19.2, 43.5)	25.7 (18.7, 35.5)	0.76
Total power (mm^2)	439 (250, 829)	388 (182, 873)	0.92
VLF (ms^2)	140 (83.7, 285)	160 (67.5, 347)	0.96
LF (ms^2)	173 (79.3, 292)	137 (60.2, 350)	0.62
HF (ms^2)	65.3 (28.4, 137)	65.5 (30.8, 157)	0.97
HF/LF	0.39 (0.26, 0.81)	0.43 (0.23, 0.86)	0.66

3.3 **Summary**

In conclusion, individuals participating in the ten year follow-up study were younger than participants lost to follow-up and performed better on cognitive function tests at baseline than individuals lost to follow-up. Individuals lost to follow-up were less independent with activities of daily living at baseline and performed more poorly on assessments of gait and balance. In terms of past medical history and medication use at baseline the two groups did not significantly differ. Of the tests of NCVI only the RR interval post carotid sinus massage differed between follow-up participants and participants lost to follow-up. Finally, ambulatory blood pressure monitoring showed that ten year follow-up participants tended to have lower nocturnal and 24-hour systolic blood pressure than non-participants and had lower daytime blood pressure variability.

Chapter 4 The Long-term Associations between Autonomic Function, Neurocardiovascular Instability and Cognition

4.1 Introduction

Several studies have shown a relationship between impaired cognitive function and hypertension (Sharp et al., 2011, Nagai et al., 2010, Birns and Kalra, 2009, Eftekhari et al., 2007). Chronic hypotension, particularly among older people, has been associated with cognitive impairment and cognitive decline (Power et al., 2011, Guo et al., 1996, Morris et al., 2000, Hestad et al., 2005, Richmond et al., 2011). Disorders of neurocardiovascular instability (NCVI), notably orthostatic hypotension and carotid sinus hypersensitivity, have been shown to be more common among people with dementia, and NCVI has been associated with poorer performance on cognitive tests in community cohorts (Andersson et al., 2008, Mehrabian et al., 2010, Matsubayashi et al., 1997, Kenny et al., 2004, Yap et al., 2008, Pearce, 2007). Similarly, abnormal autonomic function in the form of reduced heart rate variability and impaired response to autonomic function tests have been shown to be more evident in people with cognitive impairment and dementia (Allan et al., 2007, Algotsson et al., 1995, Allan et al., 2005, Elmstahl et al., 1992, Giubilei et al., 1998, Kim et al., 2006).

The direction of the association between impaired neurocardiovascular function and cognition remains unclear (Rose et al., 2010, Britton et al., 2008). It is hypothesised that failure of neurocardiovascular autoregulation to maintain peripheral blood pressure may result in recurrent cerebral hypoperfusion, in turn causing cerebral white matter disease resulting in among other symptoms cognitive impairment and cognitive decline.

4.2 Aim

To examine the long-term association between neurocardiovascular instability, autonomic function and cognition in community-dwelling older people.

4.3 Methods

4.3.1 Tests of Neurocardiovascular Function

Tests of neurocardiovascular function performed at baseline are described in detail in section 2.3, page 42.

4.3.2 Cognitive tests

Cognitive tests used included MMSE, CAMCOG total scores, CAMCOG memory and CAMCOG executive. Simple Reaction Time, Complex Reaction Time, Digit Vigilance Time, Power of Attention and Cognitive Reaction Time. These were described in section 2.6, page 48.

4.3.3 Defining Outcome Variables

Analysis of change in cognition is complex and presents a number of methodological challenges. Four methods have therefore been used to examine cognition at follow-up and change in cognition

4.1.1.1 Cognitive Performance at Follow-up

In each case, the association between baseline blood pressure or heart rate variable and raw cognitive score / reaction time at follow-up has been examined.

4.1.1.2 Change in MMSE and CAMCOG Scores

Change in cognitive score was calculated by subtracting follow-up score from baseline score. Negative integers therefore indicate an increase/improvement in cognitive function while positive integers indicate a decline/ worsening of cognitive function.

4.1.1.3 *Cognitive Decline*

Reliable change indices (RCI) aim to determine the amount of change in a cognitive test score that is necessary to be deemed statistically reliable. It estimates the probability that change in a test score between assessments is due to a change in an individual's ability to perform the task, not due to measurement error, practice effect and / or regression to the mean. Two authors have published RCI for the MMSE in this age group ranging from 4-5 points (Stein et al., 2010, Hensel et al., 2007). Studies suggesting an RCI of five points have included patients who developed dementia, where as those reporting and RCI of 4 or less have included only "cognitively intact

older individuals" (Hensel et al., 2007). Baseline variables associated with a drop of four or more points in the MMSE was therefore examined in this study, as there were few participants with dementia.

Published reliable change indices are not available for the total CAMCOG. Changes in total CAMCOG scores were reviewed. Several individuals had undergone a decline in total CAMCOG score of five or more points. None had increased by five or more points. Baseline variables associated with dropping five or more points on the CAMCOG over the follow-up period were therefore examined.

4.1.1.4 Cognitive Impairment

Finally, participants were defined as cognitively impaired or cognitively normal according to their MMSE and CAMCOG scores. A cut off of <24 was chosen to indicate cognitive impairment for the MMSE and is associated with 87.0% sensitivity and 82.4% specificity for dementia / delirium (Anthony et al., 1982). For the CAMCOG, a cut-off score of 80 was chosen. This has been associated with a 92% sensitivity and 96% specificity (Roth et al., 1986). Incident cognitive impairment was defined as having a CAMCOG>80 at baseline but CAMCOG ≤80 at follow-up or having an MMSE≥24 at baseline but <24 at follow.

4.4 Statistics

4.4.1 Comparison between Baseline and Follow-up Cognition

Baseline and follow-up cognitive scores were compared using the Related Samples Wilcoxon Signed Rank Test. Incidence of cognitive impairment at baseline and follow-up were compared using Chi square tests. Where one or more cells had an expected count of less than five, Fisher's exact test was used. Correlation between baseline reaction times and follow-up reaction times were examined using Pearson's Correlation Coefficient.

4.4.2 Association between baseline neurocardiovascular assessment and cognition at follow-up

Non-normally distributed data were compared between groups using the Mann-Whitney U test. Normally distributed data were compared using a T-test.

4.4.3 **Covariates**

4.5 **Multivariable linear regression analysis and multiple logistic regression adjusted for age, sex and risk factors known to be associated with cognitive function and blood pressure. They included: number of years in education, smoking status, alcohol consumption, PMH of diabetes, PMH of cardiovascular or cerebrovascular disease, use of psychoactive medication, use of cardioactive medication, Cornell depression score and relevant cognitive score at baseline Results**

4.5.1 **Cognitive Function at Ten Year Follow-up**

Of the 104 individuals participating in the follow-up assessment, two individuals withdrew prior to cognitive assessment, one died and one individual was registered blind and unable to complete the cognitive tests. Data from another individual with severe visual impairment were excluded from the analysis, as she was unable to complete the full battery of cognitive tests. Hence, 99 individuals completed the full battery of cognitive tests at baseline and ten years follow-up.

4.5.2 **Comparison of CAMCOG and MMSE scores at Baseline and Follow-up**

MMSE and CAMCOG scores at baseline and MMSE and CAMCOG scores at ten-year follow-up examination were compared for the 99 individuals who underwent cognitive testing at both assessments. MMSE, CAMCOG total, CAMCOG memory and CAMCOG executive scores were all significantly lower at ten year follow-up than at baseline ($P<0.001$ in all cases) (Table 4-1).

Table 4-1: CAMCOG and MMSE Scores at Baseline and Follow-up

Variable	Baseline scores N = 99	Ten Year Follow-up N = 99	P
	Median (IQR range)	Median (IQR range)	
MMSE	29.0 (28.0, 30.0)	28.0 (26.0, 30.0)	<0.001
CAMCOG Total Score	98.0 (94.0, 100.0)	94.0 (90.0, 97.0)	<0.001
CAMCOG Memory Score	24.0 (22.0, 24.0)	23.0 (21.0, 24.0)	<0.001
CAMCOG Executive Score	22 (19.0, 24.0)	20.0 (17.0, 23.0)	<0.001

At baseline, all participants achieved a total CAMCOG score of 80 or more and MMSE score of 24 or more, indicating none had cognitive impairment. Four individuals were found to have a CAMCOG score of ≤80 at follow-up. This increase was not statistically significant. Similarly, four individuals were found to have MMSE score of <24 at ten years but this increase was not significant. As non of the ten year follow-up participants had an MMSE <24 or total CAMCOG ≤80 at baseline these individual were defined as having incident cognitive impairment. Only one individual had a total CAMCOG ≤80 and an MMSE ≤23 (Table 4-2).

Table 4-2: Cognitive Impairment at Baseline and Follow-up

Variable	Baseline scores N = 99	Ten Year Follow-up N = 99	P
	Frequency	Frequency	
MMSE <24	0	4	0.12
Total CAMCOG score ≤80	0	4	0.12

4.5.3 Change in CAMCOG and MMSE Over Ten Year Follow-up

The majority of subjects showed a decrease in MMSE score and in all domains of the CAMCOG. However, no change in cognitive scores or an improvement in cognitive scores was not uncommon (Table 4-3). Seven individuals showed an improvement on both the MMSE and CAMCOG total score. Median decrease in MMSE was one point. Median decrease total CAMCOG over follow-up was 4 points (Table 4-4).

Table 4-3 Number of Participants Showing a Decrease, No Change or an Increase in CAMCOG and MMSE Score over Ten year Follow-up

	Decrease in score of ≥ 1 point	**No change in score**	**Increase in score of ≥ 1 point**
	Frequency	**Frequency**	**Frequency**
MMSE	60	22	17
CAMCOG total score	79	3	17
CAMCOG memory score	49	26	24
CAMCOG executive score	58	14	27

Table 4-4 Change in MMSE and CAMCOG Score Over Follow-up

	Change in cognition *baseline score minus score at ten years* **Median (IQ range)**
MMSE	1.0 (0, 2.0)
CAMCOG total score	4.0 (1.0, 7.0)
CAMCOG memory score	0 (0, 2.0)
CAMCOG executive score	1.0 (-1.0, 3.0)

Ten individuals showed a decrease of four or more points on the MMSE. Only one individual showed an increase of four or more points on MMSE (Figure 4-1). Forty-four participants showed a decline of five or more points on the total CAMCOG score. By contrast, only 17 participants showed an increase in total CAMCOG score. The maximum increase observed was 4 points (Figure 4-2).

Figure 4-1 Histogram Showing Change in MMSE Score *(Negative results indicate an increase in score over ten year follow-up)*

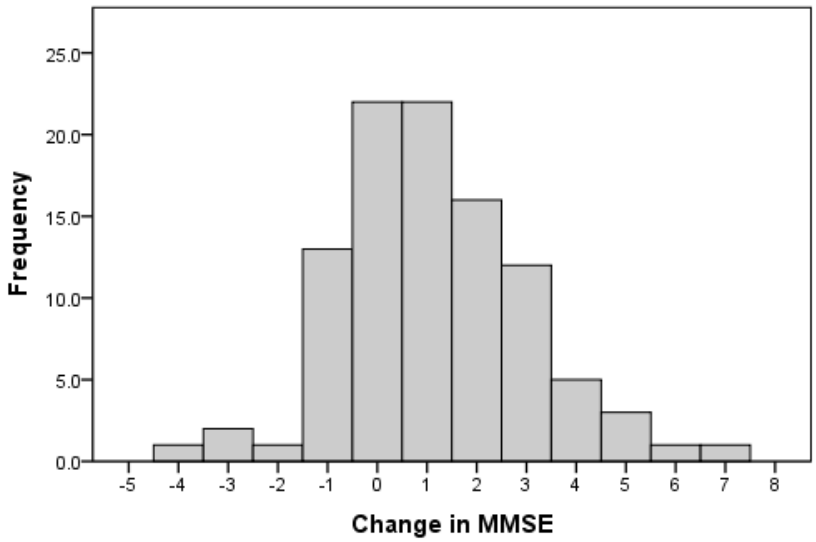
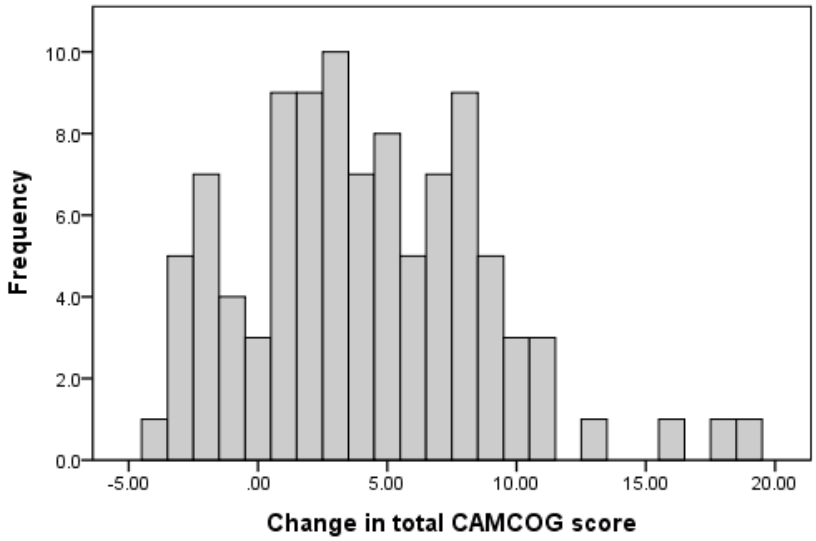


Figure 4-2 Histogram Showing Change in Total CAMCOG Score *(Negative results indicate an increase in score over ten year follow-up*)



4.5.4 **Reaction Times at Ten Year Follow-up**

All ninety-nine individuals completing MMSE and CAMCOG also completed assessment of reaction times using Computerised Mental Performance Assessment System (COMPASS) (Table 4-5). All COMPASS scores at year 10 follow-up, except CRT, were correlated with equivalent baseline CDR score (r range from 0.32 – 0.59) (Table 4-6).

Table 4-5 COMPASS Results at Follow-up

	Median (IQ range)
Choice Reaction Time (ms)	622.4 (562.2, 671.5)
Simple Reaction Time (ms)	445.3 (407.5, 522.8)
Digit Vigilance Reaction Time (ms)	545.0 (515.1, 584.5)
Cognitive Reaction Time (ms)	159.7 (113.1, 223.4)
Power of Attention (ms)	1648.0 (1512.0, 1793.2)

Table 4-6 Correlation between Baseline CDR Results and Equivalent COMPASS Result at Follow-up

		Year 10 COMPASS results				
Baseline CDR results		**Simple Reaction Time (ms)**	**Choice Reaction Time (ms)**	**Digit Vigilance (ms)**	**Cognitive Reaction Time (ms)**	**Power of Attention (ms)**
Simple Reaction Time (ms)	r	0.32				
	P	**0.002**				
Choice Reaction Time (ms)	r		0.42			
	P		**<0.001**			
Digit Vigilance (ms)	r			0.59		
	P			**<0.001**		
Cognitive Reaction Time (ms)	r				0.07	
	P				0.50	
Power of Attention (ms)	r					0.51
	P					**<0.001**

4.6 Ambulatory Blood Pressure Monitoring and Cognitive Performance at Follow-up

Of the 99 individuals who underwent cognitive testing at ten year follow-up, ninety-eight had ambulatory BP monitored at baseline.

4.6.1 **Baseline Hypertension and Cognition at Follow-up**

Ninety-six individuals had ten or more daytime recordings and therefore had sufficient data to calculate if they were hypertensive at baseline according to NICE guidelines (mean daytime BP > 135/85). There were no differences in cognitive function at ten years for individuals with mean daytime BP >135/85 on ABPM at baseline and those without (Table 4-7). Similarly, there were no associations between hypertension status and change in cognition over follow-up period (Table 4-8)

Table 4-7 Cognitive Function at Follow-up by Baseline Hypertension Status (Mean Daytime BP ≥ 135/85)

Variable	**No Hypertension N= 52**	**Hypertension N= 44**	**P**
	Median (IQ range)	**Median (IQ range)**	
MMSE	29.0 (27.0, 29.0)	28.0 (25.0, 29.0)	0.60
CAMCOG total	94.5 (90.0, 97.0)	93.0 (89.0, 97.0)	0.44
CAMCOG memory	23.0 (21.3, 24.0)	23.0 (21.0, 24.0)	0.99
CAMCOG executive	21.0 (17.3, 23.8)	19.0 (17.0, 22.8)	0.24
CRT (ms)	622.2 (553.8, 679.6)	618.6 (562.2, 669.0)	0.64
SRT (ms)	436.8 (398.0, 499.8)	455.8 (410.2, 544.9)	0.27
VigRT (ms)	545.5 (516.0, 588.2)	537.4 (511.9, 537.4)	0.62
CogRT (ms)	162.6 (126.4, 256.6)	155.2 (95.9, 189.5)	0.11
POA (ms)	1650 (1508, 1753)	1638 (1486, 1850)	0.79

Table 4-8 Change in MMSE and CAMCOG Scores by Baseline Hypertension Status (Hypertension = Mean Daytime BP ≥ 135/85)

Variable	No Hypertension N= 52	Hypertension N= 44	P
	Median (IQ range)	Median (IQ range)	
Change in MMSE	1.0 (0.0, 2.0)	1.0 (0.0, 2.8)	0.37
Change in CAMCOG total	3.0 (1.0, 7.0)	5.0 (1.3, 7.8)	0.32
Change in CAMCOG memory	0.0 (-1.0, 2.0)	1.0 (0.0, 2.0)	0.73
Change in CAMCOG executive	1.0 (-1.0, 2.8)	2.0 (0.0, 5.0)	0.12

Hypertension status at baseline was not associated with either an MMSE score <24 points at follow-up or a CAMCOG total score of ≤80 at follow-up (Table 4-9).

Table 4-9 Association between Hypertension at Baseline and Cognitive Impairment at Follow-up

Variable	No Hypertension N= 52	Hypertension N= 44	P
	Number (%)	Number (%)	
MMSE <24	3 (5.7)	1 (2.2)	0.62
CAMCOG ≤80	3 (5.7)	1 (2.2)	0.62

Hypertension at baseline was associated with dropping five or more points on the total CAMCOG score (P= 0.03), but it was not associated with a drop in MMSE score of four or more points (Table 4-10). The association between baseline hypertension status and decline in CAMCOG total of ≥ 5 points remained after adjusting for covariates (Table 4-11).

Table 4-10 Association between Hypertension at Baseline and Cognitive Decline at Follow-up

Variable	No Hypertension N= 52	Hypertension N= 44	P
	Number (%)	Number (%)	
Drop in MMSE of ≥4 points	5 (8.7)	5 (11.4)	1.00
Drop in total CAMCOG ≥ 5 points	18 (31.5)	25 (56.8)	**0.03**

Table 4-11 Logistic Regression Examining independent Association Between Hypertension at baseline and Fall of ≥ 5 Points on CAMCOG Total Score over Follow-up

		95% C.I.		
	OR	Lower	Upper	P
Age	1.16	1.03	1.31	**0.02**
Sex	1.04	0.38	2.85	0.94
Diabetes	2.74	0.16	46.64	0.49
Current smoker (Y/N)	0.62	0.11	3.51	0.59
Cardioactive medication	1.75	0.61	5.01	0.30
Years in education	1.00	0.84	1.18	0.96
Any Cardiovascular or Cerebrovascular Disease	0.56	0.19	1.67	0.30
Any Psychoactive Medication	1.40	0.37	5.29	0.62
Consumes Alcohol (Y/N)	1.85	0.60	5.77	0.29
Cornell Depression Score	1.14	0.99	1.32	0.06
Baseline Total CAMCOG Score	0.93	0.81	1.06	0.28
Hypertension	3.01	1.16	7.81	**0.02**

Because the NICE criteria are stricter than many definitions of hypertension these analyses were repeated with hypertension defined as a mean daytime BP greater than 150/90. This did not reveal any additional significant associations between hypertension and cognitive function at year 10 or change in cognitive function.

4.6.2 **Daytime Ambulatory Blood Pressure at Baseline and Cognition Follow-up**

CAMCOG and MMSE scores at ten years were not associated with daytime mean BP or BP variability. Lower mean systolic BP was associated with longer cognitive reaction times and longer choice reaction times, indicating poorer cognition (Table 4-12). Greater daytime diastolic BP variability was associated with longer digit vigilance reaction time (Table 4-12). After adjusting for potential covariates, only the association

between mean daytime systolic BP and cognitive reaction time remained significant (Table 4-13).

Table 4-12 Spearman Correlation between Daytime Ambulatory BP Results and Cognitive Scores at Follow-up

		Day mean systolic pressure (mmHg)	Day mean diastolic pressure (mmHg)	Day time SD SBP (mmHg)	Day time SD DBP (mmHg)
MMSE	**r**	-0.05	-0.09	-0.05	-0.04
	P	0.61	0.38	0.66	0.70
CAMCOG total score	**r**	-0.01	0.05	-0.14	-0.11
	P	0.93	0.64	0.19	0.28
CAMCOG memory score	**r**	0.00	0.07	-0.07	-0.05
	P	0.99	0.51	0.52	0.65
CAMCOG executive score	**r**	-0.03	-0.02	-0.18	-0.20
	P	0.79	0.88	0.08	0.05
CRT (ms)	**r**	**-0.22**	-0.10	0.03	0.13
	P	**0.03**	0.32	0.79	0.22
SRT (ms)	**r**	0.10	-0.08	0.05	0.03
	P	0.32	0.45	0.66	0.79
VigRT (ms)	**r**	-0.11	-0.02	0.15	**0.23**
	P	0.28	0.82	0.15	**0.03**
CogRT(ms)	**r**	**-0.26**	-0.04	-0.01	0.09
	P	**0.01**	0.69	0.95	0.36
POA (ms)	**r**	-0.11	-0.10	0.07	0.15
	P	0.28	0.32	0.50	0.15

Table 4-13 Multiple Linear Regression Examining Independent Associations between Daytime Mean Systolic BP and Cognitive Reaction Time.

	B	95.0% Confidence Interval for B		P
Age (years)	-1.16	-9.40	7.08	0.78
Sex	-12.64	-96.40	71.13	0.76
Hypertension	23.97	-62.63	110.56	0.58
Cardioactive medication	-73.43	-164.01	17.15	0.11
Years in education	4.73	-7.70	17.16	0.45
Psychotropic medication	30.79	-61.63	123.21	0.51
Diabetes	17.81	-81.91	117.53	0.72
Any cardiovascular or cerebrovascular disease	4.48	-74.40	83.36	0.91
Consumes alcohol	-12.75	-53.46	27.96	0.53
Cornell depression score	-2.13	-11.86	7.60	0.66
Smoking status	40.40	-23.19	104.00	0.21
CogRT at baseline (ms)	0.13	-0.24	0.50	0.48
Daytime mean systolic BP (mmHg)	-2.36	-4.51	-0.20	**0.03**
Dependent Variable: Cognitive Reaction Time at Follow-up Model Adjusted $R^2 = 0.12$				

Greater decline in total CAMCOG score was associated with greater daytime diastolic BP variability [r=0.20 (P<0.05)] (Table 4-14). This was no longer significant after adjusting for potential covariates.

Table 4-14: Spearman Correlation between Baseline Daytime Ambulatory BP Results and Change in Cognitive Scores at Follow-up.

		Day mean systolic pressure (mmHg)	Day mean diastolic pressure (mmHg)	Day time SD SBP (mmHg)	Day time SD DBP (mmHg)
MMSE	**r**	0.12	0.12	0.04	-0.01
	P	0.23	0.24	0.71	0.89
total CAMCOG	**r**	0.07	0.07	0.19	0.20
score	**P**	0.52	0.51	0.06	**<0.05**
CAMCOG	**r**	0.06	0.09	0.17	0.16
memory score	**P**	0.59	0.38	0.10	0.12
CAMCOG	**r**	0.14	0.07	0.02	0.01
executive score	**P**	0.19	0.52	0.83	0.96

4.6.3 Night-time Ambulatory Blood Pressure at Baseline and Cognition at Follow-up

Eighty-four individuals had five or more baseline, night-time, ABPM readings and were therefore eligible to be included in the analysis of nocturnal data. Greater night-time diastolic BP variability was associated with poorer MMSE and total CAMCOG scores at year ten (Table 4-15). After adjusting for potential covariates, these associations remained of borderline significance, P=0.05 (Table 4-16 and Table 4-17). Further adjustment was made for mean night-time diastolic BP, but this did not significantly alter the models. COMPASS reaction times were not related to night-time ABPM results (Table 4-15).

Table 4-15 Spearman Correlation between Night-time 24-hour Ambulatory BP Results and Cognitive Scores at Follow-up

		Night-time mean systolic pressure (mmHg)	Night-time mean diastolic pressure (mmHg)	Night-time SD SBP (mmHg)	Night-time SD DBP (mmHg)
MMSE	**r**	0.05	-0.04	-0.13	**-0.25**
	P	0.67	0.75	0.24	**0.02**
CAMCOG total score	**r**	0.01	0.01	-0.20	**-0.26**
	P	0.92	0.94	0.06	**0.02**
CAMCOG memory score	**r**	0.02	0.03	-0.14	-0.13
	P	0.87	0.76	0.20	0.24
CAMCOG executive score	**r**	-0.05	0.02	-0.05	-0.08
	P	0.66	0.86	0.64	0.46
CRT (ms)	**r**	-0.07	0.01	-0.11	-0.02
	P	0.52	0.95	0.30	0.83
SRT (ms)	**r**	0.13	-0.05	0.03	-0.15
	P	0.25	0.65	0.78	0.18
VigRT (ms)	**r**	-0.03	-0.05	-0.12	-0.16
	P	0.80	0.66	0.30	0.14
CogRT (ms)	**r**	-0.15	0.04	-0.12	0.08
	P	0.18	0.73	0.27	0.49
POA (ms)	**r**	0.00	-0.04	-0.08	-0.13
	P	0.97	0.75	0.45	0.26

Table 4-16 Linear Regression Examining Independent Predictors of MMSE at Follow-up

	B	95% CI		P
Age	-0.12	-0.22	-0.01	**0.03**
Sex	-0.42	-1.30	0.46	0.35
Hypertension	-0.23	-1.46	1.01	0.72
Diabetes	0.43	-1.97	2.83	0.72
Current smoker (Y/N)	-0.07	-1.69	1.55	0.93
Cardioactive medication	0.10	-1.00	1.21	0.85
Years in education	0.18	0.03	0.33	0.02
Any Cardiovascular or Cerebrovascular Disease	0.26	-0.67	1.19	0.58
Any Psychoactive Medication	0.67	-0.46	1.81	0.24
Consumes Alcohol (Y/N)	0.13	-0.79	1.06	0.77
Cornell Depression Score	-0.05	-0.18	0.07	0.39
Baseline MMSE	0.60	0.28	0.92	**<0.01**
Night-time SD DBP (mmHg)	-0.15	-0.31	0.00	**0.05**
Dependent Variable: MMSE at Follow-up Model Adjusted R^2 =0.27				

Table 4-17 Linear Regression Examining Independent Predictors of CAMCOG at Follow-up

	B	95% CI		P
Age	-0.28	-0.52	-0.04	**0.02**
Sex	-0.09	-2.12	1.95	0.93
Hypertension	-0.40	-3.26	2.46	0.78
Diabetes	-3.00	-8.53	2.52	0.28
Current smoker (Y/N)	1.92	-1.82	5.67	0.31
Cardioactive medication	-0.82	-3.38	1.74	0.53
Years in education	0.29	-0.08	0.66	0.12
Any Cardiovascular or Cerebrovascular Disease	0.87	-1.28	3.03	0.42
Any Psychoactive Medication	-0.63	-3.19	1.93	0.63
Consumes Alcohol (Y/N)	-1.54	-3.71	0.62	0.16
Cornell Depression Score	-0.27	-0.56	0.02	0.06
Baseline Total CAMCOG	1.02	0.74	1.30	**<0.01**
Night-time SD DBP (mmHg)	-0.36	-0.72	0.00	**0.05**
Dependent Variable: Total CAMCOG at Follow-up Model Adjusted R^2 =0.52				

In univariate analysis, greater decline in MMSE and total CAMCOG score were also associated with increased night-time diastolic BP variability (Table 4-18). These

findings remained significant after adjusting for potential covariates (Table 4-19 and Table 4-20). Once again, adding mean nocturnal DBP into the model did not alter the model fit or variables significantly associated with change in total CAMCOG over follow-up.

Table 4-18 Spearman Correlation between Night-time 24-hour Ambulatory BP Results and Change in Cognitive Scores at Follow-up

		Night-time mean systolic pressure (mmHg)	Night-time mean diastolic pressure (mmHg)	Night-time SD SBP (mmHg)	Night-time SD DBP (mmHg)
Change in MMSE	**r**	-0.01	0.03	0.12	**0.23**
	P	0.91	0.75	0.26	**0.03**
Total CAMCOG score	**r**	0.01	0.09	0.20	**0.26**
	P	0.96	0.43	0.07	**0.02**
CAMCOG memory score	**r**	0.15	0.17	0.12	0.00
	P	0.17	0.11	0.26	1.00
CAMCOG executive score	**r**	0.11	0.03	0.02	0.08
	P	0.30	0.80	0.84	0.46

Table 4-19 Multiple Linear Regression Examining Independent Predictors of Change in MMSE over Follow-up

	B	95% CI		P
Age	0.12	0.01	0.22	**0.03**
Sex	0.42	-0.46	1.30	0.35
Hypertension	0.23	-1.01	1.46	0.72
Diabetes	-0.43	-2.83	1.97	0.72
Current smoker (Y/N)	0.07	-1.55	1.69	0.93
Cardioactive medication	-0.10	-1.21	1.00	0.85
Years in education	-0.18	-0.33	-0.03	**0.02**
Any Cardiovascular or Cerebrovascular Disease	-0.26	-1.19	0.67	0.58
Any Psychoactive Medication	-0.67	-1.81	0.46	0.24
Consumes Alcohol (Y/N)	-0.13	-1.06	0.79	0.77
Cornell Depression Score	0.05	-0.07	0.18	0.39
Baseline MMSE	0.40	0.08	0.72	**0.02**
Night-time SD DBP (mmHg)	0.15	0.00	0.31	**<0.05**
Dependent Variable: Change in MMSE over Follow-up Model Adjusted R^2 =0.12				

Table 4-20 Multiple Linear Regression Examining Independent Predictors of Change in Total CAMCOG over Follow-up

	B	95% CI		P
Age	0.28	0.04	0.52	**0.02**
Sex	0.09	-1.95	2.12	0.93
Hypertension	0.40	-2.46	3.26	0.78
Diabetes	3.00	-2.52	8.53	0.28
Current smoker (Y/N)	-1.92	-5.67	1.82	0.31
Cardioactive medication	0.82	-1.74	3.38	0.53
Years in education	-0.29	-0.66	0.08	0.12
Any Cardiovascular or Cerebrovascular Disease	-0.87	-3.03	1.28	0.42
Any Psychoactive Medication	0.63	-1.93	3.19	0.63
Consumes Alcohol (Y/N)	1.54	-0.62	3.71	0.16
Cornell Depression Score	0.27	-0.02	0.56	0.06
Baseline Total CAMCOG	-0.02	-0.30	0.26	0.89
Night-time SD DBP (mmHg)	0.36	0.00	0.72	**<0.05**
Dependent Variable: Change in Total CAMCOG over Follow-up Model Adjusted R^2 =0.13.				

4.6.4 Twenty-four Hour Ambulatory Blood Pressure at Baseline and Cognition at Follow-up

All ninety-eight individuals who had undergone cognitive assessment at follow-up had a minimum of 16 BP recordings during the 24-hour period and met the criteria for analysis. MMSE and CAMCOG scores at ten years were not associated with baseline 24-hour ambulatory BP variables (Table 4-21). Longer cognitive reaction times (indicating poorer cognition) were associated with lower mean systolic BP [r = - 0.24, (P = 0.02)]. This remained significant after adjusting for covariates [B -2.56 (P=0.04)] (Table 4-22).

Table 4-21: Spearman Correlation between Baseline 24-hour Ambulatory BP Results and Cognitive Scores at Follow-up.

		24hr mean systolic pressure (mmHg)	24hr mean diastolic pressure (mmHg)	24hr SD SBP (mmHg)	24hr SD DBP (mmHg)
MMSE	**r**	-0.03	-0.10	-0.09	-0.07
	P	0.77	0.33	0.39	0.51
CAMCOG total	**r**	-0.03	0.02	-0.16	-0.08
score	**P**	0.75	0.82	0.11	0.45
CAMCOG	**r**	-0.03	0.02	-0.13	-0.06
memory score	**P**	0.74	0.83	0.21	0.54
CAMCOG exec	**r**	-0.06	-0.02	-0.15	-0.16
score	**P**	0.54	0.82	0.13	0.11
CRT (ms)	**r**	-0.18	-0.08	-0.03	0.07
	P	0.08	0.44	0.80	0.52
SRT (ms)	**r**	0.13	-0.08	0.06	0.07
	P	0.22	0.41	0.58	0.50
VigRT (ms)	**r**	-0.12	-0.04	0.09	0.20
	P	0.26	0.68	0.37	0.06
CogRT (ms)	**r**	**-0.24**	-0.01	-0.06	0.01
	P	**0.02**	0.89	0.55	0.91
POA (ms)	**r**	-0.08	-0.10	0.04	0.14
	P	0.45	0.35	0.69	0.19

Table 4-22 Multiple Linear Regression Examining Independent Predictor of Cognitive Reaction Time at Follow-up

	B	95.0% Confidence Interval for B		P
Age (years)	-0.40	-8.62	7.82	0.92
Sex	-10.45	-94.15	73.25	0.80
Hypertension	24.62	-62.29	111.54	0.57
Cardioactive medication	-72.66	-163.37	18.06	0.11
Years in education	4.23	-8.19	16.66	0.50
Psychotropic medication	34.07	-58.33	126.46	0.47
Diabetes	19.22	-80.81	119.26	0.70
Any cardiovascular or cerebrovascular disease	1.76	-77.16	80.68	0.96
Consumes alcohol	-11.66	-52.57	29.24	0.57
Cornell depression score	-2.21	-11.96	7.53	0.65
Current smoker	43.00	-21.00	106.99	0.18
CogRT (ms)	0.13	-0.23	0.50	0.47
24hr mean systolic pressure (mmHg)	-2.56	-4.99	-0.14	**0.04**
Dependent variable: Cognitive Reaction Time at Follow-up Model Adjusted $R^2 = 0.12$				

Greater 24-hour systolic BP variability was significantly associated with greater decline in total CAMCOG score over follow-up period [r = 0.21 (P=0.04)] (Table 4-23). This association did not quite reach statistical significance after adjusting for relevant covariates [B= 0.26, (P=0.06)]. Change in MMSE and change in CAMCOG executive and memory subscores were not associated with 24-hour BP variables (Table 4-23).

Table 4-23 Spearman Correlation between Baseline 24-hour Ambulatory BP Results and Change in Cognitive Scores at Follow-up.

Change in Score		24hr mean systolic pressure (mmHg)	24hr mean diastolic pressure (mmHg)	24hr SD SBP (mmHg)	24hr SD DBP (mmHg)
MMSE	**r**	0.09	0.12	0.17	0.08
	P	0.38	0.25	0.10	0.41
CAMCOG	**r**	0.08	0.08	**0.21**	0.13
total score	**P**	0.41	0.43	**0.04**	0.21
CAMCOG	**r**	0.12	0.17	0.15	0.12
memory score	**P**	0.25	0.10	0.14	0.23
CAMCOG	**r**	0.15	0.05	0.07	0.03
exec score	**P**	0.15	0.61	0.49	0.73

4.6.5 **Diurnal Variation at Baseline and Cognition at Follow-up**

Eighty-four individuals had 10 or more daytime ABPM recordings and five or more night-time recordings. These participants were included in the analysis of diurnal variation. Percentage diurnal variation was not associated with performance on cognitive tests at ten years or cognitive decline (Table 4-24 and Table 4-24).

Table 4-24: Spearman Correlation between Ambulatory BP Diurnal Variation Results and Cognitive Scores at Follow-up.

	Systolic Diurnal Variation (%)	Diastolic Diurnal Variation (%)
	r (P)	**r (P)**
MMSE	-0.15 (0.16)	-0.06 (0.58)
CAMCOG total score	-0.09 (0.44)	-0.02 (0.87)
CAMCOG memory score	-0.01 (0.95)	0.05 (0.65)
CAMCOG executive score	-0.02 (0.85)	-0.06 (0.62)
CRT (ms)	-0.22 (0.05)	-0.14 (0.22)
SRT (ms)	-0.12 (0.30)	-0.06 (0.60)
VigRT (ms)	-0.13 (0.26)	0.01 (0.92)
CogRT (ms)	0.03 (0.82)	0.04 (0.71)
POA (ms)	-0.16 (0.16)	-0.06 (0.58)

Table 4-25 Spearman Correlation between Ambulatory BP Diurnal Variation Results and Change in Cognitive Scores at Follow-up

	Systolic Diurnal Variation (%)	Diastolic Diurnal Variation (%)
	R (P)	R (P)
Change in MMSE	0.19 (0.08)	0.08 (0.47)
Change in total CAMCOG score	0.15 (0.18)	0.09 (0.43)
Change in CAMCOG memory score	-0.15 (0.17)	-0.14 (0.22)
Change in CAMCOG executive score	0.13 (0.25)	0.15 (0.17)

4.6.6 **Dipping Status at Baseline and Cognition at Follow-up**

Participants were classified according to dipping status (non-dipper; <10% diurnal variation, dipper; 10-20% diurnal variation and extreme dippers; >20% diurnal variation). Cognitive scores and reaction times at ten years were not significantly different for non-dippers, dippers and extreme dippers (Table 4-26). Similarly, cognitive decline was not significantly different between groups (Table 4-26).

Table 4-26 Cognitive Function at Follow-up by Ambulatory BP Dipping Status

	Non dipper N= 35 Median (IQR)	**Dipper N = 38 Median (IQR)**	**Extreme dipper N= 11 Median (IQR)**	**P**
MMSE	29.0 (27.0, 29.0)	29.0 (26.0, 30.0)	28.0 (26.5, 29.0	0.23
CAMCOG total	94.0 (90.0, 96.5)	94.5 (90.0, 97.0)	94.00 (88.5, 95.0)	0.33
CAMCOG memory	23.0 (21.0, 24.0)	23.0 (22.0, 25.0)	22.0 (16.0, 24.0)	0.27
CAMCOG executive	20.0 (17.0, 23.0)	20.0 (17.0, 23.0)	19.0 (16.0, 24.0)	0.85
CRT (ms)	623.2 (584.5, 688.8)	637.3 (596.8, 668.2)	594.7 (531.0, 605.3)	0.05
SRT (ms)	457.1 (414.3, 559.3)	443.1 (395.6, 481.7)	412.6 (391.3, 589.8)	0.84
VigRT (ms)	558.7 (528.0, 598.8)	541.7 (509.7, 570.2)	532.0 (532.0, 584.8)	0.63
CogRT (ms)	138.4 (99.7, 213.7)	171.8 (142.9, 230.2)	107.6 (169.9, 184.9)	0.68
POA (ms)	1702.9 (1536.4, 1812.7)	1649.4 (1499.1, 1695.4)	1602.0 (1441.3, 1973.1)	0.98

Table 4-27 Change in Cognitive Function at Follow-up by Ambulatory BP Dipping Status.

	Non dipper N= 35 Median (IQR)	**Dipper N = 38 Median (IQR)**	**Extreme dipper N= 11 Median (IQR)**	**P**
MMSE	1.00 (-0.05, 2.00)	1.00 (0, 3.00)	2.00 (1.00, 2.50)	0.20
Total CAMCOG	3.00 (1.00, 7.00)	3.5 (2.00, 7.00)	5.00 (3.00, 7.50)	0.35
CAMCOG memory	1.00 (0.00, 2.50)	0 (-1.00, 2.00)	0 (0, 1.00)	0.90
CAMCOG executive	1.00 (-0.50, 2.50)	1.50 (-1.00, 5.00)	1.00 (-0.50, 4.50)	0.85

4.6.7 Ambulatory Blood Pressure Monitoring at Baseline and Incident Cognitive Impairment

The association between ambulatory blood pressure parameters and scoring ≤80 on the CAMCOG or <24 on MMSE was examined to determine if ABPM recordings were associated with incident cognitive impairment at ten years.

Daytime and 24-hour ambulatory BP parameters were not associated with CAMCOG total ≤80 or MMSE <24 at ten year follow-up. Lower night-time mean systolic BP was associated with reduced odds of scoring <24 on MMSE at follow-up (Table 4-28). This was no longer significant after adjusting for potential covariates.

Table 4-28 Logistic Regression Examining Association between Baseline Ambulatory BP Records and Cognitive Impairment

	MMSE <24			CAMCOG ≤ 80		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
DAY						
Mean SBP (mmHg)	0.96	0.88, 1.03	0.24	0.97	0.90, 1.05	0.45
Mean DBP (mmHg)	0.95	0.85, 1.07	0.42	0.93	0.81, 1.06	0.26
SD SBP (mmHg)	1.00	0.76, 1.32	1.00	0.99	0.75, 1.30	0.94
SD DBP (mmHg)	1.07	0.71, 1.60	0.76	0.70	0.38, 1.27	0.24
NIGHT						
Mean SBP (mmHg)	0.90	0.80, 0.99	**0.04**	0.96	0.87, 1.06	0.41
Mean DBP (mmHg)	0.90	0.77, 1.05	0.18	0.99	0.86, 1.15	0.94
SD SBP (mmHg)	0.96	0.72, 1.28	0.78	1.01	0.73, 1.40	0.94
SD DBP (mmHg)	1.02	0.73, 1.42	0.92	1.06	0.75, 1.50	0.76
24-hour						
Mean SBP (mmHg)	0.93	0.85, 1.02	0.12	0.97	0.89, 1.05	0.40
Mean DBP (mmHg)	0.93	0.81, 1.06	0.28	0.92	0.80, 1.06	0.92
SD SBP (mmHg)	1.02	0.76, 1.38	0.88	0.99	0.73, 1.34	0.95
SD DBP (mmHg)	1.06	0.71, 1.58	0.78	0.59	0.32, 1.10	0.10

4.6.8 **Ambulatory Blood Pressure Monitoring at Baseline and Cognitive Decline**

ABPM parameters were not associated with a fall of four or more points on MMSE score. A fall of five or more points on total CAMCOG was associated with greater daytime systolic and diastolic BP variability, greater night-time diastolic BP variability, greater 24-hour mean systolic and diastolic pressures and greater SBP and DBP variability (Table 4-29). Multiple binary logistic regression was performed to determine if these findings were independent of potential covariates. All but the association with night-time mean diastolic BP remained significant.

Table 4-29 Logistic Regression Examining Association between Baseline Ambulatory BP Records and Cognitive Decline

	Drop in MMSE of ≥ 4 points			Drop in CAMCOG OF ≥ 5 points		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Daytime						
Mean SBP (mmHg)	1.01	0.97, 1.05	0.75	1.03	1.00, 1.06	0.06
Mean DBP (mmHg)	1.00	0.94, 1.06	0.93	1.04	1.00, 1.08	0.06
SD SBP (mmHg)	0.95	0.78, 1.16	0.62	1.13	1.00, 1.27	**<0.05**
SD DBP (mmHg)	0.97	0.73, 1.30	0.85	1.31	1.07, 1.60	**0.01**
Night-time						
Mean SBP (mmHg)	1.00	0.94, 1.05	0.88	1.02	0.98, 1.05	0.30
Mean DBP (mmHg)	1.02	0.94, 1.10	0.62	1.05	0.99, 1.11	0.09
SD SBP (mmHg)	0.99	0.82, 1.20	0.92	1.09	0.97, 1.23	0.16
SD DBP (mmHg)	1.19	0.97, 1.47	0.97	1.19	1.02, 1.40	**0.03**
24-hour						
Mean SBP (mmHg)	1.01	0.96, 1.06	0.70	1.03	1.00, 1.07	**0.04**
Mean DBP (mmHg)	1.02	0.95, 1.09	0.69	1.05	1.00, 1.10	**0.04**
SD SBP (mmHg)	0.87	0.69, 1.09	0.21	1.21	1.05, 1.39	**0.01**
SD DBP (mmHg)	0.79	0.56, 1.13	0.20	1.22	1.01, 1.47	**0.04**

4.7 Response to Active Stand at Baseline and Cognitive Performance at Follow-up

4.7.1 Orthostatic Hypotension at Baseline and Cognition at Follow-up

Ninety-four individuals had active stand at baseline and full cognitive testing at ten year follow-up. Of these 76 met the diagnostic criteria for OH described by the American Academy of Neurology. Of whom, 59 had systolic OH and 68 had diastolic OH. Presence or absence of OH as defined by AAN was not associated with cognitive performance at ten years or change in cognitive performance (Table 4-30). Nor were systolic or diastolic OH associated with cognitive function at follow-up when examined separately (Table 4-31 and Table 4-32).

Table 4-30 Cognitive Function at Ten Years by Presence or Absence of OH at Baseline

	OH N=76	**No OH N=18**	
	Median (IQ range)	**Median (IQ range)**	**P**
MMSE	28.0 (26.0, 29.0)	29.0 (27.0, 29.0)	0.98
CAMCOG total	93.5 (89.5, 96.0)	95.0 (90.0, 98.0)	0.08
CAMCOG memory	23.0 (21.0, 24.0)	23.0 (22.0, 25.0)	0.12
CAMCOG executive	20.0 (17.0, 23.0)	20.5 (18.0, 22.0)	0.40
CRT (ms)	627.6 (559.4, 669.8)	611.9 (565.0, 646.8)	0.63
SRT (ms)	451.0 (405.8, 541.1)	431.1 (416.4, 455.6)	0.62
VigRT (ms)	543.8 (516.3, 586.4)	558.7 (508.8, 584.8)	0.77
CogRT (ms)	158.0 (108.1, 214.4)	155.7 (121.2, 216.7)	0.86
POA (ms)	1654.0 (1512.0,1818.5)	1622.1 (1499.1, 1717.2)	0.50
Change in Cognitive Scores			
MMSE	1.0 (0, 2.0)	1.0 (0, 2.0)	0.89
CAMCOG total	4.0 (1.5, 8.8)	2.0 (-2.0, 7.0)	0.11
CAMCOG memory	1.0 (0, 2.0)	0 (-1.0, 2.0)	0.22
CAMCOG executive	2.0 (-0.5, 3.5)	0.0 (-1.0, 3.0)	0.51

Table 4-31 Cognitive Function at Ten Years by Presence or Absence of Systolic OH at Baseline

	Systolic OH N=59	**No Systolic OH N= 35**	
	Median (IQ range)	**Median (IQ range)**	**P**
MMSE	28.0 (26.0, 29.0)	29.0 (27.0, 29.0)	0.67
CAMCOG total	93.0 (90.0, 96.0)	95.0 (90.0, 97.5)	0.12
CAMCOG memory	23.0 (21.0, 24.0)	23.0 (22.0, 25.0)	0.26
CAMCOG executive	20.0 (17.0, 22.5)	20.0 (18.0, 22.5)	0.32
CRT (ms)	627.7 (555.7, 669.3)	611.5 (565.0, 673.2)	0.94
SRT (ms)	440.8 (400.2, 522.8)	449.3 (416.4, 545.7)	0.63
VigRT (ms)	540.3 (511.8, 588.6)	549.2 (515.2, 584.7)	0.52
CogRT (ms)	155.6 (113.1, 206.0)	158.5 (108.1, 230.2)	0.84
POA (ms)	1638.4 (1504.4, 1817.7)	1652.6 (1499.1, 1785.8)	0.62
Change in Cognitive Scores			
MMSE	1.0 (0, 2.5)	1 .0 (0, 2.0)	0.53
CAMCOG total	4.0 (2.0, 8.0)	3.0 (0, 7.0)	0.16
CAMCOG memory	1.0 (0, 2.0)	0 (-1.0, 2.0)	0.12
CAMCOG executive	2.0 (-0.5. 4.0)	1.0 (-1.0, 2.5)	0.22

Table 4-32 Cognitive Function at Ten Years by Presence or Absence of Diastolic OH at Baseline

	Diastolic OH N= 68	**No Diastolic OH N= 26**	
	Median (IQ range)	**Median (IQ range)**	**P**
MMSE	28.0 (26.0, 29.0)	28.5 (26.0, 29.0)	0.70
CAMCOG total	94.0 (89.5, 96.0)	94.0 (90.0, 98.0)	0.40
CAMCOG memory	23.0 (21.0, 24.0)	22.5 (21.0, 25.0)	0.76
CAMCOG executive	20.0 (17.0, 23.0)	19.5 (18.0, 22.0)	0.87
CRT (ms)	621.1 (552.0, 668.8)	623.2 (566.2, 673.2)	0.88
SRT (ms)	451.0 (405.8, 523.0)	438.1 (412.6, 509.7)	0.67
VigRT (ms)	544.4 (518.3, 586.4)	551.8 (508.3, 587.2)	0.67
CogRT (ms)	150.2 (103.8, 214.4)	161.7 (127.2, 216.7)	0.62
POA (ms)	1643.5 (1500.1, 1818.5)	1650.3 (1519.7, 1757.2)	0.92
Change in Cognitive Scores			
MMSE	1.0 (0, 2.0)	1.0 (0, 3.0)	0.47
CAMCOG total	4.0 (1.0, 7.5)	3.5 (-2.0, 7.0)	0.38
CAMCOG memory	1.0 (0, 2.0)	0 (-1.0, 2.0)	0.33
CAMCOG executive	1.0 (-1.0, 3.0)	1.5 (0, 5.0)	0.69

4.7.2 Symptomatic Orthostatic Hypotension at Baseline and Cognition at Ten Year Follow-up

Of the 76 participants meeting the AAN criteria for OH at baseline, 12 had symptoms of dizziness, pre-syncope or syncope. Symptomatic OH was associated with longer choice reaction times and greater decline in CAMCOG memory subscore (Table 4-33). After adjusting for potential covariates, these findings remained significant for change in CAMCOG memory score but not for Choice Reaction Time (Table 4-34).

Table 4-33 Cognitive Function at Ten Years by Presence or Absence of Symptomatic OH at Baseline

	Asymptomatic N= 82	**Symptomatic OH N= 12**	
	Median (IQ range)	**Median (IQ range)**	**P**
MMSE	28.0 (26.0, 29.0)	28.5 (26.0, 29.8)	0.95
CAMCOG total	94.0 (90.0, 97.0)	93.0 (86.3, 95.8)	0.29
CAMCOG memory	23.0 (21.0, 24.0)	22.0 (18.0, 23.0)	0.08
CAMCOG executive	20.0 (17.0, 23.0)	19.0 (17.3, 22.8)	0.87
CRT (ms)	611.5 (551.8, 663.4)	668.4 (615.6, 704.6)	**0.04**
SRT (ms)	442.3 (408.3, 527.3)	452.4 (393.8, 570.2)	0.73
VigRT (ms)	544.4 (512.7, 518.8)	567.9 (540.0, 600.0)	0.18
CogRT (ms)	154.0 (107.0, 208.8)	200.5 (123.7, 258.8)	0.20
POA (ms)	1635 (1482, 1813)	1666 (1585, 1810)	0.28
Change in Cognitive Scores			
MMSE	1.0 (0, 2.0)	1.0 (-0.75, 2.8)	0.66
CAMCOG total	3.5 (1.0, 7.0)	5.0 (2.3, 8.8)	0.39
CAMCOG memory	0 (-1.0, 2.0)	1.5 (1.0, 4.5)	**<0.01**
CAMCOG executive	1.5 (-1.0, 4.3)	1.0 (-0.8, 2.0)	0.56

Table 4-34 Multiple Linear Regression Examining the Independent Predictors of Change in CAMCOG memory score.

	B	95% CI	P
Age	0.09	0.00, 0.18	0.06
Sex	0.59	-0.30, 1.48	0.19
High blood pressure	0.59	-0.36, 1.54	0.22
Diabetes	0.61	-0.52, 1.74	0.29
Smoker yes or no	-0.52	-1.38, 0.34	0.23
Any cardioactive drug	0.52	-0.49, 1.53	0.31
Years in education	-0.35	-1.23, 0.52	0.43
Any cardiovascular or cerebrovascular disease	-0.18	-0.32, -0.05	**0.01**
Psychotropic Medication	-0.03	-0.91, 0.84	0.94
Consumes alcohol yes / no	0.09	-0.02, 0.19	0.11
Cornell	-0.17	-1.24, 0.90	0.75
CAMCOG Memory Score	0.20	-0.02, 0.41	0.07
Symptomatic OH	1.19	0.02, 2.35	**<0.05**
Dependent variable: Change in CAMCOG memory subscore over Follow-up Adjusted Model $R^{2 =}$ 0.23			

4.7.3 Orthostatic Hypotension at Baseline and Cognitive Impairment

Of the 94 participants who underwent active stand at baseline and cognitive testing at ten year follow-up, four had an MMSE score <24 at follow-up and 4 had a total CAMCOG score of ≤80 at follow-up. Neither of these outcomes was associated with the presence or absence of OH as defined by AAN, OH subtypes or symptomatic OH (Table 4-35).

Table 4-35 Association between Orthostatic Hypotension, Orthostatic Hypotension Subtypes and Cognitive Impairment

	Frequency (%)	**Frequency (%)**	**P**
	AAN OH N= 76	**No AAN OH N=18**	
MMSE <24	2 (3)	2 (11)	0.16
Total CAMCOG ≤80	0 (0)	4 (22)	1.00
	Systolic OH N= 59	**No Systolic OH N= 35**	
MMSE <24	4 (7)	0 (0)	0.29
Total CAMCOG ≤80	4 (7)	0 (0)	0.29
	Diastolic OH N=65	**No Diastolic OH N=26**	
MMSE <24	2 (31)	2 (8)	0.32
Total CAMCOG ≤80	4 (6)	0 (0)	0.57
	Symptomatic OH N=12	**Asymptomatic N=82**	
MMSE <24	0	4	1.00
Total CAMCOG ≤80	0	4	1.00

4.7.4 Orthostatic Hypotension at Baseline and Cognitive Decline

Similarly, OH status was not associated with cognitive decline (defined as a drop of four or more points in MMSE score or a drop of ≥5 points on CAMCOG total score) (Table 4-36).

Table 4-36 Orthostatic Hypotension, Orthostatic Hypotension Subtypes and Cognitive Decline

	Frequency (%)	**Frequency (%)**	**P**
	OH N= 76	**No OH N=18**	
Drop in MMSE of ≥4 points	9 (12)	1 (6)	0.68
Drop in total CAMCOG ≥5 points	37 (49)	6 (33)	0.24
	Systolic OH N= 59	**No Systolic OH N= 35**	
Drop in MMSE of ≥4 points	8 (14)	2 (6)	0.31
Drop in total CAMCOG ≥5 points	29 (49)	14 (40)	0.40
	Diastolic OH N=65	**No Diastolic OH N=26**	
Drop in MMSE of ≥4 points	8 (12)	2 (8)	0.72
Drop in total CAMCOG ≥5 points	32 (49)	11 (42)	0.55
	Symptomatic OH N=12	**Asymptomatic N=82**	
Drop in MMSE of ≥4 points	1 (8)	9 (11)	1.00
Drop in total CAMCOG ≥5 points	7 (58)	36 (44)	0.35

4.7.5 Continuous Response to Active Stand at Baseline and Cognition at Ten Year Follow-up

There were no significant associations between continuous blood pressure response to active stand and cognitive scores at follow-up (Table 4-37). There was an association between diastolic nadir in response to active stand and change in CAMCOG executive subscore (Table 4-38). These data were no longer significant after adjusting for potential covariates.

Table 4-37 Spearman Correlation between Continuous Haemodynamic Response to Active Stand and Cognitive Function at Follow-up

		Systolic Nadir (mmHg)	Diastolic Nadir (mmHg)	Systolic Vasodepression (mmHg)	Diastolic Vasodepression (mmHg)
Year 10 MMSE	r	-0.05	-0.13	-0.04	0.15
	P	0.61	0.22	0.69	0.14
Year 10 CAMCOG total score	r	-0.04	0.01	-0.11	0.01
	P	0.74	0.92	0.29	0.91
Year 10 CAMCOG memory score	r	-0.04	0.03	-0.11	0.03
	P	0.68	0.80	0.28	0.81
Year 10 CAMCOG executive score	r	-0.03	-0.05	-0.06	0.05
	P	0.75	0.66	0.57	0.63
CRT (ms)	r	-0.19	-0.05	0.16	0.02
	P	0.06	0.64	0.13	0.89
SRT (ms)	r	0.11	0.01	-0.05	-0.02
	P	0.28	0.94	0.66	0.82
VigRt (ms)	r	0.05	-0.04	-0.08	0.06
	P	0.63	0.73	0.44	0.59
CogRT (ms)	r	-0.25	-0.05	0.17	0.03
	P	0.02	0.64	0.10	0.78
POA (ms)	r	-0.07	-0.04	0.06	0.01
	P	0.54	0.74	0.55	0.97

Table 4-38 Spearman Correlation between Continuous Haemodynamic Response to Active Stand and Change in Cognitive Function over Follow-up Period

		Systolic Nadir (mmHg)	Diastolic Nadir (mmHg)	Systolic Vasodepression (mmHg)	Diastolic Vasodepression (mmHg)
Change in MMSE	r	0.02	0.05	0.08	-0.10
	P	0.82	0.65	0.46	0.35
Change in total CAMCOG score	r	0.04	0.05	0.10	0.00
	P	0.68	0.64	0.32	0.98
Change in CAMCOG memory score	r	-0.06	-0.06	0.17	0.08
	P	0.59	0.56	0.10	0.47
Change in CAMCOG executive score	r	0.17	**0.22**	0.00	-0.16
	P	0.10	**0.03**	0.97	0.13

4.7.6 Continuous Response to Active Stand at Baseline and Cognitive Impairment

Continuous haemodynamic responseto active stand was not associated with incident cognitive impairment (Table 4-39).

Table 4-39 Logistic Regression Examining the Association between Continuous Response to Active Stand and Cognitive Impairment

Variable	MMSE<24			CAMCOG ≤80		
	OR	95% CI	P	OR	95% CI	P
Systolic Nadir (mmHg)	1.01	0.97, 1.04	0.77	0.99	0.96, 1.03	0.72
Diastolic Nadir (mmHg)	1.09	1.00, 1.20	0.08	0.98	0.92, 1.04	0.50
Systolic vasodepression (mmHg)	0.94	0.87, 1.02	0.13	1.01	0.96, 1.07	0.63
Diastolic vasodepression (mmHg)	0.85	0.75, 0.98	0.02	0.93	0.90, 1.11	0.93

4.7.7 Continuous Response to Active Stand at Baseline and Cognitive Decline

Similarly, continuous haemodynamic response to active stand was not associated with a decline in MMSE of four or more points or a decline in total CAMCOG score of five or more points (Table 4-40)

Table 4-40 Logistic Regression Examining the Association between Continuous Response to Active Stand and Cognitive Decline over Follow-up

Variable	OR	95% CI	P
	Drop in MMSE ≥ 4 Points		
Systolic Nadir (mmHg)	0.99	0.97, 1.02	0.42
Diastolic Nadir (mmHg)	0.98	0.94, 1.03	0.46
Systolic Vasodepression (mmHg)	1.02	0.99, 1.06	0.27
Diastolic Vasodepression (mmHg)	1.04	0.97, 1.11	0.31
	Drop in total CAMCOG ≥ 5Points		
Systolic Nadir (mmHg)	1.01	0.99, 1.03	0.25
Diastolic Nadir (mmHg)	1.01	0.98, 1.04	0.51
Systolic Vasodepression (mmHg)	1.01	0.99, 1.03	0.46
Diastolic Vasodepression (mmHg)	1.01	0.97, 1.06	0.64

4.8 Response to Carotid Sinus Massage at Baseline and Cognitive Performance at Follow-up

4.8.1 Carotid Sinus Hypersensitive at Baseline and Cognition at Follow-up

Eighty-eight participants underwent CSM at baseline and full cognitive testing at ten year follow-up. Twenty-eight participants were diagnosed with carotid sinus hypersensitivity at baseline. Neither cognitive scores at ten years or change in cognitive score over follow-up period were significantly influenced by CSH status at baseline (Table 4-41).

Table 4-41 Cognitive Function at Follow-up According to CSH Status at Baseline

	CSH N=28	**No CSH N=60**	
	Median (IQ range)	**Median (IQ range)**	**P**
Scores at Follow-up			
MMSE	27.0 (26.0, 29.0)	29.0 (27.0, 29.0)	0.08
CAMCOG total	92.0 (87.0, 96.0)	94.5 (91.0, 98.0)	0.12
CAMCOG memory	22.5 (21.0, 24.0)	23.0 (21.0, 24.0)	0.55
CAMCOG executive	20.5 (16.5, 22.5)	20.5 (18.0, 22.0)	0.26
CRT (ms)	600.7 (550.7, 654.6)	629.1 (566.2, 668.2)	0.24
SRT (ms)	451.0 (411.7, 539.5)	440.8 (405.8, 509.8)	0.69
VigRT (ms)	543.3 (416.3, 569.6)	545.5 (511.7, 587.2)	0.64
Cog RT (ms)	150.2 (109.4, 194.0)	158.7 (114.9, 230.2)	0.55
POA (ms)	1636.5 (1530.1, 1802.6)	1648.9 (1501.7, 1758.1)	0.90
Change in Cognitive Function of Follow-up			
MMSE	1.0 (0, 2.5)	1.0 (0, 2.0)	0.42
CAMCOG total	4.5 (1.0, 7.0)	3.0 (1.0, 7.0)	0.51
CAMCOG memory	1.0 (0, 2.0)	0 (0, 2.0)	0.53
CAMCOG executive	1.0 (-1.0, 3.0)	2.0 (-1.0, 3.0)	0.39

4.8.2 Symptomatic Carotid Sinus Hypersensitivity at Baseline and Cognitive Impairment at Follow-up

Twelve of the participants with CSH had symptoms during carotid sinus massage. Cognitive function at ten years did not differ between the symptomatic and asymptomatic groups. Similarly, cognitive decline over the follow-up did not differ according to presence of absence of symptoms during carotid sinus massage (Table 4-42).

Table 4-42 Cognitive Function at Follow-up According to Symptomatic CSH Status at Baseline

	Symptomatic CSH N=12	**Asymptomatic N=76**	
	Median (IQ range)	**Median (IQ range)**	**P**
Scores at Follow-up			
MMSE	28.5 (27.0, 29.0)	28.0 (26.0, 29.0)	0.77
CAMCOG total	91.5 (88.3, 95.0)	94.0 (90.0, 97.8)	0.29
CAMCOG memory	23.0 (18.5, 24.0)	23.0 (21.0, 24.0)	0.51
CAMCOG executive	19.0 (16.3, 20.8)	20.5 (18.0, 23.0)	0.56
CRT (ms)	580.9 (539.3, 657.6)	627.6 (583.1, 668.2)	0.10
SRT (ms)	419.9 (381.3, 581.4)	449.6 (412.6, 509.7)	0.52
VigRT (ms)	544.6 (478.0, 597.3)	545.0 (515.1, 584.0)	0.96
Cog RT (ms)	160.1 (97.5, 199.9)	154.7 (114.9, 230.2)	0.51
POA (ms)	1587 (1388, 1808)	1649 (1525, 1774)	0.34
Change in Cognitive Function of Follow-up			
MMSE	1.0 (-0.75, 2.0)	1.0 (0, 2.0)	0.88
CAMCOG total	5.0 (1.5, 6.75)	3.0 (1.0, 7.0)	0.60
CAMCOG memory	2.0 (-0.75, 3.0)	0 (0, 1.75)	0.24
CAMCOG executive	1.5 (-1.5, 4.5)	2.0 (-1, 3.0)	0.71

4.8.3 **Carotid Sinus Hypersensitivity at Baseline and Cognitive Impairment**

Of those participants who had carotid sinus massage at baseline, 3 had total CAMCOG score of $\leq$80 and 3 had and MMSE <24. These outcomes were not associated with presence of carotid sinus hypersensitivity at baseline or presence or absence of symptomatic CSH at baseline (Table 4-43).

Table 4-43 Carotid Sinus Hypersensitivity and Cognitive Impairment

	CSH N= 28 Frequency (%)	**No CSH N= 60 Frequency (%)**	**P**
MMSE <24	1 (4)	2 (3)	1.00
Total CAMCOG ≤80	1 (4)	2 (3)	1.00
	Symptomatic CSH N= 12 Frequency (%)	**Asymptomatic N= 76 Frequency (%)**	**P**
MMSE <24	0	3 (5)	1.00
Total CAMCOG ≤80	0	3 (5)	1.00

4.8.4 Carotid Sinus Hypersensitivity at Baseline and Cognitive Decline over Follow-up

Similarly, decline in MMSE, defined as a drop of four or more points on MMSE, was not associated with CSH at baseline or symptomatic CSH. Nor was decline in CAMCOG, when defined as a drop of ≥ 5 points (Table 4-44).

Table 4-44 Carotid Sinus Hypersensitivity and Cognitive Decline

	CSH N= 28 Frequency (%)	**No CSH N= 60 Frequency (%)**	**P**
Drop in MMSE of ≥4 points	4 (14)	5 (8)	0.46
Drop in total CAMCOG ≥ 5 points	14 (50)	24 (40)	0.38
	Symptomatic CSH N= 12 Frequency (%)	**Asymptomatic N= 76 Frequency (%)**	**P**
Drop in MMSE of ≥4 points	0	9 (11)	0.35
Drop in total CAMCOG ≥ 5 points	7 (58)	31 (40)	0.25

4.8.5 Continuous Haemodynamic Response to CSM at Baseline and Cognition at Follow-up

Continuous haemodynamic response to CSM at baseline was not associated with performance on MMSE, CAMCOG or COMPASS at ten years or change in cognitive performance over follow-up period (Table 4-45 and Table 4-46)

Table 4-45: Spearman Correlation between Continuous Haemodynamic Response to CSM and Cognitive Function at Follow-up

		Max RR interval	Max Vaso-depression	Minimum Systolic Nadir	Max delta RR
MMSE	r	-0.08	-0.06	-0.08	-0.10
	P	0.46	0.57	0.46	0.34
CAMCOG total	r	-0.16	-0.10	-0.01	-0.17
	P	0.15	0.33	0.93	0.12
CAMCOG memory	r	-0.16	-0.14	-0.01	-0.17
	P	0.13	0.18	0.95	0.11
CAMCOG executive	r	-0.09	0.01	-0.02	-0.09
	P	0.41	0.95	0.89	0.41
CRT (ms)	r	-0.08	-0.04	-0.09	-0.07
	P	0.44	0.68	0.43	0.50
SRT (ms)	r	0.00	0.06	-0.04	0.01
	P	0.97	0.59	0.74	0.94
VigRT (ms)	r	-0.01	-0.05	-0.09	-0.01
	P	0.92	0.67	0.39	0.93
CogRT (ms)	r	-0.08	-0.08	-0.05	-0.07
	P	0.49	0.48	0.64	0.53
POA (ms)	r	-0.06	-0.02	-0.09	-0.05
	P	0.58	0.86	0.42	0.63

Table 4-46 Spearman Correlation between Continuous Haemodynamic Response to CSM and Change in Cognitive Function over Follow-up

Change in		Max RR interval	Max Vaso-depression	Minimum Systolic Nadir	Max delta RR
MMSE	r	0.13	0.07	0.08	0.15
	P	0.22	0.52	0.46	0.17
CAMCOG total	r	0.10	0.02	0.07	0.12
	P	0.35	0.82	0.54	0.27
CAMCOG memory	r	0.12	0.07	0.02	0.13
	P	0.26	0.50	0.87	0.22
CAMCOG executive	r	-0.07	-0.13	0.16	-0.06
	P	0.49	0.22	0.14	0.56

4.8.6 Continuous Haemodynamic Response to CSM at Baseline and Cognitive Impairment

No association was observed between haemodynamic response to CSM at baseline and scoring less than 24 points on MMSE at follow-up or ≤80 points on total CAMCOG at follow-up (Table 4-47).

4.8.7 Continuous Haemodynamic Response to CSM at Baseline and Cognitive Decline

Similarly decline in MMSE, defined as a drop of four or points on MMSE, was not associated with haemodynamic response to CSM at baseline (Table 4-48). Nor was decline in CAMCOG total score, defined as a drop of ≥ 5 points, associated with response to CSM at baseline (Table 4-48).

Table 4-47 Logistic Regression Examining Association between Continuous Response to CSM at baseline and Cognitive Impairment at Follow-up

	MMSE<24			Total CAMCOG ≤ 80		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Max RR interval (s)	0.83	0.34, 2.00	0.67	0.99	0.52, 1.91	0.99
Max Vasodepression (mmHg)	1.00	0.94, 1.07	0.99	0.99	0.92, 1.06	0.73
Minimum Systolic Nadir (mmHg)	1.00	0.95,1.07	0.90	0.97	0.90, 1.03	0.29
Max Delta RR (s)	0.90	0.41, 2.0	0.80	1.02	0.53, 1.94	0.96

Table 4-48 Logistic Regression Examining Association between Continuous Response to CSM at baseline and Cognitive Decline over Follow-up

	OR	**95% CI**	**P**
Drop in MMSE of ≥4 points			
Max RR interval (s)	0.89	0.57, 1.41	0.62
Max Vasodepression (mmHg)	1.00	0.96, 1.04	0.82
Minimum Systolic Nadir (mmHg)	0.68	0.98, 1.03	0.68
Max Delta RR (s)	0.90	0.57, 1.43	0.66
Drop in total CAMCOG ≥5 points			
Max RR interval (s)	1.13	0.89, 1.43	0.31
Max Vasodepression (mmHg)	1.01	0.98, 1.03	0.61
Minimum Systolic Nadir (mmHg)	1.01	0.99, 1.02	0.34
Max Delta RR (s)	1.15	0.90, 1.47	0.27

4.9 Response to Autonomic Function Tests at Baseline and Cognition at Follow-up

Data from one or more autonomic function test was available for 94 or the 99 participants who underwent cognitive testing at follow-up. Numbers of participants completing each of the autonomic function tests at baseline and full cognitive testing at follow-up are shown below (Table 4-49). Eighty-six participants completed all five tests required for classification of autonomic function as normal or abnormal using modified Ewing criteria.

Table 4-49 Number of participants completing individual autonomic function tests

Autonomic Function Test	Number of participants
Blood pressure and heart rate response to standing	91
Blood pressure response to isometric exercise	93
Blood pressure and heart rate response Valsalva manoeuvre	94
Blood pressure response to cold stimulation	91
Heart rate response to deep breathing	89

4.9.1 Abnormal Autonomic Function at Baseline and Cognition

Comparing participants with abnormal autonomic function at baseline with those with normal baseline autonomic function as defined by modified Ewing criteria did not reveal any difference in cognitive scores or reaction times at follow-up (Table 4-50). Participants with abnormal autonomic function however did have significantly greater decline in total CAMCOG scores over the follow-up period (Table 4-50). This was no longer significant after adjusting for potential confounding variables.

Table 4-50 Comparison of Cognitive Performance at Follow-up and Change in Cognitive Performance for Participants with Normal and Abnormal Autonomic Function at Baseline by Ewing Classification

	Normal Autonomic function N=57	**Abnormal Autonomic function N =29**	**P**
	Median (IQR)	**Median (IQR)**	
Cognitive Function at Follow-up			
MMSE	29.0 (27.0, 29.0)	27.0 (26.0, 29.0)	0.36
CAMCOG total	94.0 (90.0, 97.0)	94 (86.0, 97.0)	0.50
CAMCOG memory	23.0 (21.0, 24.0)	23.0 (21.0, 24.0)	0.80
CAMCOG executive	20.0 (18.0 22.0)	19.0 (17.0, 21.0)	0.43
CRT (ms)	618.3 (566.1, 655.8)	659.3 (656.6, 732.0)	0.15
SRT (ms)	440.6 (402.5, 541.1)	450.7 (428.8, 514.6)	0.46
VigRT (ms)	545.0 (512.0, 584.8)	545.0 (524.2, 566.0)	0.88
CogRT (ms)	49.4 (108.1, 230.2)	183.6 (121.8, 219.4)	0.27
POA (ms)	1620.7 (1499.1, 1754.0)	1663.7 (1563.4, 1818.5)	0.30
Change in Cognitive Function			
MMSE	1.0 (0, 2.0)	1.0 (0, 3.0)	0.11
Total CAMCOG	3.0 (1.0, 7.0)	6.0 (2.0, 9.0)	**0.04**
CAMCOG memory	0 (-1.0, 2.0)	1.0 (0, 2.0)	0.23
CAMCOG executive	2.0 (-1.0, 5.0)	1.0 (0.0, 3.0)	0.66

4.9.2 Abnormal Autonomic Function at Baseline, Cognitive Impairment and Cognitive Decline

Presence of cognitive impairment as defined as MMSE<24 or total CAMCOG ≤80 was not associated with abnormal autonomic function at baseline. Similarly, a drop in MMSE score of four or more points or a decline in CAMCOG total score of ≥5 points was not associated with abnormal autonomic function at baseline (Table 4-51)

Table 4-51 Cognitive impairment and Cognitive Decline at Ten Years by Autonomic Function

	Normal Autonomic Function N=57	**Abnormal Autonomic Function N=29**	**P**
MMSE <24	3 (5%)	1 (3%)	1.00
Total CAMCOG ≤80	2 (4%)	1 (3%)	1.00
Drop in MMSE of ≥4 points	3 (5%)	3 (27%)	1.00
Drop in total CAMCOG ≥5 points	19 (33%)	16 (55%)	0.10

4.9.3 Continuous Response to Individual Autonomic Function Tests at Baseline and Cognition at Follow-up

Examining the association between cognitive function at ten years and haemodynamic response to individual autonomic function tests at baseline showed that greater BP response to placing a hand in cold water was associated with shorter digit vigilance reaction time; greater systolic BP overshoot during Valsalva manoeuvre was associated with better CAMCOG executive score and shorter digit vigilance reaction time at ten years; greater heart rate response to Valsalva manoeuvre was associated with shorter simple reaction time, shorter digit vigilance reaction time and shorter power of attention; and, finally, that greater 30:15 ratio in response to standing was associated with shorter choice reaction time (Table 4-52). None of these associations remained significant after adjusting for potential covariates.

Table 4-52 Spearman Correlation between Continuous Haemodynamic Response to Individual Autonomic Function and Cognitive Score at Follow-up

		Stand SBP drop (mmHg)	Cold pressor DBP difference (mmHg)	Isometric Exercise DBP difference (mmHg)	Valsalva SBP overshoot (mmHg)	30:15 Ratio	Valsalva ratio	Heart rate response to deep breathing
MMSE	r	-0.07	0.12	0.03	0.03	0.07	0.07	0.09
	P	0.51	0.24	0.75	0.77	0.47	0.47	0.41
CAMCOG total score	r	-0.11	0.13	0.00	0.19	0.12	0.18	0.09
	P	0.29	0.23	0.99	0.07	0.27	0.09	0.40
CAMCOG memory score	r	-0.10	0.12	-0.11	0.15	0.14	0.19	0.05
	P	0.35	0.27	0.28	0.14	0.17	0.06	0.62
CAMCOG executive score	r	-0.05	0.00	-0.09	0.26	0.07	0.18	-0.11
	P	0.60	0.98	0.41	**0.01**	0.52	0.09	0.32
CRT (ms)	r	0.10	-0.18	-0.01	-0.12	-0.22	-0.10	-0.19
	P	0.35	0.09	0.92	0.26	**0.04**	0.35	0.08
SRT (ms)	r	0.01	-0.01	-0.16	-0.18	-0.05	**-0.27**	-0.17
	P	0.93	0.91	0.13	0.09	0.61	**0.01**	0.11
VigRT (ms)	r	-0.09	**-0.23**	0.07	-0.20	-0.17	**-0.25**	-0.18
	P	0.39	**0.03**	0.54	**0.05**	0.12	**0.02**	0.10
CogRT (ms)	r	0.15	-0.13	0.11	0.07	-0.11	0.15	0.00
	P	0.17	0.24	0.30	0.50	0.30	0.16	0.98
POA (ms)	r	0.03	-0.12	-0.05	-0.17	-0.19	**-0.23**	-0.20
	P	0.75	0.27	0.61	0.10	0.07	**0.03**	0.07

Examination of the associations between continuous response to autonomic function tests and change in cognitive function over ten year follow-up showed that smaller active stand 30:15 ratio was associated with greater declines in CAMCOG total score and CAMCOG memory score. Smaller heart rate ratio in response to Valsalva were associated with greater decline in CAMCOG memory score and larger heart rate changes in response to deep breathing were associated with greater decline in CAMCOG executive score over ten years (Table 4-53).

Table 4-53 Spearman Correlation between Continuous Haemodynamic Response to Individual Autonomic Function and Change in Cognitive Score at Follow-up

		Stand SBP drop (mmHg)	Cold pressor DBP difference (mmHg)	Isometric Exercise DBP difference (mmHg)	Valsalva SBP overshoot (mmHg)	30:15 Ratio	Valsalva ratio	Heart rate response to deep breathing
Change in MMSE	r	0.02	-0.05	0.02	0.06	-0.17	-0.04	0.00
	P	0.83	0.66	0.86	0.56	0.11	0.74	0.99
Change in total CAMCOG score	r	0.11	-0.04	-0.11	-0.08	-0.31	-0.17	-0.01
	P	0.27	0.70	0.30	0.45	**<0.01**	0.09	0.93
Change in CAMCOG memory score	r	0.16	-0.08	-0.02	-0.15	-0.28	**-0.31**	-0.02
	P	0.12	0.46	0.81	0.15	**0.01**	**<0.01**	0.86
Change in CAMCOG executive score	r	0.03	0.19	-0.02	-0.03	-0.06	0.07	0.23
	P	0.77	0.07	0.84	0.74	0.54	0.49	**0.03**

After adjusting for covariates, only the associations between 30:15 ratio and change in total CAMCOG remained significant. Lower 30:15 ratio was associated with greater decline in total CAMCOG score over the follow-up period (Table 4-54). There was a borderline association between 30:15 ratio and change in CAMCOG memory score (Table 4-55).

Table 4-54 Linear Regression Examining the Independent Association Between 30:15 Ratio and Change in CAMCOG Total Score

	B	95% CI		P
Age	0.20	-0.05	0.45	0.12
Sex	0.66	-1.41	2.73	0.53
High blood pressure	1.12	-1.37	3.61	0.37
Diabetes	1.37	-4.30	7.05	0.63
Smoker (yes / no)	-2.51	-6.67	1.64	0.23
Any cardioactive drug	0.38	-2.16	2.91	0.77
Years in education	-0.18	-0.54	0.19	0.34
Any cardiovascular or cerebrovascular disease	-1.60	-3.84	0.65	0.16
Psychotropic Medication	0.31	-2.35	2.96	0.82
Consumes alcohol (yes / no)	1.92	-0.25	4.09	0.08
Cornell	0.36	0.08	0.64	**0.01**
CAMCOG Total Score at Baseline	-0.15	-0.42	0.13	0.29
30:15 ratio	-13.41	-23.74	-3.08	**0.01**
Dependent variable: Change in Total CAMCOG score over Follow-up Adjusted Model $R^{2 =}$ 0.14				

Table 4-55 Linear Regression Examining the Independent Association Between 30:15 Ratio and Change in CAMCOG Memory Score

	B	95% CI		P
Age	0.06	-0.04	0.16	0.25
Sex	0.41	-0.45	1.27	0.34
High blood pressure	-0.15	-1.19	0.89	0.78
Diabetes	1.72	-0.57	4.02	0.14
Smoker (yes / no)	-0.10	-1.79	1.58	0.90
Any cardioactive drug	1.34	0.27	2.41	**0.02**
Years in education	-0.13	-0.27	0.01	0.07
Any cardiovascular or cerebrovascular disease	-0.82	-1.75	0.11	0.08
Psychotropic Medication	-0.27	-1.39	0.85	0.63
Consumes alcohol (yes / no)	0.36	-0.52	1.23	0.42
Cornell	0.06	-0.05	0.18	0.30
CAMCOG Memory Score at Baseline	-0.26	-0.49	-0.04	**0.02**
30:15 ratio	-4.09	-8.29	0.11	0.06
Dependent variable: Change in CAMCOG Memory Score Adjusted Model R^2= 0.25				

4.9.4 Continuous Response to Individual Autonomic Function Tests at Baseline and Incident Cognitive Impairment

Haemodynamic response to autonomic function tests was not associated with cognitive impairment defined as MMSE <24 or total CAMCOG ≤80 (Table 4-56)

Table 4-56 Association between Haemodynamic Response to Autonomic Function Tests at Baseline and Cognitive Impairment at Follow-up

	MMSE <24			Total CAMCOG ≤80		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
30:15 Ratio	7.21	0.01, 138573	0.70	0.01	0.00, 264	0.30
Cold pressor DBP difference (mmHg)	0.98	0.85, 1.13	0.78	1.02	0.89, 1.17	0.78
Isometric Exercise BP difference (mmHg)	1.02	0.97, 1.08	0.48	0.95	0.88, 1.02	0.14
Valsalva SBP overshoot (mmHg)	1.03	0.99, 1.06	0.18	0.96	0.91, 1.01	0.13
Valsalva ratio	0.22	0.00, 15.6	0.49	0.22	0.00, 29.1	0.55
Heart rate response to deep breathing (B.P.M)	0.98	0.84, 1.13	0.74	1.09	0.92, 1.28	0.32

4.9.5 Continuous Response to Individual Autonomic Function Tests at Baseline and Cognitive Decline

Greater 30:15 ratio was associated with significantly lower odds ratio of a fall in MMSE of four or more points or fall in total CAMCOG of five or more points. Greater Valsalva overshoot was associated with increased OR of fall in MMSE of four or more points (Table 4-57). None of these associations was significant after adjusting for potential covariates.

Table 4-57 Logistic Regression Examining Association between Haemodynamic Response to Autonomic Function Tests and Cognitive Decline

	Drop in MMSE of ≥ 4 points			Drop in CAMCOG TOTAL of ≥ 5 points		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
30:15 Ratio	0.01	0.00, 0.96	**0.05**	0.01	0.00, 0.98	**0.05**
Cold pressor DBP difference (mmHg)	0.92	0.82, 1.03	0.13	1.00	0.95, 1.06	0.96
Isometric Exercise DBP difference (mmHg)	0.98	0.93, 1.03	0.34	0.97	0.94, 1.01	0.97
Valsalva SBP overshoot (mmHg)	1.03	1.00, 1.05	**0.04**	1.00	0.99, 1.02	1.00
Valsalva ratio	6.25	0.61, 63.8	0.12	0.69	0.16, 3.04	0.62
Heart rate response to deep breathing (B.P.M)	0.99	0.88, 1.11	0.84	1.00	0.94, 1.06	0.88

4.10 **Heart Rate Variability at Baseline and Cognition at Follow-up**

Of the 99 individuals who underwent full cognitive testing at follow-up, 88 had heart rate variability assessed at baseline. Of these 80 had recordings where less than 10% of the beats were interpolated or ectopic beats and were therefore suitable for analysis.

4.10.1 **Heart Rate Variability at Baseline and Cognition at Follow-up**

Examining the association between heart rate variability and cognition at ten years did not show any associations between HRV parameters and MMSE or CAMCOG. An association was observed between the cognitive reaction time and HF/LF ratio (Table 4-58). This was not significant after adjusting for covariates. There was no association between HRV parameters and change in cognitive scores (Table 4-59).

Table 4-58 Spearman Correlation between Heart Rate Variability and Cognitive Function at Follow-up

		SD RR (ms)	Total Power (ms^2)	Very low frequency (ms^2)	low frequency (ms^2)	high frequency (ms^2)	HF/LF Ratio
MMSE	**r**	-0.06	0.00	0.00	0.04	0.01	0.03
	P	0.61	0.97	1.00	0.74	0.92	0.80
Total CAMCOG	**r**	0.01	0.07	0.13	0.12	-0.03	-0.21
	P	0.95	0.50	0.22	0.25	0.79	0.05
CAMCOG m	**r**	-0.02	0.02	0.06	0.07	-0.09	-0.19
	P	0.86	0.88	0.61	0.53	0.38	0.08
CAMCOG executive	**r**	0.04	0.08	0.07	0.16	0.03	-0.11
	P	0.73	0.45	0.54	0.14	0.77	0.31
CRT (ms)	**r**	-0.02	-0.06	-0.06	-0.08	-0.01	0.09
	P	0.84	0.59	0.59	0.44	0.90	0.41
SRT (ms)	**r**	-0.02	0.03	0.08	0.03	-0.07	-0.15
	P	0.85	0.79	0.44	0.76	0.53	0.15
VigRt (ms)	**r**	-0.08	-0.03	-0.04	-0.01	-0.01	-0.03
	P	0.49	0.76	0.74	0.93	0.91	0.79
CogRT (ms)	**r**	0.02	-0.05	-0.09	-0.09	0.05	0.22
	P	0.87	0.64	0.40	0.40	0.66	**0.04**
POA (ms)	**r**	-0.06	-0.04	-0.01	-0.04	-0.05	-0.04
	P	0.61	0.72	0.90	0.71	0.62	0.71

Table 4-59 Spearman Correlation between Heart Rate Variability and Cognitive Decline over Follow-up

		SD RR (ms)	Total Power (ms^2)	Very low frequency (ms^2)	low frequency (ms^2)	high frequency (ms^2)	HF/LF Ratio
Change in MMSE	**r**	0.01	-0.03	-0.03	-0.08	-0.07	-0.06
	P	0.93	0.75	0.76	0.45	0.50	0.55
Change in total CAMCOG score	**r**	-0.04	-0.10	-0.17	-0.12	-0.07	0.07
	P	0.73	0.35	0.12	0.27	0.51	0.55
Change in CAMCOG memory score	**r**	0.14	0.13	0.10	0.12	0.11	0.01
	P	0.19	0.21	0.34	0.25	0.31	0.91
Change in CAMCOG executive score	**r**	-0.06	-0.08	-0.05	-0.08	-0.14	-0.13
	P	0.60	0.48	0.62	0.44	0.20	0.24

4.10.2 **Heart Rate Variability at Baseline and Cognitive Impairment**

Heart rate variability was not associated with an MMSE <24 at follow-up or a total CAMCOG of ≤ 80 (Table 4-60)

Table 4-60 Logistic Regression Examining Association between Baseline Heart Rate Variability and Cognitive Impairment at Follow-up

	MMSE <24			**Total CAMCOG ≤80**		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
SDRR (ms)	0.96	0.83, 1.11	0.56	0.93	0.83, 1.05	0.24
Total Power (ms^2)	1.00	0.99, 1.01	0.84	1.00	0.99, 1.00	0.44
VLF (ms^2)	1.00	0.99, 1.01	0.63	1.00	0.99, 1.00	0.88
LF (ms^2)	1.00	0.99, 1.01	0.59	0.99	0.98, 1.01	0.28
HF (ms^2)	0.98	0.93, 1.02	0.32	0.99	0.96, 1.01	0.24
HF/LF ratio	0.41	0.01, 24.8	0.67	2.24	0.89, 5.69	0.09

4.10.3 **Heart Rate Variability at Baseline and Cognitive Decline**

Similarly there were no significant associations between heart rate variability and decline in MMSE of ≥4 points or a decline in total CAMCOG score of ≥5 points.

Table 4-61 Logistic Regression Examining Association between Baseline Heart Rate Variability and Cognitive Decline Over Follow-up

	OR	95% CI	P
	Drop in MMSE of ≥ 4 points		
SDRR (ms)	1.03	0.97, 1.08	0.39
Total Power (ms^2)	1.00	0.99, 1.00	0.96
VLF (ms^2)	1.00	0.99, 1.00	0.78
LF (ms^2)	1.00	0.99, 1.00	0.52
HF (ms^2)	1.00	0.99, 1.00	0.41
HF/LF ratio	2.14	0.92, 4.96	0.08
	Drop in CAMCOG TOTAL of ≥ 5 points		
SDRR (ms)	0.99	0.96, 1.03	0.72
Total Power (ms^2)	1.00	0.99, 1.00	0.51
VLF (ms^2)	1.00	0.99, 1.00	0.41
LF (ms^2)	1.00	0.99, 1.00	0.21
HF (ms^2)	1.00	0.99, 1.00	0.57
HF/LF ratio	1.95	0.84, 4.52	0.12

4.11 **Summary of Key Findings in Chapter 4.**

To summarise the following associations were noted in this chapter.

4.11.1 **Change in Cognition**

Scores on the MMSE and CAMCOG were significantly lower at ten year follow-up than at baseline

4.11.2 **Hypertension and Cognition**

Among participants who were hypertensive at baseline a significantly higher proportion were found to have a drop in total CAMCOG score of ≥5 points indicating cognitive decline. This remained significant after adjusting for age, sex, cardiovascular risk factors and cardioactive medication including antihypertensive medication.

4.11.3 **Ambulatory Blood Pressure and Cognition**

Lower daytime mean systolic BP was associated with longer cognitive reaction time a longer choice reaction time. After adjusting for covariates this only remained significant for the association between mean systolic BP and cognitive reaction time. Longer cognitive reaction times were also associated with lower 24 hour mean systolic BP.

Greater nighttime BP variability at baseline was independently associated with poorer MMSE and total CAMCOG scores at follow-up. Greater decline in these scores was also indepently associated with greater nocturnal diastolic BP variability at baseline

Decline in total CAMCOG of ≥5 points was independently associated with greater daytime systolic and diastolic BP variability, greater 24 hour mean systolic and diastolic BP and greater 24 hour systolic and diastolic BP variability.

4.11.4 **Active Stand**

Orthostatic hypotension was not associated with cognition at ten years. Symptomatic OH was associated greater change in CAMCOG memory. There were no significant associations between cognitive function at follow-up and degree of vasodepression or BP nadir during active stand.

4.11.5 **Carotid Sinus Massage**

CSH and CSS at baseline were not associated with cognitive function at follow-up. Nor were they associated with change in cognition, incident cognitive impairment or cognitive decline. Similarly, degree of vasodepression and / or RR interval post CSM were not associated with cognitive function at follow-up or change in cognitive function over the ten year follow-up interval.

4.11.6 **Autonomic Function**

Abnormal autonomic function at baseline was associated with a greater change in total CAMCOG score over the ten year follow-up interval but this did not remain significant after adjusting for covariates. When autonomic tests were examined individually longer 30:15 ratio was independently associated with greater decline in CAMCOG total score. After adjusting for potential covariates, heart rate variability at baseline, was not

associated with cognition at follow-up or change in cognition over the follow-up interval.

4.12 **Discussion**

Comparison of baseline and follow-up scores showed that there had been a significant decline in MMSE scores, total CAMCOG scores and CAMCOG subscores over the ten year follow-up period. This is in keeping with other longitudinal studies which have consistently shown an age-related cognitive decline, particularly among people aged 60 years and over (Salthouse, 2009, Park et al., 2003). None of the follow-up participants scored below 24 on the MMSE at baseline or below 80 on the total CAMCOG at baseline. At follow-up, 4% of participants were defined as cognitively impaired using these cut-offs. This is markedly lower than the reported prevalence of cognitive impairment in the MRC study, that found 18.3% of a community-dwelling UK adults aged ≥75 years have an MMSE<24 and suggests that the sample in this study is not be fully representative of the wider general population (Rait et al., 2005).

Individuals lost to follow-up prior to the year ten assessment scored significantly worse on cognitive tests at baseline compared to individuals participating in year ten follow-up. Similarly, compared to the year ten follow-up cohort, the group lost to follow-up had significantly longer reaction times at baseline (indicating poorer cognition). None of the 15 individuals with cognitive impairment at baseline (total CAMCOG <80) participated in the ten year follow-up examination (eight had died, four no longer lived in the recruitment area and three declined to participate in the ten year follow-up). There was also a suggestion that, compared to individuals lost to follow-up, autonomic function among ten year follow-up participants may have been better preserved at baseline, but this did not reach statistical significance.

These data suggest that the follow-up cohort was not representative of the baseline population from which participants were recruited. Every effort was made to make the study as accessible as possible to frail older people. All assessments, except the MRI scan, were conducted in participants' homes and provision was made for a personal consultee. However, attrition appears to have been greatest in the people with cognitive impairment at baseline. This is a common challenge in longitudinal studies involving

older people and must to be borne in mind when interpreting the result of the ten year follow-up (Chatfield et al., 2005).

Few associations were found between hypertension and either cognitive function at follow-up or change in cognitive function over the follow-up period. Hypertension at baseline was significantly associated with increased odds of finding that the total CAMCOG score had declined by ≥5 points but not with a decline of ≥4 points on MMSE. The failure to show an association between hypertension and decline in MMSE score may be a result of the ceiling effect observed with the MMSE. This is dealt with in further detail later in the discussion.

Several points should be noted when examining associations between blood pressure and cognition. Firstly, the age of participants in this study at baseline ranged from 65-83 years. It is possible that the relationship between blood pressure and cognition is not uniform across this age range. Studies suggest hypertension in midlife is associated impaired cognitive function in later life (Wolf et al., 2007, Knopman et al., 2009, Singh-Manoux and Marmot, 2005). However hypertension in later life, particularly among individuals aged 80 and over, appears to be less strongly associated with cognitive impairment and may even be associated with superior cognitive function (Herbert et al., 2004, Tervo et al., 2004, Solfrizzi et al., 2004). In this study, greater mean 24-hour BP and daytime mean BP at baseline were independently associated with shorter cognitive reaction time at ten year follow-up (indicating better cognitive function). Hypotension in later life has also been associated with impaired cognitive function and some authors suggest a U or J shaped relationship between BP and cognitive function in older people (Glynn et al., 1999, Bohannon et al., 2002, Ruitenberg et al., 2001, Morris et al., 2001b). The small sample size in this study meant it was not possible to examine if there was an interaction between age, blood pressure and cognition.

The relationship between hypertension and cognition may also be modified by the duration of hypertension. Recent studies have shown that cognition is affected only in individuals with long duration of hypertension, regardless of age (Power et al., 2013). Although hypertensive status at baseline was known, duration of hypertension prior to baseline assessment, and degree of BP control following baseline assessment was not known. It is likely that BP control has improved in this cohort since baseline

assessment. During the study follow-up period control of cardiovascular risk factors became a public health priority (Redwood, 2007). Since 2005, general practitioners in England have been financially incentivised to identify patients with hypertension and optimise BP control. Examination of GP records and ambulatory BP recordings at baseline and follow-up revealed significantly fewer unrecognised hypertensive patients within the cohort at follow-up and that significantly more individuals were treated to target BP at follow-up compared with baseline (McDonald et al., 2013). These improvements in hypertension management may have weakened the association between hypertension and cognition.

In an attempt to control for the effects of antihypertensive treatment on outcomes in this study, adjustment was made in multivariable models for "use of antihypertensive medication" or "use of cardioactive medication". Controlling for use of antihypertensive medication makes no allowance for duration of treatment, degree of BP control attained or compliance with medication. Furthermore, it is increasingly recognised that antihypertensive agents, particularly ACE inhibitors and angiotensin receptor blockers have class specific neuroprotective properties (Macquin-Mavier et al., 2013). Because of the small sample size, adjustment could not be made for individual classes of antihypertensive agents. Class specific effects will therefore not have been accounted for in the analysis.

Analysis of the association between BP variability and cognition also revealed mixed results. After adjusting for potential covariates, greater night-time diastolic BP variability was independently associated with poorer MMSE and total CAMCOG score at follow-up, and with greater decline in these scores over the follow-up period. Daytime and 24-hour BP variability were not associated with cognition at follow-up or change in cognition over the follow-up period. Greater daytime and 24-hour systolic and diastolic BP variability were, however, both independently and significantly associated with increased odds of participants' total CAMCOG score having fallen five or more points over the follow-up interval. These findings suggest greater BP variability maybe associated with subsequent cognitive decline.

There are no other published studies examining the long-term association between 24-hour blood pressure variability and cognition. Cross-sectional studies examining 24-

hour BP variability have shown that increases in both systolic and diastolic BP variability are associated with poorer cognitive function (Sakakura et al., 2007, Kerr, 2009). Sakakura showed that participants with greatest BP variability scored significantly less well on the MMSE and Kerr et al showed increased greater BP variability was associated with deficits in attention, processing speed and executive function (Sakakura et al., 2007, Kerr, 2009). Studies have also shown increased systolic and diastolic BP variability among patients with cognitive impairment (Bellelli et al., 2002, Kanemaru et al., 2001, Marti-Fabregas et al., 2001).

In addition to BP variability, 24 ABPM recordings also allow calculation of diurnal variation and nocturnal BP dipping pattern. In this study, percentage diurnal variation was not associated with cognition at follow-up or change in cognition over the follow-up period. Similarly, dipping status was not associated with cognition at ten years, cognitive decline or incident cognitive impairment. Only one other study has examined the longitudinal association between blood pressure diurnal variation and cognitive impairment. Yamamoto et al followed-up 177 older people who had presented with a first lacunar infarct and had undergone 24-hour ABPM (Yamamoto et al., 2005). Participants were defined as dippers or non-dippers. Twenty-six participants developed incident dementia over a mean follow-up period of 8.7 years. In contrast to the findings of this study non-dipping status was a significant, independent risk factor for incident dementia (RR, 7.1; 95% CI, 2.2 to 22.0) (Yamamoto et al., 2005).

Most data regarding the association between BP diurnal variation and cognition come from cross-sectional studies. Several studies have shown an association between loss of normal dipping pattern and cognitive impairment or dementia (Bellelli et al., 2004, Guo et al., 2009, van Boxtel et al., 1998, Yamamoto et al., 2005). In addition, smaller percentage changes between daytime and nigh-time BP have been associated with poorer cognitive function, particularly executive function (Kerr, 2009, Ohya et al., 2001). The low rate of incident cognitive impairment in this study and the small number of participants in each group (dippers N= 38, non-dipper N=35, extreme-dipper N=11) may have limited the power of the study to detect small differences in cognition between groups or an association with incident cognitive impairment.

This follow-up study did not show any statistically significant associations between the components of neurocardiovascular instability (OH and CSH) and cognitive function at follow-up, cognitive decline over the follow-up period or incident cognitive impairment at ten year follow-up. Similarly, the sizes of haemodynamic responses to the active stand or carotid sinus massage were not associated with cognitive performance at ten years.

Abnormal autonomic function at baseline was not associated with cognition at follow-up. Although univariate analysis revealed abnormal autonomic function was associated with a significantly greater decline in CAMCOG total score, this was not significant after adjusting for potential demographic and cardiovascular covariates. This suggests that the relationship between abnormal autonomic function and cognitive decline is secondary to age and other vascular risk factors. Abnormal autonomic function was not significantly associated with incident cognitive impairment.

Examining associations between the response to individual autonomic function tests and cognitive scores at follow-up did not reveal any significant independent associations with the tests of parasympathetic or sympathetic function. Lower 30:15 ratio at baseline was however independently associated with greater decline in total CAMCOG score over the follow-up period.

Few associations were observed between heart rate variability at baseline and cognition at follow-up and these were not significant after adjusting for covariates, again suggesting that the observed association is secondary to age and cardiovascular risk factors. No associations were observed between HRV and cognitive decline over follow-up period or incident cognitive impairment.

Overall, after adjusting for potential covariates, there were few associations between altered autonomic function and / or neurocardiovascular instability at baseline and cognitive impairment or cognitive decline at follow-up. These findings are in keeping with other longitudinal studies examining the association between autonomic function, NCVI and cognitive function (Viramo et al., 1999, Rose et al., 2010, Yap et al., 2008, Elmstahl and Rosen, 1997, Britton et al., 2008).

Viramo et al followed-up 651 community-dwelling people aged ≥70 years and found neither systolic or diastolic OH predicted cognitive decline at a 2.5 year follow-up (Viramo et al., 1999). Rose et al showed a weak association between OH and performance on Digital Symbol Subtraction Test and Word Fluency Test. However after adjusting for demographic and cardiovascular risk factor, this finding was no longer statistically significant(Rose et al., 2010). Yap et al followed up 2321 community-dwelling Chinese older people. Despite finding a cross-sectional association between OH and cognitive impairment at baseline, they found no association between OH and cognitive decline over a one year follow-up period (Yap et al., 2008). Only one longitudinal study has found an association OH and cognition. The study was small with just 33 healthy woman, but with a longer follow-up period (5 years). Women who developed cognitive decline had significantly greater orthostatic fall in BP at baseline (Elmstahl and Rosen, 1997).

To my knowledge, there are no studies examining the long-term association between CSH and cognition and only one longitudinal study has examined the longitudinal association between HRV and cognition. Britton et al examined HRV in 5375 middle-aged people. In keeping with the findings of this study, they found that there was no association between HRV and cognition at five and twelve years follow-up or decline in cognition during the intervening seven years between follow-up cognitive assessments (Britton et al., 2008).

The lack of long-term association between NCVI, autonomic dysfunction and cognition found in longitudinal studies is in contrast to findings from cross-sectional studies. Several studies report a higher prevalence of OH among patients with dementia than among aged matched controls and poorer cognitive function has been observed among individuals with OH (Matsubayashi et al., 1997, Mehrabian et al., 2010, Allcock et al., 2006, Andersson et al., 2008). Similarly, cross-sectional studies have shown CSH to be more common among people with dementia, and a greater degree of vasodepression in response to CSH has been associated with more severe white matter disease among patients with dementia (Ballard et al., 2000, Kenny et al., 2004). Several studies have compared HRV and response to autonomic function tests among healthy controls and patients with dementia (Allan et al., 2007, Algotsson et al., 1995, Allan et al., 2005, Elmstahl et al., 1992, Giubilei et al., 1998, Kim et al., 2006). Most have shown altered

response to autonomic function tests and reduced HRV in patients with dementia, particularly patients with Parkinson's disease dementia and dementia of Lewy body (Allan et al., 2007, Algotsson et al., 1995, Allan et al., 2005, Elmstahl et al., 1992, Giubilei et al., 1998, Kim et al., 2006). Population studies have also shown cognitive impairment to be more common among those with reduced HRV, particularly parasympathetic activity (Kim et al., 2006).

It was the initial hypothesis that episodic hypotension results in cognitive decline due to cerebral hypoperfusion and anoxic damage to cerebral white matter. However, the fact that this study and other longitudinal studies have not demonstrated an association between NCIV and cognitive impairment raises questions about the direction of the relationship, possibly indicating that the reported cross-sectional associations between NCVI and cognitive decline result from concurrent neurodegeneration of CNS structures integral for normal cognition and control of the autonomic nervous system.

Several studies support the hypothesis that autonomic nervous system dysfunction is a consequence of dementing diseases rather than a precipitating risk factor. Patients with alpha synucleopathies such as Parkinson's disease dementia and dementia of Lewy body frequently demonstrate both autonomic dysfunction and cognitive impairment(Jellinger, 2011). In both conditions, Lewy bodies are found throughout the autonomic nervous system. Lewy bodies are also found in the brain stem, including the dorsal vagus nerve nucleus, important in the autonomic control of the cardiovascular system (Korczyn and Gurevich, 2010, Allan et al., 2007). Cardiac MIBG-I uptake is severely reduced in PD and DLB indicating sympathetic nerve damage (Oka et al., 2007). PD, DLB and AD have also all been associated with an underactive cholinergic system and in AD anti-cholinesterase inhibitors may normalise heart rate response to tilt testing (Allan et al., 2007). Alzheimer's disease has been associated with early involvement of the insula. The insula has been implicated in autonomic control and insula pathology is associated with arrhythmia and autonomic dysfunction (Royall et al., 2006). Cross-sectional associations between cognition and autonomic impairment may therefore be a feature of wider neurodegenerative processes associated with dementia, and the lack of longitudinal findings may indicate autonomic and cognitive dysfunction progress concurrently in these conditions.

Alternatively, features of the study may have precluded detection of a longitudinal association between episodic hypotension and cognition. The sample size was small, potentially limiting the power of the study to detect small differences in reaction times or changes in cognitive function between groups. Review of the study's power showed that when comparing the CSH and OH positive groups with "normal" individuals there was ≥80 percent power to detect differences between groups of; ≥1.5 point on MMSE and CAMCOG memory score, ≥2.5 points on CAMCOG executive score and ≥3 points on total CAMCOG score. When comparing COMPASS scores between these groups, the study had power to detect differences of 30 – 75 ms depending on reaction time. It could therefore be argued that the study has sufficient power to detect clinically significant changes in cognitive function. The surprisingly small number of participants with MMSE <24 in the cohort did, however, limit the study's power to detect associations with incident cognitive impairment.

The challenges in measuring cognitive decline should also be noted. In order to measure change it is important to administer the same cognitive tests. However, with repeated attempts ability to perform the test may improve. This practice effect can compensate for true deteriorations in cognitive function and may obscure associations with cognitive decline. Unsolicited comments from patients revealed they had checked the date, practiced serial sevens and reminded themselves who the Prime Minster was before the follow-up assessment. This was particularly problematic for the questions contained in the MMSE which many of participants had been routinely asked if admitted to hospital and were therefore very familiar with the test.

The MMSE had a marked ceiling effect; 38% of participants had an MMSE score of 30 at baseline and 19.2% had an MMSE score of 30 at follow-up. In order to detect change in cognitive performance accurately the test used must be able to measure cognitive performance at all levels of function. If the test has a ceiling effect, individuals who attain the highest cognitive scores at baseline and follow-up may have undergone cognitive decline not detected by the test. Persons with the highest scores on the MMSE could only change in one direction meaning random variation in test scores will not be evenly distributed around the initial score (Morris et al., 1999). Several variables in this study were associated with a decline in CAMCOG total score of >5 points but not with decline on MMSE >4. In contrast to the MMSE, the CAMCOG did not appear to have a

ceiling effect. This may account for some of the inconsistencies observed in this study. Statistical methods that allow inclusion of cognitive test results from additional time points may allow for better control of random variation in cognitive scores and regression towards the mean. Follow-up cognitive testing had also been conducted at 2 and 5 years. Exploratory analysis was conducted to examine if random effects modelling or generalised estimating equations would allow inclusion of these data in the analysis. The data however did not meet the required model assumptions of random effects modelling, most notably the residuals were not normally distributed and despite attempts to transform the data this could not be rectified. Boththese statistical methods usually require attrition from the study to be random which was not the case in this sample. Attrition in this study was associated with poorer cognitive function and older age at baseline. Reaction times are continuous data without ceiling effect and may therefore allow better detection of change. Unfortunately, due to the differences in the way CDR and COMPASS handle data it was not possible to assess change in reaction times.

The long-follow-up interval increased the likelihood of an individual dying before the final assessment. Individuals who developed cognitive impairment but died before the ten year follow-up assessment have not been accounted for in this analysis. As cognitive impairment is associated with increased mortality it possible that the individuals who have died were more likely to have developed cognitive impairment (Dewey and Saz, 2001). Autonomic dysfunction and NCVI have also been associated with premature mortality (Fedorowski et al., 2010, Verwoert et al., 2008, Rose et al., 2006, Masaki et al., 1998, Maser et al., 2003). It is therefore possible that individuals with more severe autonomic disease at baseline have died before year 10 cognitive assessment could be completed. These issues are examined in detail in the Chapter 8, page 238.

It should also be noted that testing of NCVI and autonomic function poses difficulties. Prevalence of neurocardiovascular and autonomic dysfunction increases with increasing age. Neurocardiovascular function was only measured at baseline. It is likely that some of the individuals without NCVI at baseline may have developed abnormalities of BP control over the follow-up period but these have not been accounted for. This may lead to an underestimate of the role of NCVI in subsequent cognitive decline or impairment.

Finally it may be that NCVI is only associated with cognitive impairment / decline in select subgroups. In order for systemic hypotension to cause cerebral hypoperfusion, BP must fall below the lower limit of cerebral autoregulation. Although many participants experienced large changes in systemic BP, it is not known if these changes caused BP to fall outside the limits of cerebral autoregulation. Symptoms of dizziness, presyncope and syncope are thought to be a potential clinical marker of cerebral hypoperfusion. The relatively low number of participants reporting symptoms during the active stand and carotid sinus massage may suggest that most individuals maintained cerebral perfusion through effective cerebral autoregulation. Interestingly, symptomatic orthostatic hypotension was independently associated with greater decline in CAMCOG memory. Other recently published studies also suggest that NCVI only threatens cognitive function in select patient groups. Frewen et al showed that OH was only associated with impaired cognition in individuals with supine hypertension (Frewen et al., 2013). Hypertension is known to alter the cerebral autoregulation such that the lower limit of autoregulation is elevated. It is possible that hypertension predisposes individual to cerebral hypoperfusion during episodes of OH.

In conclusion, this study has not shown an association between NCVI and change in cognitive function over ten year follow-up in healthy community-dwelling people. Further, larger, studies are needed to examine if there are select subgroups for which CSH and OH are associated with future cognitive decline.

Chapter 5 The Long-term Association between Neurocardiovascular Function and Depression

5.1 Introduction

The vascular depression hypothesis posits that depression, at least in some older people, is a result of cerebrovascular disease(Taylor et al., 2013). Late-life depression is associated with white matter hyperintensities (WMH), believed to be a hallmark of small vessel cerebrovascular disease (Taylor et al., 2013, Alexopoulos, 2006, Chen et al., 2006, de Groot et al., 2000, Firbank et al., 2005, Godin et al., 2008, Firbank et al., 2004). Community studies, however, have often failed to show an association between conventional vascular risk factors and depression in later life (Valkanova and Ebmeier, 2013). It has been suggested that this may be because the cerebrovascular changes as evidenced by WMH result from atypical risk factors such as cerebral hypoperfusion secondary to age-related changes in autonomic function and neurocardiovascular instability (Vasudev et al., 2011, Richardson et al., 2009).

5.2 Aim

To establish the long-term associations between autonomic dysfunction, NCVI and depression in older community-dwelling adults.

5.3 Methods

5.3.1 Tests of Neurocardiovascular Function

Tests of neurocardiovascular function performed at baseline are described in detail in section 2.3, page 42.

5.3.2 Examination of Depression

The Cornell depression scale was used at baseline and follow-up to assess depressive symptoms among participants. This 19-itemed semi-structured interview takes into account information obtained from the participant and a relative or carer(Alexopoulos et al., 1988a). The score was developed initially for use among older people with dementia but has since been validated in non-demented older people (Alexopoulos et al., 1988b). Scores of 10 or more are indicative of probable major depression. Cornell scores have

been associated with severity of depressive symptoms, higher scores indicating more severe depression (Alexopoulos et al., 1988a).

5.3.3 **Outcome Variables**

Initial analysis considered the associations between baseline neurocardiovascular function and three outcome variables.

1. Cornell score obtained at follow-up assessment
2. Change in Cornell score over the follow-up period. Follow-up score was subtracted from baseline score. Positive integers therefore indicate an improvement in depressive symptoms, while negative integers indicate a worsening of depressive symptoms.
3. Cornell score ≥10 at follow-up, indicating probable severe depression at follow-up

To take account of medication, analyses were then repeated with two further dependent variables

1. Cornell score ≥ 10 and /or use of antidepressant medication at follow-up.
2. *Incident depression*: Cornell score ≥ 10 and /or use of antidepressant medication at follow-up, but no use of antidepressant medication at baseline and baseline Cornell score ≤10.

5.4 **Results**

5.4.1 **Depression Scores at Year 10 Follow-up**

Of the 104 participants taking part in follow-up examination, one individual died and two participants withdrew from the study before assessment of depression was completed. Data were incomplete for three individuals as collateral history could not be obtained. Ninety-eight participants therefore had fully completed Cornell depression score.

Median Cornell depression score was higher at follow-up than at baseline, (P=0.002) (Table 5-1). The number of individuals with Cornell scores ≥10 (indicative of probable

depression) however, had decreased from eight to six. This change was not significant (P=0.78).

Table 5-1 Comparison of Cornell Depression Score at Baseline and Follow-up for the 98 Individuals Completing Depression Assessment at year 10

Variable	**Baseline scores N = 98**	**Ten year follow-up N = 98**	**P**
	Median (IQR)	**Median (IQR)**	
Cornell depression scale score	2.0 (1.0, 5.0)	4.0 (2.0, 6.0)	**0.002**

5.5 Ambulatory Blood Pressure Recordings at Baseline and Depression at Follow-up

Of the 98 participants for whom Cornell depression scores were available at ten years, 97 had ambulatory BP monitoring at baseline. All had 16 or more BP recordings over the 24-hour period and were suitable for analysis.

5.5.1 Baseline Hypertension Status and Depression at Follow-up

Comparing individuals who were hypertensive at baseline, defined according to NICE guidelines (mean daytime BP >135/80 on baseline ABPM), with normotensive participants did not reveal any significant difference in Cornell score at ten years or change in Cornell scores (Table 5-2). There was no association between hypertension status and participants having a Cornell score of 10 or more at follow-up (Table 5-3).

Table 5-2 Association between Hypertension Status at Baseline and Depression Scores at Follow-up

	Hypertension N=44	**No Hypertension N=53**	**P**
	Median (IQ range)	**Median (IQ range)**	
Cornell score at year ten	3.0 (2, 6)	4.0 (1.5, 6)	0.65
Change in Cornell score	-1 (-3.5, 0.5)	-1 (-3.0, 1.0)	0.85

Table 5-3 Association between Hypertension Status and Frequency of Cornell Depression Scores ≥10

	Hypertension N=43	**No Hypertension N=52**	**P**
	Frequency (percentage)	**Frequency (percentage)**	
Cornell score ten or more at year ten	2 (5%)	4 (8%)	0.69

Because the NICE criteria are stricter than many definitions of hypertension, these analyses were repeated with hypertension defined as a mean daytime BP ≥150/90. This did not reveal any additional significant associations between BP ≥ 150/90 and Cornell depression score at follow-up, or change in Cornell depression score. Similarly, a Cornell score of ten or more was not associated with BP ≥ 150/90.

5.5.2 Ambulatory BP Results at Baseline and Cornell Depression Score at Follow-up

Examining the continuous relationship between Cornell scores at follow-up and 24-hour ABPM variables did not show any significant associations. Nor were any associations observed between daytime or night-time BP variables and Cornell scores at ten years (Table 5-4). Similarly, no associations were observed between change in Cornell scores over the follow-up interval and ABPM variables (Table 5-5).

Table 5-4 Spearman Association between 24-hour ABPM Variables and Cornell Score at Follow-up

		Mean systolic pressure (mmHg)	Mean diastolic pressure (mmHg)	SD SBP	SD DBP
24-hour					
Cornell Score Year 10	r	0.07	0.06	0.03	0.15
	P	0.47	0.55	0.74	0.14
Daytime					
Cornell Score Year 10	r	0.08	0.06	0.09	0.15
	P	0.42	0.54	0.38	0.15
Night-time					
Cornell Score Year 10	r	0.10	0.13	-0.01	0.13
	P	0.38	0.26	0.90	0.25

Table 5-5 Association between 24-hour ABPM Variables and Change in Cornell Score over Follow-up

		Mean systolic pressure (mmHg)	Mean diastolic pressure (mmHg)	SD SBP	SD DBP
24-hour					
Change in Cornell Score	r	0.01	-0.03	0.08	0.06
	P	0.92	0.77	0.43	0.55
Daytime					
Change in Cornell Score	r	0.01	-0.03	0.02	-0.03
	P	0.92	0.75	0.89	0.79
Night-time					
Change in Cornell Score	r	-0.07	-0.14	-0.01	0.01
	P	0.53	0.20	0.93	0.93

There was no association between ABPM recordings and incidence of Cornell depression score ≥10 (indicative of depression) at follow-up (Table 5-6).

Table 5-6 Logistic Regression Examining Association between ABPM Recordings and Cornell Score of ≥10 at Follow-up

	OR	95% CI	P
Daytime			
Mean Systolic Pressure (mmHg)	1.01	0.96, 1.06	0.65
Mean Diastolic Pressure (mmHg)	1.00	0.93, 1.09	0.95
SD SBP (mmHg)	0.95	0.74, 1.22	0.70
SD DBP (mmHg)	0.85	0.56, 1.28	0.44
Night-time			
Mean Systolic Pressure (mmHg)	1.02	0.95, 1.09	0.60
Mean Diastolic Pressure (mmHg)	1.00	0.90, 1.12	0.95
SD SBP (mmHg)	0.94	0.72, 1.22	0.63
SD DBP (mmHg)	1.00	0.74, 1.35	0.99
24-hour			
Mean Systolic Pressure (mmHg)	1.01	0.95, 1.07	0.77
Mean Diastolic Pressure (mmHg)	0.98	0.89, 1.08	0.71
SD SBP (mmHg)	1.01	0.79, 1.29	0.93
SD DBP (mmHg)	0.94	0.64, 1.37	0.74

5.5.3 **Diurnal Variation at Baseline and Depression Scores at Ten years**

Eighty-three patients had the 10 or more daytime ABPM recordings and the five or more night-time recordings required to calculate diurnal variation. Diurnal variation was not associated with year 10 Cornell score or change in Cornell score (Table 5-7). Participants were classified as dippers (n= 37), non-dippers (n= 36) and extreme dippers (n= 10). There was no significant difference in Cornell score at ten years or change in Cornell score between groups.

Table 5-7 Association between 24 ABPM Diurnal Variation, Cornell Depression Score at Follow-up and Change in Cornell Score over Follow-up

	Systolic Diurnal Variation (%)	**Diastolic Diurnal Variation (%)**
	r (P)	**r (P)**
Cornell score at ten years	-0.02 (0.84)	0.01 (0.97)
Change in Cornell score	0.07 (0.52)	0.07 (0.55)

5.6 Response to Active Stand at Baseline and Depression Score at Year 10

Ninety-three participants underwent active stand at baseline and completed the Cornell depression scale at year 10.

5.6.1 Orthostatic Hypotension at Baseline and Depression Score at Follow-up

There was no association between presence or absence of OH as defined by AAN at baseline and Cornell depression score at year 10, or change in depression score (Table 5-9). Neither Cornell depression score at ten years nor change in depression score were associated OH subtypes or symptomatic OH (Table 5-9).

Table 5-8 Cornel Depression Score at Follow-up and Change in Depression Score over Follow-up Period by AAN OH Status

	OH (AAN definition) N=75	**No OH (AAN definition) N=18**	**P**
	Median (IQ range)	**Median (IQ range)**	
Cornell depression score at year 10	4.0 (2.0, 6.0)	3.0 (3.0, 6.3)	0.95
Change in Cornell depression score.	-1.0 (-3.0, 0.0)	-0.5 (-1.3, 1.3)	0.27

Table 5-9 Cornel Depression Score at Follow-up and Change in Depression Score over Follow-up Period by Systolic and Diastolic OH Status

	Median (IQ range)	**Median (IQ range)**	**P**
	Systolic OH N=58	**No Systolic OH N= 35**	
Cornell depression score at year 10	4.0 (2.0, 6.25)	3.0 (2.0, 6.0)	0.65
Change in Cornell depression score.	-1.0 (-4.0, 0.3)	-1.0 (-2.0, 1.0)	0.54
	Diastolic OH N=67	**No Diastolic OH N=26**	
Cornell depression score at year 10	4.0 (2.0, 6.0)	3.0 (2.0, 6.0)	0.89
Change in Cornell depression score.	-1.0 (-4.0, 0)	0 (-1.0, 2.0)	0.10
	Symptomatic OH N=12	**No Symptoms N=81**	
Cornell depression score at year 10	5 (2.3, 7.8)	3.0 (2.0, 6.0)	0.42
Change in Cornell depression score.	-1.0 (-3.0, 1.0)	-1 (-3.0, 0.8)	0.91

5.6.2 Orthostatic Hypotension at Baseline and Cornell Depression Score ≥ 10 at Follow-up

Of the 93 participants who underwent active stand at baseline and completed the Cornell depression scale at year 10, six had Cornell depression scores of 10 or more at follow-up. Neither OH as defined by AAN or subtypes of OH, were associated with Cornell score of 10 or more at follow-up (Table 5-10).

Table 5-10 Association between OH (and OH subtypes) and a Cornell Score of 10 or more at follow-up

	Frequency (%)	**Frequency (%)**	**P**
	OH N= 75	**No OH N= 18**	
Cornell score ≥ 10	5 (6)	1 (6)	1.00
	Systolic OH N= 58	**No Systolic OH N=35**	
Cornell score ≥ 10	5 (9)	1 (3)	0.40
	Diastolic OH N= 67	**No Diastolic OH N= 31**	
Cornell score ≥ 10	4 (6)	2 (6)	1.00
	Symptomatic OH= 12	**No Symptoms = 81**	
Cornell score ≥ 10	0	6 (7)	1.00

5.6.3 Continuous Response to Active Stand at Baseline and Depression Score at Follow-up

Continuous haemodynamic response to active stand was not associated with Cornell depression score at year 10, change in depression score over follow-up period or scoring ≥10 on the Cornell depression scale (Table 5-11 and Table 5-12).

Table 5-11 Spearman Correlation between Haemodynamic Response to Active Stand, Cornell Depression Score and Change in Depression Score over Follow-up

		Systolic Nadir (mmHg)	**Diastolic Nadir (mmHg)**	**Systolic Vasodepression (mmHg)**	**Diastolic Vasodepression (mmHg)**
Year 10 Cornell score	r	0.09	0.06	0.02	-0.09
	P	0.39	0.60	0.82	0.37
Change in Cornell	r	0.15	0.14	-0.11	-0.16
score over ten years	P	0.16	0.19	0.32	0.14

Table 5-12 Logistic Regression Analysis Examining the Association between Continuous Response to Active Stand and Scoring ≥ 10 on Cornell Depression Scale

	OR	95% CI	P
Systolic Nadir (mmHg)	1.02	0.99, 1.05	0.14
Diastolic Nadir (mmHg)	1.02	0.96, 1.08	0.58
Systolic Vasodepression (mmHg)	1.01	0.97, 1.05	0.69
Diastolic Vasodepression (mmHg)	0.98	0.89, 1.07	0.59

5.7 Response to Carotid Sinus Massage at Baseline and Depression Score at Follow-up

Eighty-seven participants underwent carotid sinus massage at baseline and completed the Cornell depression scale at follow-up.

5.7.1 Carotid Sinus Hypersensitivity at Baseline and Depression Score at Follow-up

Comparing participants with CSH to those without CSH did not reveal any significant difference in Cornell depression scores at follow-up or any difference in change in Cornell scores over the follow-up period (Table 5-13).

Table 5-13 Association between Carotid Sinus Hypersensitivity, Cornell Depression Score at Follow-up and Change in Depression Score

	CSH N=28	No CSH N=59	
	Median (IQ range)	**Median (IQ range)**	**P**
Cornell depression score at year 10	5.0 (2.0, 7.0)	3.0 (2.0, 6.0)	0.24
Change in Cornell depression score	-1.0 (-4.0, 0.8)	-1.0 (-3.0, 1.0)	0.76

5.7.2 Carotid Sinus Hypersensitivity at Baseline and Cornell Score ≥ 10

Seven per cent of participants with CSH had Cornell scores of 10 or more at follow-up versus 3% of participant without CSH at baseline. This was not significantly different (P= 0.66).

5.7.3 Continuous Haemodynamic Response to Carotid Sinus Massage at Baseline and Cornel Depression Score at Follow-up

Continuous haemodynamic response to CSM at baseline was not associated with Cornell depression score at year 10 or change in depression score over follow-up period (Table 5-14). Greater, minimum systolic nadir was, however, associated with scoring 10 or more on the Cornell depression scale (Table 5-15).

Table 5-14 Spearman Correlation between Continuous Haemodynamic Response to CSM and Follow-up Cornell Depression Scores

		Max RR interval (ms)	Max Vaso-depression (mmHg)	Minimum Systolic Nadir (mmHg)	Max delta RR (ms)
Cornell at year 10	**r**	0.11	0.05	-0.15	0.13
	P	0.32	0.62	0.16	0.24
Change in Cornell score.	**r**	-0.04	0.08	0.11	-0.04
	P	0.68	0.48	0.33	0.69

Table 5-15 Logistic Regression Examining Association between Response to CSM and Cornell Score ≥ 10

	OR	95% CI	P
Maximum RR interval (s)	1.23	0.83, 1.83	0.30
Maximum Vasodepression (mmHg)	0.97	0.91, 1.03	0.26
Minimum Systolic Nadir (mmHg)	1.03	1.00, 1.05	**0.04**
Maximum delta RR interval (s)	1.27	0.86, 1.88	0.24

5.8 Response to Autonomic Function Tests at Baseline and Depression Score at Follow-up

Of the 98 participants who completed the Cornell depression scale at follow-up, 93 had results from one or more autonomic function test. The number of participants undergoing each of the tests is shown in Table 5-16.

Table 5-16 Number of Participants Completing Cornell Depression Score at Ten Years and Each Autonomic Function Test at Baseline

Autonomic Function Test	Number of participants
Blood pressure and heart rate response to standing	93
Blood pressure response to isometric exercise	92
Blood pressure and heart rate response Valsalva manoeuvre	93
Blood pressure response to cold stimulation	90
Heart rate response to deep breathing	88

Eighty-five participants had completed Cornell depression scale at follow-up and had results from sufficient tests at baseline to classify participants as having abnormal or normal autonomic function according to modified Ewing criteria.

5.8.1 Abnormal Autonomic Function at Baseline and Depression Score at Follow-up

Abnormal versus normal autonomic function at baseline was not associated with Cornell score at ten years or change in Cornell score over follow-up period. Nor was it associated with a Cornell score or 10 or more at follow-up (Table 5-17).

Table 5-17 Association between Abnormal Autonomic Function at Baseline and Cornell Score at Ten Years, Change in Cornell Scores and Cornell Score ≥10 at Ten Years.

	Normal Autonomic function N=57	**Abnormal Autonomic function N =29**	**P**
	Median (IQR)	**Median (IQR)**	
Year 10 Cornell Score	4.0 (1.5, 6.0)	3.5 (2.0, 6.6)	0.97
Change in Cornell score	-1.0 (-3.0, 1.0)	-1.0 (-2.8, 0)	0.71
	Frequency (%)	**Frequency (%)**	**P**
Cornell score at year 10 ≥ 10 points	4 (7)	1 (3)	1.00

5.8.2 **Response to Individual Autonomic Function Tests at Baseline and Depression Score at Follow-up**

Examining association between response to individual autonomic tests and depression scores as continuous variables did not show any associations (Table 5-18).

Table 5-18 Association between Continuous Response to Individual Autonomic Function Tests and Cornell Score at Year 10

		Stand SBP drop (mmHg)	Cold pressor DBP difference (mmHg)	Isometric Exercise DBP difference (mmHg)	Valsalva SBP overshoot (mmHg)	30:15 Ratio	Valsalva ratio	Heart rate response to deep breathing
Year 10 Cornell Score	**r**	0.02	0.19	0.06	-0.04	-0.19	-0.11	0.12
	P	0.82	0.07	0.57	0.73	0.07	0.31	0.26
Change in Cornell Score	**r**	-0.10	-0.03	0.11	0.06	0.08	0.07	-0.07
	P	0.32	0.76	0.32	0.54	0.47	0.52	0.54

Similarly, there were no associations observed between continuous response to individual autonomic function tests and attaining a score of 10 or more on the Cornell scale at ten year follow-up.

Table 5-19 Results of Logistic Regression Examining Association between Continuous Response to Individual Autonomic Function Tests and Attaining a score of ≥10 on Cornell Depression Scale at Follow-up.

Variable	Cornell at Ten years ≥ 10 points		
	OR	95% CI	P
Stand SBP drop (mmHg)	1.01	0.97, 1.05	0.69
Cold pressor DBP difference (mmHg)	1.12	0.99, 1.26	0.06
Isometric Exercise DBP difference (mmHg)	0.99	0.93, 1.05	0.70
Valsalva SBP overshoot (mmHg)	1.00	0.97, 1.03	0.98
30:15 ratio	0.06	0.00, 442	0.54
Valsalva ratio	0.83	0.04, 17.5	0.90
Heart rate response to deep breathing	1.09	0.93, 1.29	0.30

5.9 Heart Rate Variability at Baseline and Depression Score at Follow-up

Eighty six participants had heart rate variability recorded at baseline and completed the Cornell depression scale at follow-up. Of these 78 had recordings where ≤ 10% of the beats were interpolated or edited and were suitable for analysis.

5.9.1 Heart Rate Variability at Baseline and Depression Score at Follow-up

Year 10 Cornell score was not associated with baseline heart rate variability parameters. Change in Cornell score over the follow-up period was however associated with high frequency power spectra and HR:LF ratio (Table 5-20). Examining the data further revealed one extreme outlier. With this individual removed, the association between HF HRV and change in Cornell score was no longer significant. However, greater HF:LF ratio remained associated with greater decline in Cornell. After adjusting for age, sex, years in education, diabetes, hypertension, cardiovascular disease and use of tobacco, alcohol, cardioactive medications and psychoactive medication HF power and HF/LF ratio were no longer independently associated with change in Cornell score over ten year follow-up.

Table 5-20 Association between baseline HRV parameters and Cornell score at year 10

		SD RR (ms)	Total Power (ms^2)	Very low frequency (ms^2)	low frequency (ms^2)	high frequency (ms^2)	HF/LF Ratio
Year 10 Cornell score	r	-0.11	-0.13	-0.13	-0.04	-0.18	-0.16
	P	0.33	0.24	0.27	0.70	0.12	0.16
Change in Cornell Score	r	0.06	0.10	0.06	0.00	0.24	0.23
	P	0.61	0.39	0.57	0.97	**0.03**	**0.04**

5.9.2 **Heart Rate Variability at Baseline and Cornell Score of ≥ 10 at Follow-up**

HRV parameters at baseline were not significantly associated with having a Cornell score of 10 or more points at follow-up (Table 5-21).

Table 5-21 Association between Baseline HRV Parameters and a Cornell Score of 10 or More Points at Follow-up.

Variable	**Cornell at Ten years ≥ 10 points**		
	OR	**95% CI**	**P**
SDRR (ms)	1.03	0.96, 1.10	0.42
Total Power (ms^2)	1.00	1.00, 1.01	0.25
VLF (ms^2)	1.00	1.00, 1.01	0.05
LF (ms^2)	1.00	1.00, 1.01	0.39
HF (ms^2)	1.00	0.99, 1.01	0.55
HF/LF ratio	0.05	0.01, 5.28	0.20

5.9.3 **Alternative Analyses**

Few associations have been identified in this study between autonomic function, and / or neurocardiovascular function at baseline and depression at follow-up. To account for use of antidepressants further analyses were performed with two additional derived dependent variables

1. *Any indication of depression*: Participants were classed as having "any indication of depression" if they reported taking antidepressants, or scored 10 or

more on the Cornell at follow-up assessment. Seventeen per cent of participants met these criteria

2. *Incident depression*: participants were diagnosed with "incident depression" if they had *any indication of depression* at follow-up, but were not taking antidepressants at baseline and had scored less than 10 on Cornell assessment at baseline. Ten per cent of participants met this definition.

The analyses presented in this chapter were repeated for these two new dependent variables. The only additional association identified that had not been apparent on the initial analysis was with response to CSM: a diagnosis of mixed CSH was associated and incident depression. Twenty-nine percent of participants with mixed CSH at baseline had incident depression at follow-up versus five percent of subjects without mixed CSH (P=0.02). Logistic regression showed this finding remained significant after adjusting for potential covariates [OR 13.5 (95% CI 1.87, 97.6) P=0.01].

5.10 **Summary of Key Results in Chapter 5**

Cornell Depression scores where higher at follow-up than at baseline but number of participants scoring ≥10 had decreased suggesting prevalence of severe depression had not increased.

5.10.1 **Hypertension**

Hypertension was not associated with cornell score at follow-up, depression or incident depression.

5.10.2 **Ambulatory BP recordings**

Neither mean BP nor BP variability were associated with depression, indecent depression or Cornell score at follow-up.

5.10.3 **Active Stand and Carotid Sinus Massage.**

OH, CSH or CSS were not associated with Cornell scores at follow-up or prevalence of depression. Similarly, degree of haemodynamic response to active stand or CSM was not associated with depression at ten years. Mixed CSH (but not pure cardioinhibitory or vasodepresser CSH) was associated with incident depression.

5.10.4 **Autonomic Function**

Abnormal autonomic function as defined by Ewing criteria was not associated with Cornell score or with the prevalence of severe depression or incident depression. The response to individual autonomic function tests was not associated with depression at follow-up. Measures of heart rate variability were not independently associated with depression at follow-up or scoring ten or more on Cornell depression scale.

5.11 **Discussion**

In this study, no association was found between hypertension status at baseline and depression at follow-up or change in Cornell score over the follow-up period. This is interesting as hypertension is a strong risk factor for white matter hyperintensities which in turn have been associated with depression in later life (Chen et al., 2006, de Groot et al., 2000, Firbank et al., 2005, Godin et al., 2008, Firbank et al., 2004). A meta-analysis by Valkanov et al identified 14 studies comparing the prevalence or incidence of late-life depression among people with hypertension. In total, the studies included over 20,000 participants. In keeping with the findings of this study, there was no association between hypertension and depression (Valkanova and Ebmeier, 2013).

This study was the first population-based study to examine the longitudinal associations between autonomic nervous system function, neurocardiovascular instability and depression. These data consistently showed no significant association between BP and HR control at baseline and performance on Cornell score at the follow-up examination. Similarly, it did not identify any independent associations between HR and BP control at baseline and change in Cornell score over the follow-up period.

The findings of this study are in contrast to a number of cross-sectional studies examining the association between BP control and depression (Scuteri et al., 2009, Jun et al., 2012, Sunbul et al., 2013, Richardson et al., 2009, Vasudev et al., 2011, Pearce, 2007, Kayano et al., 2012). Cross-sectional studies using 24-hour ambulatory BP monitoring have shown depression to be associated with increased 24-hour and daytime BP variability, non-dipping status and decreased diurnal variation (Scuteri et al., 2009, Jun et al., 2012, Sunbul et al., 2013, Kayano et al., 2012). Similarly 2 cross-sectional studies using beat-to-beat monitoring to compare systolic BP response to standing among depressed older people and controls found systolic vasodepression was

significantly greater in depressed patient and systolic OH was significantly more common among individuals with depression than controls (Richardson et al., 2009, Vasudev et al., 2011). A more recent community study oscillometric measures of postural change in BP found that symptomatic OH but not asymptomatic OH was associated with higher Centre for Epidemiology Depression score among community dwelling older people (Regan et al., 2013). CSH has also been associated with higher Cornell depression scores and greater number of people scoring 10 or more points on the Cornell score in cross-sectional studies (Pearce, 2007).

Several cross-sectional studies have examined the association between autonomic nervous system function and depression. These have been reviewed by two authors (Grippo and Johnson, 2009, Rottenberg, 2007). All used HRV as a measure of autonomic function, rather than cardiovascular autonomic function tests. Grippo et al and Rottenburg et al report mixed results, some studies have shown decreased HRV in patients with depression while others, in keeping with our findings, have shown no association (Grippo and Johnson, 2009, Rottenberg, 2007). Two studies have examined changes in HRV associated with changes in depressive symptoms among patients treated for depression (Voss et al., 2008, Antipova, 2011). Antipova et al found heart rate variability was significantly lower in depressed patients compared to controls. After six weeks treatment with serotonin selective reuptake inhibitor antidepressants mood improved but HRV was unchanged. At six months, HRV was normalising in 30% of participants (Antipova, 2011). Voss et al investigated HRV in controls and people with depression at three time points; T1 unmediated, T2 medicated and T3 after 18 month follow-up (Voss et al., 2008). They found non-medicated patients had significantly lower HRV than controls. At T2, after introduction of medication, these differences became more pronounced. However, at T3 HRV among depressed patients normalised, suggesting reduced HRV might be secondary to depression.

There are several reasons why our longitudinal findings may be in contrast to previous cross-sectional studies. Firstly, the direction of the association between depression and autonomic function / neurocardiovascular instability cannot be ascertained from cross-sectional studies. It was our hypothesis that impaired autonomic nervous system function and NCVI would result in cerebral hypoperfusion, white matter damage and consequently vascular depression. However, depression may result directly or indirectly

in altered autonomic function. This could occur by several mechanisms. Firstly, depression is associated with altered behaviour that may result in changes to BP and autonomic function. Depressed patients have been shown to be less active than controls and decreased activity is associated with reduced resting heart rate and blood pressure variability (Volkers et al., 2003). Disturbed sleep patterns, commonly seen in depression, are associated with altered 24-hour BP variability and diurnal variation. Furthermore, patients with depression are often less responsive to emotional stimuli (Rottenberg, 2007). The observation that HRV normalised among depressed patients as mood improves supports the idea that depression itself may contribute to abnormal autonomic nervous system activity (Antipova, 2011, Voss et al., 2008).

A further potential confounder in cross-sectional studies examining the association between autonomic function NCVI and depression is use of medication. Antidepressants, particularly tricyclic antidepressants, have been associated with altered BP regulation and orthostatic hypotension(Glassman and Bigger Jr, 1981). Both tricyclic and SSRI antidepressant medication has been associated with reductions in HRV (Voss et al., 2008, Delaney et al., 2010, Glassman and Bigger Jr, 1981). Conversely, antihypertensive and cardioactive medications are recognised to have class specific effect on mood. Renin-angiotensin-aldosterone affecting medications are believed to have antidepressant effects and have been associated with lower use of antidepressants while beta-blockers have been implicated in depression (Nasr et al., 2011, Beers and Passman, 1990). It is therefore possible that the associations between depression and NCVI / autonomic dysfunction observed in cross-sectional studies is a result of the direct and indirect effects of depression on the autonomic nervous system, rather than a result of autonomic dysfunction leading to depression as was initially hypothesised.

Alternatively, our study may have been underpowered to detect weak associations between NCVI and depression. The sample size was small and only 6% of participants in this study were depressed at the follow-up assessment. This is lower than reported rates of depression detected in similar populations using symptom assessment scales (Luppa et al., 2012). A meta-analysis of 12 studies using depressive symptom rating scales to estimate prevalence of depression among older people aged 75 years reported a pooled prevalence of depression of 17.1% (95% CI 9.7–26.1%) (Luppa et al., 2012). It

would therefore appear that this study sample is not typical of the general population in terms of prevalence of depression.

Baseline rates of depression among follow-up participants and participants lost to follow-up were examined to determine if the low prevalence of depression in the cohort was a result of selection bias. Participants lost to follow-up did not significantly differ from follow-up participants in terms of Cornell scores at baseline or incidence of depression at baseline. However, participants who developed depression following baseline assessment may have disproportionately declined participation in the follow-up phase of the study. Depression has been shown to be associated with increased attrition from studies and the impact of depression on attrition appears to increase with age (Mirowsky and Reynolds, 2000).

The small number of patients with depression in the study meant that it was difficult to separate participants with long-term depression from participants with late-life depression. It has been suggested that depression developing in middle age and persisting into later life has a different aetiology to depression starting in later life. It is possible that NCVI and autonomic dysfunction are risk factors only for late-life depression. In an attempt to increase the statistical power of the study and examine incident depression we widened the definition of depression by including participants taking antidepressants. This showed an association between mixed CSH and incident depression. However the model had poor fit and given the extensive multiple testing this finding should be interpreted with caution.

None of the participants in this study were under the care of psychiatrists for depression and few were taking antidepressant medication. Most of the previous studies examining associations between NCVI and depression have recruited depressed participants from secondary care (Vasudev et al., 2012, Colloby et al., 2011). Depressed participants in this study may have had less severe depression than participants in studies that recruited patients from secondary care.

In conclusion, this study does not support the hypothesis that episodic hypotension underlies depression in later life in unselected community-dwelling older people. Larger

studies may be needed to identify weak associations and to ensure an adequate number of individuals with severe depression are included.

Chapter 6 The Long-term Association between Neurocardiovascular Function and Falls, Gait and Balance

6.1 Introduction

Impaired blood pressure control and NCVI are frequently cited in guidelines as risk factors for falls in older people (NICE, 2013, Panel on Prevention of Falls in Older Persons and British Geriatrics, 2011, Beauchet et al., 2011).

Falls may directly result from cerebral hypoperfusion resulting in unrecognised syncope; alternatively, they may result from impaired gait and balance secondary to cerebral white matter hyperintensities (Shaw and Kenny, 1997) (Frith and Davison, 2013, Willey et al., 2013, Kreisel et al., 2013, Callisaya et al., 2013, Soumaré et al., 2009, DeCarli, 2013).

6.2 Aims

- To examine the long-term association between autonomic function, NCVI and falls among community-dwelling older people
- To examine the long-term association between autonomic function, NCVI and gait and balance among community-dwelling older people in order to better understand the mechanism by which NCVI and falls may be associated

6.3 Methods

6.3.1 Assessment of Neurocardiovascular Function

Autonomic function tests and tests of NCVI were conducted at baseline as described in section 2.3, page 42.

6.3.2 Assessment of Falls

All participants were interviewed by the same trained assessor. Participants were asked, "have you had a fall in the last 12 months?" The interviewer explained, "a fall is any time you have fallen or found yourself on the ground, a piece of furniture, stairs or a wall without meaning to." Participants were asked how many falls they had had in the last 12 months, and if they had experienced any prodromal symptoms, loss of

consciousness or injuries in association with each reported fall. Finally, participants were asked if they had been given a diagnosis as to the cause of the fall and if they had been seen in A&E or been hospitalised because of the fall.

Three categorical variables were derived from the falls history obtained during interview with participants.

- *Faller*: Participants were defined as a *faller* if they had fallen one or more times during the 12 months prior to assessment.
- *Recurrent Faller*: Participants were defined as a *recurrent faller* if they had fallen two or more times during the 12 months prior to the assessment.
- *Injurious fall*: An injurious fall was any fall resulting in a fracture, head injury, strain, sprain, cut, bruise, persistent pain, a visit to an accident and emergency department or admission to hospital.

6.3.3 **Assessment of Gait and Balance**

Gait and balance were assessed in participants' homes by a single trained observer using the Tinetti POAM assessment (Tinetti, 1986). Several versions of the Tinetti assessment have been developed (Kopke and Meyer, 2006). At both assessments, the same tools were used. The balance score can be scored from zero to 26 (higher scores indicating better balance) and the gait score is scored from 0-9 (again higher scores indicating better performance).

6.4 **Statistics**

Associations between two categorical variables were examined using Chi square tests. If more than 20% of cells had an expected count of five or less, Fisher's exact test was used instead.

Differences in Tinetti scores were compared between groups using Mann-Whitney U test. Spearman correlation was used to examine the association between Tinetti score and continuous response to tests of neurocardiovascular function.

Logistic regression was used to examine associations between continuous explanatory variables and falls, recurrent falls and injurious falls . Odds ratio and 95% confidence intervals are reported.

Negative binomial regression (which is a form of linear regression more appropriate when analysing data that have a high frequency of negative counts) was used to examine variables associated with the number of falls in the year prior to follow-up examination. Incident rate ratios and 95% confidence intervals are reported.

6.4.1 **Covariates**

Covariates were determined by review of the literature. In addition to age and sex, the following recognised risk factors for falling were included: previous stroke, Parkinson's disease, diabetes, use of psychoactive medication, use of cardioactive medication, history of one or more falls at baseline, cognition (measured using CAMCOG total score), Tinetti scores and BMI (Tinetti et al., 1988, Campbell et al., 1989, Nevitt et al., 1989, Schwartz et al., 2002).

6.5 **Results**

6.5.1 **Prevalence of Falls at Follow-up**

Of the 104 people consenting to participate in the follow-up study, all of them completed the falls history. Comparing baseline and follow-up falls histories showed that more individuals reported having had a fall in the 12 months prior to assessment at follow-up than at baseline, 32% versus 27%. These differences were not statistically significant (P=0.44). The number of participants reporting recurrent falls (defined as 2 or more falls in the 12 months prior to assessment) was, however, significantly greater at follow-up than at baseline, [15.4% and 9.6% respectively (P< 0.05)]. There was not a significant difference in the number of participants sustaining injuries because of a fall in the year prior to baseline assessment or the year prior to follow-up [19.2% v 20.2% respectively (P=0.23)].

For fallers, the median number of falls in the 12 months prior to assessment at baseline and at follow-up was 1 (IQ range 1, 2 in both cases). Table 6-1 shows the number of falls prior to assessment reported by participants at baseline and at follow-up.

Table 6-1: Number of Falls in Year Prior to Assessment

Number of Falls	Baseline N= 104	Follow-up N =104
0	76	71
1	18	17
2	7	9
3	0	3
4	0	3
5	0	0
6	1	1
7	1	0
≥8	1	0

6.6 Tinetti Gait and Balance Scores at Follow-up

Of the 104 participants taking part in the follow-up examination, 101 were able to complete Tinetti balance assessment and 100 completed Tinetti assessment of gait. Subjects performed more poorly on assessments of both gait and balance at follow-up compared to baseline, P≤0.001 (Table 6-2).

Table 6-2 Tinetti Gait and Balance Scores at Baseline and Follow-up

Variable	Baseline Median (IQR)	Follow-up Median (IQR)	P
Tinetti Balance	25 (23, 26)	24 (22, 25)	<0.001
Tinetti Gait	9 (8, 9)	8.5 (5, 9)	<0.001

6.7 Baseline Ambulatory Blood Pressure Recordings and Falls, Gait and Balance at Follow-up

Of the 104 participants who underwent the falls assessment at the ten year follow-up, 103 had undergone ambulatory blood pressure monitoring at baseline.

6.7.1 Hypertension at Baseline and Falls at Follow-up

One hundred participants had 10 or more daytime recordings, and could be classified as hypertensive or normotensive at baseline. Hypertension at baseline was not associated with falling, recurrent falls or injurious falls in year prior to assessment (Table 6-3).

Table 6-3 Association between Falls and Baseline Hypertension Status

	No Hypertension, N= 55	**Hypertension, N=54**	**P**
	Frequency (%)	**Frequency (%)**	
Fall	16 (29)	17 (38)	0.33
Recurrent Falls	11 (20)	5 (11)	0.24
Injurious Fall	9 (16)	12 (27)	0.21

Negative binomial regression failed to show an association between hypertensive status at baseline and number of falls in the 12 months prior to follow-up assessment [IRR 0.73 (95% CI 0.38, 1.40), P=0.35].

6.7.2 Baseline Hypertension Status and Gait and Balance at Follow-up

Of the 100 participants who had sufficient daytime recordings to classify them as hypertensive or normotensive according to NICE guidelines, 98 had completed the Tinetti balance assessment and 97 had completed the Tinetti gait assessment at follow-up. Comparing Tinetti scores for participants who had been normotensive with scores for participants who were hypertensive at baseline did not show any significant differences (Table 6-4).

Table 6-4 Tinetti Scores at Follow-up by Baseline Hypertension Status

	No Hypertension	**Hypertension**	**P**
	Median (IQ range)	**Median (IQ range)**	
Tinetti Balance Score	23.0 (21.0, 25.0)	24.0 (22.0, 25.0)	0.35
Tinetti Gait Score	8.0 (4.0, 9.0)	8.5 (5.0, 9.0)	0.74

6.7.3 Twenty-four Hour Ambulatory BP Results at Baseline and Falls, Gait and Balance at Follow-up

All individuals had 16 or more recordings during the 24-hour period and were therefore suitable for analysis of 24-hour ABPM recordings.

Greater 24-hour systolic BP variability was associated with reporting a fall in the year prior to follow-up assessment (Table 6-5). This association was no longer significant after adjusting for age and other risk factors associated with falls.

Logistic regression showed that twenty-four hour ABPM variables were not associated with recurrent falls or injurious falls. Similarly, negative binomial regression failed to show an association between 24-hour ambulatory BP monitor recordings and the number of falls reported in the year prior to follow-up assessment (Table 6-5).

Table 6-5 Unadjusted Logistic Regression Examining Association between 24-hour ABPM Results and Falls at Follow-up

	OR	**95% confidence interval**	**P**
Falls *			
Mean SBP (mmHg)	1.03	1.00, 1.06	0.08
Mean DBP (mmHg)	1.02	0.97, 1.06	0.53
SD SBP (mmHg)	1.17	1.02, 1.33	**0.02**
SD DBP (mmHg)	1.05	0.88, 1.25	0.61
Recurrent Falls*			
Mean SBP (mmHg)	0.99	0.95, 1.03	0.62
Mean DBP (mmHg)	0.97	0.91, 1.04	0.42
SD SBP (mmHg)	1.03	0.87, 1.20	0.76
SD DBP (mmHg)	0.97	0.77, 1.23	0.80
Injurious Fall *			
Mean SBP (mmHg)	1.02	0.99, 1.06	0.17
Mean DBP (mmHg)	1.02	0.96, 1.07	0.51
SD SBP (mmHg)	1.03	0.89, 1.19	0.73
SD DBP (mmHg)	0.96	0.77, 1.19	0.68
Number of Falls$^{\infty}$	**IRR**	**95% confidence interval**	**P**
Mean SBP (mmHg)	0.99	0.97, 1.01	0.68
Mean DBP (mmHg)	0.98	0.94, 1.02	0.27
SD SBP (mmHg)	1.04	0.95, 1.15	0.41
SD DBP (mmHg)	1.02	0.87, 1.18	0.85
** Logistic Regression,* $^{\infty}$ *Negative Binomial Regression*			

Spearman correlation did not show any significant associations between 24-hour ABPM results at baseline and Tinetti gait and balance scores at follow-up (Table 6-6).

Table 6-6 Spearman Correlation between 24-hour ABPM Results and Tinetti Balance and Gait Scores

	Tinetti Balance Score	**Tinetti Gait Score**
	r (P)	**r (P)**
Mean SBP (mmHg)	0.02 (0.85)	-0.05 (0.66)
Mean DBP (mmHg)	0.14 (0.17)	-0.04 (0.69)
SD SBP (mmHg)	-0.08 (0.41)	-0.03 (0.73)
SD DBP (mmHg)	0.00 (0.96)	0.03 (0.76)

6.7.4 Daytime Ambulatory BP Results at Baseline and Falls, Gait and Balance at Follow-up

One hundred participants had 10 or more daytime recordings and could be included in the daytime analysis. No associations were observed between daytime ambulatory BP parameters and falls, recurrent falls or injurious falls (Table 6-7). Similarly, negative binomial regression failed to show an association between daytime ABPM recordings and number of falls in year prior to assessment (Table 6-7).

Table 6-7 Association between Daytime ABPM Results and Falls at Follow-up

	Odds Ratio	**95% CI**	**P**
Falls *			
Mean SBP (mmHg)	1.03	1.00, 1.05	0.08
Mean DBP (mmHg)	1.02	0.98, 1.06	0.46
SD SBP (mmHg)	1.09	0.98, 1.22	0.13
SD DBP (mmHg)	1.05	0.88, 1.26	0.58
Recurrent falls*			
Mean SBP (mmHg)	0.99	0.95, 1.02	0.49
Mean DBP (mmHg)	0.97	0.92, 1.03	0.35
SD SBP (mmHg)	1.04	0.90, 1.19	0.61
SD DBP (mmHg)	1.01	0.80, 1.27	0.95
Injurious Fall *			
Mean SBP (mmHg)	1.02	0.99, 1.05	0.17
Mean DBP (mmHg)	1.02	0.99, 1.06	0.52
SD SBP (mmHg)	1.04	0.91, 1.18	0.59
SD DBP (mmHg)	1.00	0.81, 1.2	0.98
Number of Falls $^{\infty}$	**IRR**	**95% CI**	**P**
Mean SBP (mmHg)	0.99	0.97, 1.01	0.48
Mean DBP (mmHg)	0.98	0.95, 1.02	0.33
SD SBP (mmHg)	1.03	0.94, 1.13	0.49
SD DBP (mmHg)	1.01	0.87, 1.18	0.87
** Logistic Regression,* $^{\infty}$ *Negative Binomial Regression*			

Spearman correlation also failed to show any associations between daytime ABPM results at baseline and Tinetti Balance and Gait Scores at follow-up.

Table 6-8 Spearman Correlation between Daytime ABPM Results and Tinetti Balance and Gait Scores

	Tinetti Balance Score	Tinetti Gait Score
	r (P)	r (P)
Mean SBP (mmHg)	0.09 (0.40)	0.02 (0.87)
Mean DBP (mmHg)	0.18 (0.07)	0.02 (0.88)
SD SBP (mmHg)	-0.06 (0.55)	0.01 (0.91)
SD DBP (mmHg)	-0.02 (0.84)	0.00 (1.00)

6.7.5 Night-time Ambulatory BP at Baseline Results and Falls, Gait and Balance at Follow-up

Ninety-one participants had five or more nocturnal recordings and were included in the night-time analysis. No associations were observed between nocturnal ABPM parameter and falls, recurrent falls or injurious falls (Table 6-9). Similarly, no associations were observed for night-time ABPM recordings and the number of falls in the year prior to follow-up assessment (Table 6-9).

Table 6-9 Association between Night-time ABPM Results and Falls at Follow-up

	Odds Ratio	**95% CI**	**P**
Falls*			
Mean SBP (mmHg)	1.02	0.98, 1.05	0.36
Mean DBP (mmHg)	1.03	0.97, 1.08	0.32
SD SBP (mmHg)	1.03	0.91, 1.16	0.64
SD DBP (mmHg)	0.95	0.82, 1.11	0.53
Recurrent Fall*			
Mean SBP (mmHg)	0.99	0.95, 1.04	0.81
Mean DBP (mmHg)	1.01	0.95, 1.08	0.75
SD SBP (mmHg)	1.03	0.88, 1.20	0.75
SD DBP (mmHg)	0.99	0.81, 1.20	0.89
Injurious Fall*			
Mean SBP (mmHg)	1.01	0.97, 1.05	0.80
Mean DBP (mmHg)	1.01	0.95, 1.08	0.70
SD SBP (mmHg)	0.96	0.83, 1.11	0.60
SD DBP (mmHg)	0.87	0.70, 1.07	0.17
Number of Falls $^{\infty}$	**IRR**	**95% CI**	**P**
Mean SBP (mmHg)	0.99	0.96, 1.01	0.28
Mean DBP (mmHg)	0.99	0.95, 1.04	0.78
SD SBP (mmHg)	0.99	0.90, 1.09	0.89
SD DBP (mmHg)	0.97	0.86, 1.10	0.66
** Logistic Regression,* $^{\infty}$ *Negative Binomial Regression*			

No associations were observed between night-time ABPM results at baseline and Tinetti Balance and Gait Scores at follow-up

Table 6-10 Spearman Correlation between Night-time ABPM Results and Tinetti Balance and Gait Scores

	Tinetti Balance Score	Tinetti Gait Score
	r (P)	**r (P)**
Mean SBP (mmHg)	-0.05 (0.67)	-0.12 (0.26)
Mean DBP (mmHg)	0.05 (0.06)	-0.13 (0.22)
SD SBP (mmHg)	0.06 (0.58)	0.11 (0.31)
SD DBP (mmHg)	0.09 (0.41)	0.09 (0.42)

6.7.6 Baseline Diurnal Variation and Falls, Gait and Balance at Follow-up

Eighty-nine of the follow-up participants had 10 or more daytime recordings and five or more nocturnal recordings at baseline and were therefore suitable for analysis of diurnal variation. Percentage diurnal variation was not associated with falling, recurrent, or injurious falls, or number of falls in year prior to follow-up.

Table 6-11 Diurnal Variation and Falls

	OR	**95% CI**	**P**
Falls			
Systolic Diurnal variation (%)	1.04	0.98, 1.10	0.20
Diastolic Diurnal variation (%)	1.03	0.98, 1.07	0.22
Recurrent Falls			
Systolic Diurnal variation (%)	0.98	0.91, 1.05	0.54
Diastolic Diurnal variation (%)	0.99	0.93, 1.05	0.68
Injurious Fall			
Systolic Diurnal variation (%)	0.98	0.96, 1.10	0.48
Diastolic Diurnal variation (%)	1.01	0.95, 1.07	0.76
Number of Falls	**IRR**	**95% CI**	**P**
Systolic Diurnal variation (%)	1.01	0.97, 1.05	0.67
Diastolic Diurnal variation (%)	1.01	0.97, 1.05	0.67
** Logistic Regression, $^{\infty}$ Negative Binomial Regression*			

There was no association between diurnal variation in BP and Tinetti Gait and Balance Scores (Table 6-12).

Table 6-12 Spearman Correlation between ABPM Diurnal Variation and Gait and Balance Scores

	Tinetti Balance Score	Tinetti Gait Score
	r (P)	**r (P)**
Systolic Diurnal Variation (%)	0.18 (0.10)	0.12 (0.29)
Diastolic Diurnal Variation (%)	0.13 (0.24)	0.14 (0.20)

6.8 Orthostatic Hypotension at Baseline and Falls, Gait and Balance at Follow-up

Of the 104 participants who underwent falls assessment at ten years, 95 performed active stand at baseline. Presence of OH at baseline was not associated with falling in year prior to follow-up assessment or with reporting recurrent or injurious falls (Table 6-13). Symptomatic orthostatic hypotension was associated with recurrent falls on univariate analysis but after adjusting for covariates this association was no longer significant.

Table 6-13 Association between Baseline Orthostatic Hypotension Status and Falls at Follow-up

	No orthostatic Hypotension N= 18	**Orthostatic hypotension N= 77**	**P**
	Frequency (%)	**Frequency (%)**	
Falls	6 (33)	27 (35)	0.89
Recurrent Falls	1 (6)	15 (20)	0.29
Injurious Falls	2 (11)	19 (25)	0.34
	No systolic OH N= 35	**Systolic OH N= 60**	**P**
	Frequency (%)	**Frequency (%)**	
Falls	11 (31)	22 (37)	0.61
Recurrent Falls	3 (9)	13 (22)	0.10
Injurious Falls	5 (14)	16 (27)	0.16
	No diastolic OH N= 27	**Diastolic OH N= 68**	**P**
	Frequency (%)	**Frequency (%)**	
Falls	10 (37)	23 (34)	0.78
Recurrent Falls	4 (15)	12 (18)	1.00
Injurious Falls	4 (15)	17 (25)	0.28
	Symptomatic OH N= 11	**No symptoms N= 84**	**P**
	Frequency (%)	**Frequency (%)**	
Falls	6 (55)	27 (32)	0.18
Recurrent Falls	5 (45)	11 (13)	**0.02**
Injurious Falls	5 (45)	16	0.06

Negative binomial regression failed to show any association between OH, or subtypes of OH, and the reported number of falls in the year prior to follow-up assessments (Table 6-14). There was a borderline association between symptomatic OH and number of falls.

Table 6-14 Unadjusted Negative Binomial Regression Examining Associations between Number of Falls in Year Prior to Follow-up and OH as Defined by AAN and Components of OH

	IRR	**95% CI**	**P**
AAN defined OH	1.84	0.72, 4.70	0.20
Systolic OH	1.54	0.77, 3.10	0.22
Diastolic OH	1.05	0.52, 2.15	0.89
Symptomatic OH	2.23	0.97, 5.29	0.07

6.8.1 **Continuous Response to Active Stand at Baseline and Falls at Follow-up**

Logistic regression examining the association between continuous response to orthostasis at baseline and falls, recurrent falls and injurious falls in the year prior to ten year follow-up did not show any significant associations (Table 6-15). Similarly, there were no associations between continuous response to active stand and the reported number of falls in year prior to follow-up (Table 6-15).

Table 6-15 Association between Continuous Response to Orthostasis at Baseline and Falls at Follow-up

	OR	**95% CI**	**P**
Falls*			
SBP Vasodepression (mmHg)	1.00	0.98, 1.03	0.79
DBP Vasodepression (mmHg)	0.97	0.93, 1.02	0.25
SBP Nadir (mmHg)	1.01	0.99, 1.02	0.47
DBP Nadir (mmHg)	1.02	0.99, 1.06	0.18
Recurrent Falls*			
SBP Vasodepression (mmHg)	1.02	0.99, 1.05	0.29
DBP Vasodepression (mmHg)	0.98	0.92, 1.04	0.49
SBP Nadir (mmHg)	1.00	0.98, 1.02	0.99
DBP Nadir (mmHg)	1.01	099, 1.03	0.48
Injurious Fall*			
SBP Vasodepression (mmHg)	1.01	0.98, 1.04	0.53
DBP Vasodepression (mmHg)	0.99	0.94, 1.05	0.80
SBP Nadir (mmHg)	0.99	0.98, 1.01	0.45
DBP Nadir (mmHg)	1.02	0.98, 1.05	0.39
Number of Falls $^{\infty}$	**IRR**	**95% CI**	**P**
SBP Vasodepression (mmHg)	1.01	0.99, 1.03	0.36
DBP Vasodepression (mmHg)	0.98	0.95, 1.02	0.38
SBP Nadir (mmHg)	1.00	0.99, 1.01	0.67
DBP Nadir (mmHg)	1.01	0.99, 1.03	0.52
** Logistic Regression,* $^{\infty}$ *Negative Binomial Regression*			

6.8.2 Orthostatic Hypotension at Baseline and Tinetti Gait and Balance Scores at Follow-up

Of the 95 individuals who underwent active stand at baseline and participated in follow-up study, 92 completed the Tinetti balance assessment and 91 completed the Tinetti gait assessment. Comparing participants who had OH as defined by AAN at baseline with those who did not, failed to show any significant differences in follow-up gait and balance scores (Table 6-16). The same was true when systolic OH was examined in

isolation (Table 6-16). Tinetti gait scores at follow-up were higher among participants who had had diastolic OH at baseline this observation reached borderline statistical significance (P=0.05)

Table 6-16 Gait and Balance Scores at Follow-up by Presence or Absence of OH at Follow-up

	Median (IQ range)	**Median (IQ range)**	**P**
	No orthostatic Hypotension at baseline	**Orthostatic hypotension at baseline**	
	N= 18	**N= 74**	
Tinetti Balance	24 (21.75, 26)	24 (20.75, 25)	0.47
	N= 18	**N= 73**	
Tinetti Gait	7.5 (3.75, 9.00)	9 (5.5, 9)	0.30
	No systolic OH at baseline	**Systolic OH at baseline**	
	N= 35	**N= 57**	
Tinetti Balance	24 (21, 25)	24 (20, 25)	0.11
	N= 35	**N= 56**	
Tinetti Gait	8 (4, 9)	8.5 (6, 9)	0.59
	No diastolic OH at baseline	**Diastolic OH at baseline**	
	N= 25	**N= 67**	
Tinetti Balance	23 (20, 25)	24 (22, 25)	0.40
	N= 24	**N= 67**	
Tinetti Gait	6.5 (4, 9)	9 (6, 9)	0.05

6.8.3 Continuous Response to Active Stand at Baseline and Gait and Balance at Follow-up

Examining the association between continuous haemodynamic response to active stand at baseline and gait and balance scores at follow-up showed that greater diastolic vasodepression was associated with better Tinetti scores at follow-up (Table 6-17). This association was not evident after adjusting for covariates.

Table 6-17 Spearman Correlation between Continuous Response to Active Stand and Tinetti Scores at Follow-up

		Systolic vaso-depression (mmHg)	Diastolic vaso-depression (mmHg)	Systolic Nadir (mmHg)	Diastolic Nadir (mmHg)
Tinetti Balance	**r**	-0.15	0.13	0.13	0.08
	P	0.16	0.22	0.22	0.44
Tinetti Gait	**r**	0.07	**0.26**	-0.07	-0.06
	P	0.50	**0.01**	0.52	0.59

6.9 Response to Carotid Sinus Massage at Baseline and Falls, Gait and Balance at Follow-up

Of the 104 participants who gave a complete falls history at follow-up, 90 underwent carotid sinus massage at baseline. The number of these individuals with carotid sinus hypersensitivity and CSH subgroups are shown below (Table 6-18).

Table 6-18 Number of Participants who Underwent CSM at Baseline and Falls Assessment at Follow-up with CSH and CSH subgroups.

	Frequency
Carotid Sinus Hypersensitivity	28
Carotid Sinus Hypersensitivity Subgroups	
• ***Cardio inhibitory CSH***	2
• ***Vasodepressive CSH***	12
• ***Mixed CSH***	14

6.9.1 Carotid Sinus Hypersensitivity at Baseline and Falls at Follow-up

Presence or absence of carotid sinus hypersensitivity at baseline was not associated with number of individuals reporting falls, recurrent falls, or injurious falls at follow-up. Analysing the CSH subtypes separately did not alter this finding (Table 6-19).

Table 6-19 Association between Carotid Sinus Hypersensitivity and Falls at Follow-up

	No Carotid Sinus Hypersensitivity N= 61	**Carotid Sinus Hypersensitivity N=28**	**P**
	Frequency (%)	**Frequency (%)**	
Falls	18 (30)	9 (32)	0.77
Recurrent Falls	9 (15)	5 (18)	0.76
Injurious Falls	12 (20)	7 (25)	0.57
	No Cardio inhibitory CSH N= 88	**Cardio inhibitory CSH N =2**	
Falls	26 (29)	1 (50)	0.51
Recurrent Falls	13 (15)	1 (50)	0.29
Injurious Falls	18 (20)	1 (50)	0.38
	No Vasodepressive CSH N=78	**Vasodepressive CSH N=12**	
Falls	23 (29)	4 (33)	0.75
Recurrent Falls	14 (18)	0	0.20
Injurious Falls	10 (13)	2 (16)	1.00
	No mixed CSH N=75	**Mixed CSH N=14**	
Falls	23 (31)	4 (29)	1.00
Recurrent Falls	10 (13)	4 (29)	0.22
Injurious Falls	15 (20)	4 (29)	0.49
	Symptomatic CSH N=12	**Asymptomatic N=78**	
Falls	4 (33)	23 (29)	0.74
Recurrent Falls	3 (25)	9 (12)	0.39
Injurious Falls	2 (17)	19 (24)	1.00

There was no association between CSH status and reported number of falls in year prior to follow-up assessment. Similarly, CSH subtypes were not associated with number of falls (Table 6-20)

Table 6-20 Negative Binomial Regression Examining Association between CSH and CSH Subtypes and Reported Number of Falls in Year Prior to Follow-up Assessment

	IRR	**95% CI**	**P**
Carotid Sinus Hypersensitivity	1.53	0.74, 3.15	0.25
Type of Carotid Sinus Hypersensitivity			
• Mixed CSH	1.83	0.75, 4.45	0.18
• Vasodepressive CSH	0.71	0.21, 2.40	0.56
• Cardioinhibitory CSH	4.28	0.74, 24.6	0.10

To examine if symptoms during carotid sinus massage are an important predictor of falls, these analyses were repeated. There were no significant associations between symptoms during CSM and falls, recurrent fall and injurious falls (Table 6-19). Negative binomial regression did not show any association between symptoms during CSM and reported number of falls in year preceding the ten year follow-up assessment.

Examining the relationship between continuous haemodynamic response to CSM and number of participants reporting falls at follow-up did not show any significant associations (Table 6-21). There was however a significant relationship between maximum RR interval and reporting recurrent falls and delta RR interval and reporting recurrent falls (Table 6-21). These associations were no longer significant after adjusting for covariates.

Table 6-21 Association between Continuous Response to CSM and Falls at Follow-up

	Odds Ratio	**95% CI**	**P**
Falls *			
SBP vasodepression (mmHg)	1.00	0.98, 1.03	0.76
SBP nadir (mmHg)	1.00	0.98, 1.01	0.69
Maximum RR interval (s)	1.04	0.81, 1.33	0.77
Maximum delta RR (s)	1.05	0.81, 1.35	0.72
Recurrent Falls*			
SBP vasodepression (mmHg)	1.01	0.98, 1.05	0.50
SBP nadir (mmHg)	1.00	0.98, 1.02	0.79
Maximum RR interval (s)	1.34	1.02, 1.75	**0.03**
Maximum delta RR (s)	1.35	1.02, 1.77	**0.03**
Injurious Fall *			
SBP vasodepression (mmHg)	1.00	0.97, 1.03	0.95
SBP nadir (mmHg)	1.00	0.98, 1.02	0.88
Maximum RR interval (s)	1.07	0.82, 1.40	0.63
Maximum delta RR (s)	1.08	0.82, 1.42	0.60
Number of Falls $^{\infty}$	**IRR**	**95% CI**	**P**
SBP vasodepression (mmHg)	1.01	0.99, 1.03	0.29
SBP nadir (mmHg)	0.99	0.98, 1.01	0.32
Maximum RR interval (s)	1.18	0.99, 1.40	0.07
Maximum delta RR (s)	1.18	0.99, 1.40	0.06
* Binary logistic Regression, $^{\infty}$ Negative Binomial Regression			

6.9.2 **Carotid Sinus Hypersensitivity at Baseline and Tinetti Scores at Follow-up**

Of the 90 individuals who participated in follow-up examination and underwent carotid sinus massage at baseline, 89 completed the Tinetti balance assessment at follow-up and 88 completed the Tinetti gait assessment. Comparing participants who had CSH at baseline with those who did not have CSH did not reveal any differences in follow-up Tinetti scores (Table 6-22).

Table 6-22 Tinetti Scores According to Baseline CSH Status

	No Carotid Sinus Hypersensitivity	**Carotid Sinus Hypersensitivity**	**P**
	Median (IQ range)	**Median (IQ range)**	
	N= 61	**N= 28**	
Tinetti balance	24 (21.5, 25)	24 (21.0, 25.0)	0.77
	N=60	**N=28**	
Tinetti gait	8.5 (5.0, 9.0)	9.0 (5.5, 9.0)	0.64
	No Cardio inhibitory CSH	**Cardio inhibitory CSH**	
	N=87	**N=2**	
Tinetti balance	24 (21, 25)	21.5 (17.0)	0.97
	N=86	**N=2**	
Tinetti gait	9.0 (5.0, 9.0)	8.5 (8.0)	0.72
	No Vasodepressive CSH	**Vasodepressive CSH**	
	N=77	**N=12**	
Tinetti balance	24 (21.5, 25)	23 (21, 24.75)	0.55
	N=76	**N=12**	
Tinetti gait	9.0 (5.25, 9.0)	8.5 (4.25, 9.0)	0.79
	No mixed CSH	**Mixed CSH**	
	N=75	**N=14**	
Tinetti balance	24 (21, 25)	24 (21.25, 25)	0.87
	N=74	**N=14**	
Tinetti gait	8.5 (5.0, 9.0)	9.0 (6.25, 9.0)	0.50

There was no association between Tinetti gait and balance scores at ten year follow-up and continuous response to CSM at baseline (Table 6-23).

Table 6-23 Spearman Association between Continuous Haemodynamic Response to CSM and Tinetti Score at Follow-up

	Tinetti Balance r (P)	Tinetti Gait r (P)
Maximum Vasodepression (mmHg)	-0.01 (0.96)	0.03 (0.76)
Minimum Systolic Nadir (mmHg)	0.11 (0.32)	0.11 (0.33)
Max RR interval post CSM	-0.08 (0.47)	-0.02 (0.88)
Max Delta RR	-0.06 (0.55)	-0.03 (0.79)

6.10 Autonomic Function at Baseline and Falls, Gait and Balance at Follow-up

Of the 104 participants who completed the falls history at follow-up, 81 had results from all five autonomic function tests at baseline. The number of participants with results available for each of the individual autonomic function tests is shown below (Table 6-24).

Table 6-24 Number of Participants Completing Each Autonomic Function Test

Autonomic Function Test	Number of participants completing test
Active stand	95
Isometric exercise	96
Valsalva manoeuvre	98
Cold pressor	95
Deep breathing	92

Ninety participants had undergone sufficient autonomic function tests to classify autonomic function as normal or abnormal according to modified Ewing criteria. Abnormal autonomic function at baseline was not associated with falling, recurrent falls or injurious falls in the year preceding ten year follow-up assessment (Table 6-25). Similarly, negative binomial regression failed to show a significant association between abnormal autonomic function and reported number of falls in year preceding follow-up assessment [IRR 0.84 (95% CI 0.41, 1.74) P= 0.64].

Table 6-25 Association between Autonomic Function and Fall at Follow-up

	Normal Autonomic Function N =61	**Abnormal Autonomic Function N=29**	**P**
	Frequency (%)	**Frequency (%)**	
Falls	21 (34)	9 (31)	0.75
Recurrent Falls	10 (16)	5 (17)	1.00
Injurious Falls	14 (23)	5 (17)	0.54

6.10.1 Continuous Response to Individual Autonomic Function Tests at Baseline and Falls at Follow-up

Examining the association between reported falls in the year preceding the ten year follow-up assessment and continuous response to individual autonomic function tests at baseline showed that increased Valsalva ratio at baseline was significantly associated with an increased number of subjects reporting one or more falls at the follow-up assessment (Table 6-26). These associations were not significant on multivariable analysis.

Table 6-26 Association between Continuous Haemodynamic Response to Autonomic Function Tests and Number of Individual Reporting Falls, Recurrent Falls or Injurious Falls at Follow-up

	Odds Ratio	**95% confidence interval**	**P**
Falls			
Active sit DBP difference (mmHg)	1.00	0.97, 1.03	0.79
Cold pressor DBP difference (mmHg)	0.99	0.94, 1.05	0.78
Valsalva SBP overshoot (mmHg)	0.99	0.97, 1.01	0.21
Valsalva ratio	**0.15**	**0.03, 0.89**	**0.04**
30:15 ratio	0.14	0.01, 11.5	0.38
Heart rate response to deep breathing	0.99	0.90, 1.08	0.74
Recurrent Falls			
Active sit DBP difference (mmHg)	0.98	0.94, 1.02	0.38
Cold pressor DBP difference (mmHg)	0.98	0.91, 1.06	0.62
Valsalva SBP overshoot (mmHg)	0.98	0.96, 1.00	0.08
Valsalva ratio	**0.05**	**0.01, 0.74**	**0.03**
30:15 ratio	0.01	0.00, 2.25	0.09
Heart rate response to deep breathing	1.03	0.92, 1.15	0.62
Injurious Fall			
Active sit DBP difference (mmHg)	1.00	0.96, 1.03	0.79
Cold pressor DBP difference (mmHg)	0.97	0.91, 1.04	0.42
Valsalva SBP overshoot (mmHg)	1.00	0.98, 1.02	0.79
Valsalva ratio	0.17	0.02, 1.37	0.10
30:15 ratio	0.02	0.01, 4.23	0.15
Heart rate response to deep breathing	0.97	0.87, 1.08	0.53

Negative Binomial regression showed that Valsalva ratio was significantly associated with reported number of falls in year prior to follow-up. One unit increase in Valsalva ratio was associated with an 81% reduction in falls count (Table 6-27). This association was no longer significant after adjusting for covariates.

Table 6-27 Unadjusted Negative Binomial Regression Examining Association between Response to Individual Autonomic Function Tests and Reported Number of Falls in Year Preceding Follow-up Assessment

	IRR	**95% CI**	**P**
Number of Falls			
Active sit DBP difference (mmHg)	0.99	0.97, 1.01	0.32
Cold pressor DBP difference (mmHg)	0.99	0.94, 1.03	0.58
Valsalva SBP overshoot (mmHg)	0.99	0.98, 1.00	0.06
Valsalva ratio	**0.19**	**0.05, 0.78**	**0.02**
30:15 ratio	0.04	0.01, 1.67	0.09
Heart rate response to deep breathing	1.01	0.95, 1.08	0.75

6.10.2 **Autonomic Function at Baseline and Tinetti Scores at Follow-up**

Of the 90 participants who had undergone sufficient autonomic function tests to classify autonomic function as normal or abnormal according to modified Ewing criteria, 87 underwent Tinetti balance assessment and 86 underwent Tinetti gait assessment.

Participants with normal autonomic function at baseline had better Tinetti balance scores at ten year follow-up than individuals who had abnormal autonomic function at baseline, P=0.02 (Table 6-28). After adjusting for covariates, this association was no longer significant.

Table 6-28 Abnormal versus Normal Autonomic Function and Tinetti Scores at Follow-up

	Normal Autonomic Function N =61	**Abnormal Autonomic Function N=29**	**P**
	Median (IQ range)	**Median (IQ range)**	
Tinetti balance score	24 (22, 25)	22 (18.5, 24)	**0.02**
Tinetti gait score	8 (4.75, 9)	8.5 (5, 9)	0.98

Examining the association between continuous response to autonomic function tests and Tinetti scores showed that:

- greater change in diastolic BP in response to isometric exercise was associated with lower Tinetti gait score at follow-up
- greater systolic overshoot and heart rate ratio in response to Valsalva manoeuvre was associated with better Tinetti balance scores
- greater 30:15 ratio in response to active stand was associated with better Tinetti balance score (Table 6-29).

These associations were no longer statistically significant after adjusting for covariates.

Table 6-29 Spearman Correlation between Continuous Response to AFT and Tinetti Scores

		r	P
Isometric Exercise			
DBP change (mmHg)	Tinetti balance score	-0.08	0.48
	Tinetti gait score	**-0.23**	**0.03**
Cold Pressor			
DBP difference (mmHg)	Tinetti balance score	0.15	0.16
	Tinetti gait score	0.13	0.24
Valsalva Manoeuvre			
Valsalva SBP overshoot (mmHg)	Tinetti balance score	**0.24**	**0.02**
	Tinetti gait score	0.18	0.09
Valsalva ratio	Tinetti balance score	**0.31**	**<0.01**
	Tinetti gait score	0.20	0.06
Active stand			
30:15 ratio	Tinetti balance score	**0.22**	**0.03**
	Tinetti gait score	0.08	0.47
Deep breathing			
Heart rate response	Tinetti balance score	0.06	0.55
	Tinetti gait score	-0.07	0.54

6.11 Heart Rate Variability at Baseline and Falls, Gait and Balance at Follow-up

Of the 104 participants who gave a complete falls history at follow-up, 91 underwent assessment of heart rate variability at baseline. Of these, 83 participants had recordings where ≤10 percent of the beats were interpolated or ectopic.

6.11.1 Heart Rate Variability at Baseline and Falls at Follow-up

Heart rate variability at baseline was not associated with number of individuals reporting falls, recurrent falls or injurious falls in the year preceding follow-up assessment (Table 6-30). HF/LF ratio was however significantly associated with reported number of falls in year preceding follow-up [IRR 0.60 (95% CI 0.42, 0.86) P<0.01]. This was no longer the case after adjusting for covariates.

Table 6-30 Association between Heart Rate Variability and Falls

	Odds Ratio	**95% confidence interval**	**P**
Falls *			
SDNN	0.97	0.93, 1.01	0.19
Total Power	1.00	0.99, 1.01	0.90
VLF	1.00	0.99, 1.02	0.57
LF	1.00	0.99, 1.00	0.61
HF	1.00	0.99, 1.00	0.88
HF/LF	0.49	0.17, 1.39	0.18
Recurrent Falls*			
SDNN	1.02	0.97, 1.07	0.56
Total Power	1.001	1.000, 1.002	0.08
VLF	1.002	1.000, 1.003	0.06
LF	1.001	0.999, 1.003	0.48
HF	1.001	0.999, 1.003	0.17
HF/LF	1.04	0.42, 2.56	0.93
Injurious Fall *			
SDNN	1.01	0.96, 1.05	0.83
Total Power	1.00	1.00, 1.01	0.11
VLF	1.00	1.00, 1.01	0.08
LF	1.00	1.00, 1.01	0.49
HF	1.00	1.00, 1.01	0.30
HF/ LF	0.49	0.14, 1.73	0.27
Number of Falls$^{\infty}$	**IRR**	**95% confidence interval**	**P**
SDNN	1.00	0.97, 1.03	0.93
Total Power	1.00	1.00, 1.01	0.33
VLF	1.00	1.00, 1.00	0.12
LF	1.00	0.99, 1.00	0.98
HF	1.00	1.00, 1.00	0.72
HF/ LF	0.60	0.42, 0.86	**<0.01**
** Logistic Regression, $^{\infty}$ Negative Binomial Regression*			

6.11.2 **Heart Rate Variability at Baseline and Gait and Balance at Follow-up**

Of the 83 follow-up participants with satisfactory heart rate variability recordings at baseline, 81 completed the balance assessment and 80 completed the gait assessment. Analysis of the association between heart rate variability and Tinetti scores revealed that greater SDNN, total power, very low frequency power and low frequency power were associated with better gait and balance scores (

Table 6-31). These associations were not significant after adjusting for covariates

Table 6-31 Spearman Correlation between Heart Rate Variability and Tinetti Gait and Balance Scores

	Tinetti Balance **r (P)**	**Tinetti Gait** **r (P)**
SDNN	**0.28 (0.01)**	**0.30 (0.01)**
Total Power	**0.29 (0.01)**	**0.27 (0.02)**
VLF	**0.24 (0.03)**	**0.22 (0.05)**
Low Frequency	**0.35 (<0.01)**	**0.31 (<0.01)**
High Frequency	0.18 (0.12)	0.20 (0.08)
HF/LF	-0.17 (0.13)	-0.10 (0.36)

6.12 **Summer y of Key Results From Chapter 6**

The number of participants reporting falls had increased but not significantly where as the number of participants reporting recurrent falls had significantly increased. Median Tinetti scores for the cohort were significantly lower at follow-up than at baseline.

6.12.1 **Hypertension**

Hypertension at baseline was not associated with reports of falls or Tinetti scores at follow-up

6.12.2 **Ambulatory Blood Pressure Measurements**

There were no independent associations between mean BP or BP variability and falls, recurrent falls or injurious falls. Similarly mean BP and BP variability were not associated with Tinetti Scores.

6.12.3 **Orthostatic Hypotension**

Orthostatic hypotension at baseline defined according to AAN guidelines was not associated with falls, recurrent falls or injurious falls. Symptomatic OH was however associated with a greater number of participants reporting recurrent falls. This was no longer significant after adjusting for covariates including age, sex, cardiovascular risk factors and cardioactive medication. Degree of vasodepression in response to active stand was not associated with falls, recurrent fall, injurious falls or reported number of falls.

OH was not associated with performance on Tinetti assessments of gait and balance.

6.12.4 **Carotid Sinus Massage**

Carotid sinus hypersensitivity at baseline was not associated with reported falls, recurrent falls or injurious falls. There was however an association between length or RR interval post CSM and reports or recurrent falls. With long RR interval being associated with greater odds of recurrent falls. This association was no longer significant after adjusting for co-variates.

CSH was not associated with performance on Tinetti assessment of gait and balance.

6.12.5 **Autonomic Function**

Abnormal autonomic function as defined by Ewing criteria was not associated with falls, recurrent falls or injurious falls. Of the individual autonomic function tests Valsalva ratio at baseline was associated with reports of falls, recurrent falls and number of falls at follow-up however these associations were not significant after adjusting for age, sex and cardiovascular risk factors.

On univariate analysis an association was observed between abnormal autonomic function and poorer performance on the Tinetti balance score however after correcting

for covariates including age this was not long significant. Similarly associations observed between heart rate variability and Tinetti gait and balance scores were not significant after adjusting for covariates.

6.13 **Discussion**

6.13.1 **Hypertension and Falls, Gait and Balance**

There were no associations between having hypertension on ambulatory BP monitoring at baseline and falling in the year prior to follow-up or with the reported number of falls in the year prior to follow-up. Review of the literature found there are few studies examining the association between hypertension and falls. McCarthy et al identified 4 studies exploring the possible link between elevated blood pressure and falls (McCarthy et al., 2010). Three studies found that self-reported hypertension was a risk factor for falling, while the other found fallers were more likely to have hypertension than non-fallers (Chan et al., 1997, Bergland et al., 2003, Assantachai et al., 2003, Davison et al., 2005). None of these studies used objective measures of hypertension. Self-reported hypertension has been shown to underestimate the prevalence of hypertension. A further study published since McCarthy's review examined the association between hypertension and frequent falls (three or more falls in the last 6 months). In keeping with the findings of this current study, no association was found between hypertension and frequent falls (Teh and Fisher, 2012).

No association was seen between hypertension status at baseline and performance on the Tinetti gait and balance assessment at follow-up. A smaller study performed ambulatory BP monitoring in 72 older people (White et al., 2011). Gait and balance were assessed using the Tinetti score and time to walk 8 ft. and climb 3 stairs were recorded at baseline and at 2 years follow-up. Hypertension at baseline (defined as mean BP > 135/80) was associated with slower gait speed at follow-up, but not with performance on Tinetti assessment. Two other longitudinal studies have also reported the effect of hypertension on gait speed (Rosano et al., 2011, Dumurgier et al., 2010). Both found hypertension was associated with slower speed at baseline and faster declines in gait speed over follow-up. This was independent of demographic and selected comorbidities, but was attenuated by white matter disease. Shah et al developed a measure of lower limb function incorporating 2 measures of gait speed, 1 measure of chair rise capacity, and 2 measures of balance skills(Shah et al., 2006). No association

was found between systolic BP and performance on the assessment of lower limb function at baseline but greater systolic BP was associated with fast decline in function over the follow-up period. A small cross-sectional study, of 24 healthy community-dwelling older people aged 65-90 compared several measures of gait and balance including the Tinetti scores among hypertensive and normotensive patients (Jeffrey M. Hausdorff and Tanya Gurevich, 2003). Again, the group found significantly poorer performance on the Timed Up-and-Go and Pull tests among the hypertensive group compared to the controls. However, there was no significant difference in the Tinetti gait and balance scores. These findings suggest that hypertension may be associated with gait speed but not performance on Tinetti assessment, possibly because the Tinetti score is not sensitive enough to detect small changes in gait associated with hypertension in fit older people.

6.13.2 **Blood Pressure Variability and Falls, Gait and Balance**

Twenty-four hour systolic BP variability was associated with increased odds of falling in the year prior to assessment. After adjusting for relevant covariates, however, this was no longer a significant predictor of falls. Few studies have examined the association between BP variability and falling. Puisieux et al compared BP variability in three groups of older people; fallers, people with syncope and a control group (Puisieux et al., 2000). BP variability did not significantly differ between the groups. Jonsson et al examined BP variation in response to daily activities, e.g. eating, and response to nitro-glycerine (GTN). They found older people with greater BP variability in response to these activities and GTN were at risk of falls (Jonsson et al., 1990). However, the study was conducted in older people living in nursing care and included BP variability induced by a pharmacological agent. Review of the literature did not reveal any studies examining the longitudinal association between BP variability and falls.

No associations were observed in this study between BP variability and performance on Tinetti gait and balance assessment. Although increased BP variability has been associated with WMH, which in turn have been associated with gait abnormalities, no other studies were identified examining the direct association between BP variability and gait and balance in older people.

6.13.3 **NCVI and Falls Gait and Balance**

Neither orthostatic hypotension nor carotid sinus hypersensitivity were associated with reports of falling in the year prior to assessment. This is in keeping with baseline findings and with studies examining the associations between OH and falls over shorter intervals (Kerr, 2009, Ganz et al., 2007, McCarthy et al., 2010). Prospective studies among community-dwelling older people have failed to show an association between OH and suffering a fall in the following 12 months (McCarthy et al., 2010, Ganz et al., 2007). Some studies, but not all, do suggest there may be an association between OH and recurrent falls, most often defined as 2 or more falls in 12 months (McCarthy et al., 2010, Ganz et al., 2007). There may have been a trend towards this finding in our study, 22% of the systolic OH group reported recurrent falls compared to 9% of the group without systolic OH (P=0.10). The sample size in this study was small and the study may have lacked statistical power.

To my knowledge there have been no prospective studies examining the association between CSH or CSS and falls. Several studies have however compared the prevalence of CSH among fallers and age-matched controls. Sachpekidis et al reported prevalence of CSH of 18.2%, 17.6% and 66.7% among controls, accidental fallers and individuals with and unexplained fall respectively (Sachpekidis et al., 2009). Tan et al reported finding CSH among 25% of individuals investigated for falls or syncope at a regional falls and syncope centre (Tan et al., 2009). Davies et al examined rates of CSH among older people presenting to A&E with non-accidental falls and among matched controls. The group found CSH in 46% of cases versus 13% of controls and CSS in 27% of cases versus 0% of controls (Davies et al., 2001). Rafanelli et al reported rates of carotid sinus syndrome of 10.5% and 14.3% among patients presenting with unexplained falls and syncope respectively (Rafanelli et al., 2013). It is interesting that most of these studies found rates of CSH and CSS among controls and fallers lower than observed in this unselected community-dwelling population. In this cohort CSH was present in 39% of participants at baseline and CSS was present in 16%(Kerr, 2009).

Despite cross-sectional evidence supporting an association between CSH and falls, interventional studies examining the efficacy of permanent cardiac pacing for falls prevention in CSH have shown mixed results. These studies were recently reviewed by Parry and Mathews (Parry and Matthews, 2013). They found that un-blinded studies

among younger patients suggested pacing might reduce falls. However, studies among older people did not show a reduction in falls among the paced group, possibly because older patients are more likely to have multiple co-morbidities and falls are likely to be multifactorial. There is one published randomised double-blinded placebo controlled trial to examine pacing for CSS among older, recurrent fallers (Parry et al., 2009). This found a reduction in falls in both the placebo and the active arm of the trial, with no benefit in the pacing arm. The authors suggest that this study shows there is a clear anticipation effect associated with pacing resulting in reduced falls among both the placebo and pacing arms.

It was hypothesised that WMH secondary to NCVI may lead to gait and balance impairment. No independent associations between OH at baseline and Tinetti gait and balance scores at follow-up were identified. Similarly, response to CSM at baseline was not associated with Tinetti gait and balance scores at follow-up. Few studies have examined the association between hypotensive syndromes and gait and balance among the general older population. Barret et al examined gait among three groups: elderly fallers without OH, elderly fallers with OH, and a control group (Barrett et al., 2008). They hypothesised that if elderly fallers with OH were falling purely due to BP abnormalities they would have similar gait patterns to age-matched controls. The OH group and the control group had similar gait variability, which was significantly less than observed in elderly fallers without OH. Barret et al concluded that this indicates that fallers with OH are falling purely because of their vascular abnormalities and are not falling due to gait impairment as seen in fallers without OH. Interestingly, the authors found that both fallers with and those without OH spent more time in the stance phase of gait; they suggested that this was due to fear of falling (Barrett et al., 2008). A study of the association between OH, gait and balance in 91 diabetic patients also found mixed results (Cordeiro et al., 2009). OH was negatively and independently associated with performance on the Berg Balance Scale, but not with performance on timed-up-and-go. Similarly, a study among 120 patients with Parkinson's disease found OH was associated with increased postural sway, but not with timed-up-and-go or walking speed (Matinolli et al., 2009).

6.13.4 **Autonomic Function and Falls Gait and Balance**

Of the autonomic function tests, only heart rate response to Valsalva manoeuvre was associated with falls risk and these associations were no longer significant adjusting for

covariates. From the heart rate variability variables only HF:LF ratio was associated with falls, but again this was not significant after adjusting for covariates, suggesting that the associations were due to confounding risk factors. There are a few other studies examining the association between autonomic function and falls. Isik et al have compared 24-hour heart rate variability among older people who had fallen in the last 12 months and a control group who had never fallen. Time and frequency domains were examined. In keeping with our findings, heart rate variability parameters did not significantly differ between groups (Isik et al., 2012).

After adjusting for covariates neither response to autonomic function tests nor measures of HRV were associated with Tinetti scores at follow-up. These findings are in keeping with those of Aerts et al who examined the association between gait and heart rate variability among three groups: young healthy individuals, elderly healthy individuals, and people with Parkinson's disease (Aerts et al., 2009). HRV was not significantly associated with gait speed, gait swing time or swing time variability.

6.13.5 **Summary**

These data have shown few associations between autonomic function or NCVI at baseline on the one hand, and falls, gait and balance on the other. Given the extensive multiple testing, those associations that have remained significant after adjusting for covariates should be interpreted with caution. It appears from these data that recurrent hypotensive episodes may not be a risk factor for falls over long follow-up periods. This is an interesting observation as assessment of autonomic function and NCVI is frequently advocated in guidelines on the assessment and management of falls (Panel on Prevention of Falls in Older Persons and British Geriatrics, 2011).

This study has several potential limitations to. Firstly, this study relied on retrospective recall of falls. This method is widely used and was chosen at follow-up in order to reproduce baseline methods, and allow comparison of baseline and follow-up data. It should be acknowledged, however, that retrospective recall of falls is less accurate than prospective collection of falls data. Studies comparing retrospective and prospective reports of falls reported a sensitivity and specificity of 79.5 and 91.4% indicating potential for misclassification (Peel, 2000). To help maximise the accuracy of the falls histories obtained, the next of kin of participants with cognitive impairment were

interviewed to confirm the number of falls that had occurred during the 12 months prior to assessment. In all these cases, the study participants lived with their next of kin, making it more likely that the next of kin would be able to give an accurate history. In this study, 32% of participants reported falling in the twelve months prior to follow-up assessment. Reassuringly, this is in keeping with other community-based studies in similar aged populations, suggesting our sample was representative of the general population in respect to falls prevalence (Tinetti et al., 1988, Rubenstein, 2006).

It should also be noted that autonomic function tests and tests of NCVI were only performed on one occasion at baseline. BP response varies by time of day and from day-to-day (Ward and Kenny, 1996). Best practice guidelines recommend that autonomic function should be tested in the morning and repeatedly (Ward and Kenny, 1996). Although all tests were conducted in the morning, repeated testing may have identified a group for people with more persistent OH at greater risk of falling.

Some participants may have developed OH or CSH over the follow-up period, while hypotensive syndromes may have improved or resolved in others. Diagnosing NCVI based on results of autonomic function tests from a single time point may have led to misclassification of participants. NCVI is often secondary to or exacerbated by antihypertensive medication. Review of medication and BP control at baseline and follow-up revealed increased use of antihypertensive drugs at follow-up compared to baseline and tighter BP control (McDonald et al., 2013). This may have affected the prevalence of NCVI over the ten year follow-up .

Both OH and CSH were highly prevalent in the cohort at baseline. OH affected 81% of the follow-up cohort at baseline and CSH affected 31%. The high prevalence is likely due to the use of beat-to-beat monitoring. Beat-to-beat monitoring is likely to detect short-lived drops in BP that would be missed if change in BP was measured using a standard sphygmomanometer. The prevalence of OH found in our study was slightly less than that reported in other studies using beat-to-beat monitoring (Romero-Ortuno et al., 2011a).

The failure to observe an association between NCVI and falls in this study may reflect the fact that the causes of falls, particularly in older people, are often multifactorial. In a

relatively small cohort, it may be difficult to identify the association between NCVI and falls as many of the falls occurring in the cohort may be due to other risk factors.

It was hypothesised in this study that NCVI might be associated with falls due to gait and balance impairment secondary to white matter damage. Few associations were observed between NCVI or autonomic function on the one hand and performance on the Tinetti assessments of gait and balance on the other. Interestingly, studies that have used other measures of gait and balance such as gait speed, timed up-and-go and postography have suggested that there may be an association between OH and gait and balance. The failure to identify an association between NCVI and gait in this study may therefore be a consequence of the characteristics of the Tinetti scale. The Tinetti scale has a documented ceiling effect, particularly for the gait component (Hayes and Johnson, 2003) At baseline 75% of participants had a Tinetti gait score of 9 (maximum attainable score). At follow-up, 50% of participants still had a score of nine. This ceiling effect may have meant that small differences in gait and balance associated with NCVI could not be detected, particularly among better performing members of the cohort.

Although the sample size was small and the measures used in this study rather insensitive to small changes in gait and balance, these data suggest that autonomic dysfunction and NCVI are not a substantial risk factor for future falls and gait impairment in community-dwelling older people.

Chapter 7 Association between White Matter Hyperintensities Clinical Symptoms and Baseline Neurocardiovascular Function

7.1 Introduction

White matter hyperintensity volume has been associated with poorer cognition, particularly executive function, depressive symptoms, impaired gait and balance and falls(Frisoni et al., 2007, Pantoni et al., 2007, DeCarli, 2013, Culang-Reinlieb et al., 2011, O'Brien, 2013, Zheng et al., 2011). Some studies have found WMH to be more severe in people with neurocardiovascular instability and a small number of studies have documented an association between greater WMH volume and altered autonomic function (Galluzzi et al., 2009, McLaren, 2004, Gottesman et al., 2011, Longstreth et al., 1996).

7.2 Aims

1. To examine if cognition, depressive symptoms and gait and balance are associated with WMH volume in this cohort at follow-up.
2. To examine if WMH volume at follow-up is associated with control of blood pressure and heart rate at baseline

7.3 Methods

7.3.1 Tests of Neurocardiovascular Function

Tests of neurocardiovascular function were described in 2.3, page 42.

7.3.2 Assessment of Clinical Symptoms

Assessment of cognition, depression, gait, balance, and falls was performed as described in sections 2.9 and 2.10, page 51.

7.3.3 Brain Magnetic Resonance Imaging

Magnetic resonance images were obtained on a 3T MRI scanner at Newcastle Magnetic Resonance Centre. The scanning protocol is described in section 2.11, page 52. An

automated volumetric method was used to calculate total, periventricular, and regional WMH volumes.

7.4 Statistics

White matter volumes were as expected highly skewed. In keeping with convention, WMH volume as a percentage of total brain volume was log transformed to normalise the distribution. White matter hyperintensity volume was then compared between two groups using the independent T test.

White matter hyperintensity volume is highly correlated with age (Tiehuis et al., 2007). Associations between WMH volume and continuous variables were therefore examined using age-adjusted partial correlations.

If significant associations were found on initial examination, analyses were repeated adjusting for covariates. Multi-linear regression was used to assess the association between multiple linear and categorical explanatory variables and white matter volume.

7.4.1 Covariates

A review of the literature revealed the following risk factors were consistently associated with greater WMH volume: age, hypertension, cerebrovascular disease (Chowdhury et al., 2011, Basile et al., 2006, Liao et al., 1997). These were entered as covariates into multivariate analysis.

7.5 Results: White Matter Hyperintensities and Cognition, Depression and Motor Symptoms at Follow-up

7.5.1 Characteristics of MRI Cohort

Of the 104 individuals who participated in the ten year follow-up, two participants died before an MRI could be completed, two withdrew from the study, 34 declined (most often due to claustrophobia or feeling that they could not lie flat for the duration of the scan), nine had a recognised contraindication (this included pacemaker, a cardiac stent not compatible with 3T MRI, previous injury with shrapnel or recent eye surgery), one participant was housebound and two participants had known intracranial pathology that would make interpreting the scan difficult (this included a large previous subdural

haemorrhage and an acoustic neuroma). In total, 53 participants consented to MRI scan and were free from contraindication to magnetic resonance imaging.

Table 7-1 compares the characteristics at year 10 follow-up of the participants who underwent MRI scan (N = 53) with those of the individuals who did not (N = 51). The groups were well matched in terms of age and sex, P=0.72 and P=0.71 respectively. Scores on cognitive tests at year 10 assessment tended to be higher among the group that underwent MRI, but these differences were not statistically significant. Rates of mild cognitive impairment and depression were similar in the two groups. Rates of cardiovascular and/or cerebrovascular disease were lower among the MRI cohort (P = 0.05), however rates of hypertension and diabetes were similar between the two groups P=0.89 and P=0.93 respectively.

Table 7-1 Characteristics at Follow-up of Cohort Undergoing MRI and Those Not Undergoing MRI

Characteristic at Follow-up	**No MRI (N= 51)**	**MRI (N= 53)**	
	Median (IQR)	**Median (IQR)**	**P**
Age (years)	80.0 (77.0, 83.0)	79.0 (76.0, 83.5)	0.72
BMI (kg/m^2)	27.4 (23.4, 30.8)	27.4 (24.4, 31.2)	0.71
MMSE	28.0 (26.0, 29.0)	29.0 (26.0, 29.0)	0.96
CAMCOG total score	94.0 (89.0, 96.0)	96.0 (90.3, 98.0)	0.12
CAMCOG memory score	22.0 (21.0, 24.0)	23.0 (21.0, 25.0)	0.09
CAMCOG executive score	20.0 (17.0, 23.0)	20.0 (18.0, 23.0)	0.70
Cornell score	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	0.65
	Frequency (%)	**Frequency (%)**	
Sex (male)	27 (53)	30 (57)	0.71
CVD	26 (51)	17 (32)	0.05
Hypertension	29 (57)	29 (55)	0.83
Diabetes	8 (16)	8 (15)	0.93
Dementia	3 (6)	1 (2)	0.36
MCI	2 (4)	0	0.15
Depression	2 (4)	2 (4)	0.97
Cardioactive medication	37 (73)	37 (70)	0.76
Psychoactive medication	10 (20)	7 (13)	0.38

7.5.2 **White Matter Hyperintensity Volume**

Table 7-2 shows mean WMH volume in each region as percentage of brain volume. Volumes of white matter hyperintensities at all sites were significantly associated with age (Table 7-3).

Table 7-2 WMH Volume as Percentage of Total Brain Volume

WMH Volume as Percentage of Total Brain Volume	**Mean**	**Standard Deviation**
Total WMH	1.35	1.32
Periventricular WMH	0.97	0.89
Left Frontal WMH	0.34	0.33
Right Frontal WMH	0.32	0.29
Left Parietal WMH	0.19	0.28
Right Parietal WMH	0.18	0.25
Left Occipital WMH	0.08	0.08
Right Occipital WMH	0.06	0.06
Left Temporal WMH	0.06	0.07
Right Temporal WMH	0.06	0.07

Table 7-3 Association between Normalised White Matter Hyperintensity Volume and Age

Log transformed white matter hyperintensity volume	**r**	**P**
Total WMH	0.45	**0.001**
Periventricular WMH	0.48	**<0.001**
Left Frontal WMH	0.40	**0.003**
Right Frontal WMH	0.38	**0.006**
Left Parietal WMH	0.43	**0.001**
Right Parietal WMH	0.38	**0.005**
Left Occipital WMH	0.32	**0.018**
Right Occipital WMH	0.34	**0.013**
Left Temporal WMH	0.39	**0.004**
Right Temporal WMH	0.33	**0.016**

7.5.3 **White Matter Hyperintensity Volume and Cognitive Function**

All 53 participants who underwent MRI also underwent cognitive testing. One patient, whose performance on the cognitive tests was affected by severe visual impairment, was excluded from the analysis. Age-adjusted partial correlations were used to examine the association between white matter hyperintensity volume and scores on MMSE and CAMCOG scores at year ten. There were no significant associations (Table 7-4). Similarly, there were no associations between WMH volume and reaction times scored on COMPASS battery (Table 7-5).

To examine if there was a threshold effect between WMH volume and cognition, the population was divided into quintiles according to Log (total WMH volume / brain volume) and cognition in the lowest four quintiles and upper quintile of WMH volume compared. Participants with greater white matter volume performed more poorly on the MMSE, total CAMCOG and CAMCOG memory test but these differences were not statistically significant. Similarly, there were no statistically significant differences in reaction times (Table 7-6). The same procedure was repeated for the periventricular white matter load and the findings were similar (Table 7-7).

Table 7-4 Partial Correlation Adjusting for Age Examining the Association between WMH Volume and Cognitive Test Scores at Follow-up

		WMH	PVWMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
MMSE Score at Year 10	***pr***	0.03	0.02	0.00	-0.01	0.08	0.14	0.10	-0.02	0.04	0.11
	P	0.83	0.89	0.98	0.96	0.57	0.33	0.49	0.88	0.76	0.45
Total CAMCOG at Year 10	***pr***	-0.08	-0.08	-0.10	-0.09	0.02	0.04	-0.11	-0.15	-0.10	0.01
	P	0.60	0.59	0.47	0.54	0.87	0.77	0.46	0.30	0.48	0.94
CAMCOG memory score year 10	***pr***	-0.20	-0.18	-0.21	-0.15	-0.12	-0.13	-0.12	-0.16	-0.23	-0.12
	P	0.15	0.21	0.14	0.28	0.42	0.36	0.40	0.28	0.11	0.42
CAMCOG executive score year 10	***pr***	-0.13	-0.16	-0.15	-0.13	-0.06	-0.01	-0.14	-0.10	-0.14	-0.05
	p	0.35	0.27	0.29	0.37	0.68	0.96	0.32	0.47	0.34	0.75

(WMH volume expressed as percentage of total brain volume and log transformed for analysis)

Table 7-5 Partial Correlation Adjusting for Age Examining the Association between WMH Volume and Reaction Times at Follow-up

		WMH	PVWMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
Choice Reaction Time (ms)	***pr***	-0.14	-0.09	-0.14	-0.08	-0.09	-0.09	-0.14	-0.09	-0.08	-0.09
	P	0.31	0.52	0.33	0.60	0.52	0.54	0.31	0.53	0.60	0.52
Simple Reaction Time (ms)	***pr***	-0.08	-0.09	0.00	-0.03	-0.16	-0.12	-0.20	-0.29	0.00	-0.05
	P	0.57	0.52	1.00	0.85	0.26	0.38	0.17	0.04	0.98	0.74
Digit Vigilance Reaction Time (ms)	***pr***	-0.15	-0.15	-0.15	-0.11	-0.14	-0.02	-0.24	-0.22	-0.17	-0.06
	P	0.29	0.28	0.28	0.45	0.33	0.87	0.08	0.11	0.24	0.67
Cognitive Reaction Time (ms)	***pr***	-0.05	0.00	-0.12	-0.04	0.06	0.03	0.04	0.16	-0.07	-0.04
	p	0.71	1.00	0.42	0.78	0.70	0.84	0.78	0.26	0.64	0.80
Power of Attention (ms)	***pr***	-0.16	-0.13	-0.11	-0.08	-0.17	-0.13	-0.24	-0.26	-0.07	-0.09
	p	0.28	0.35	0.45	0.59	0.23	0.38	0.09	0.07	0.62	0.53
(WMH volume expressed as percentage of total brain volume and log transformed for analysis)											

Table 7-6 Comparison of the Cognitive Function at Ten Years for Participants in the Lowest 4 Quintiles and the Highest Quintile of total WMH volume.

	Lower 4 quintiles of total white matter load N= 42	**Upper quintile of white matter load N=10**	**P**
	Median (IQR)	**Median (IQR)**	
MMSE	29 (26.8, 29.0)	27.5 (24.8, 29.3)	0.28
Total CAMCOG	95 (91.8, 99.0)	93 (82.8, 96.5)	0.26
CAMCOG memory	23.5 (21.8, 25.0)	22.5 (17.5, 24.5)	0.19
CAMCOG executive function	20.0 (18.0, 23.0)	20.5 (16.0, 21.5)	0.50
Choice reaction time (ms)	627 (576, 679)	563 (536, 701)	0.47
Simple reaction time (ms)	446 (407, 542)	439 (403, 606)	0.23
Digit vigilance time (ms)	543 (512, 596)	540 (522, 559)	0.91
Cognitive reaction time (ms)	152 (113, 226)	143 (-70, 253)	0.73
Power of attention (ms)	1643 (1502, 1810)	1662 (1491, 1796)	0.69

Table 7-7 Comparison of the Cognitive Function at Ten Years for Participants in the Lowest 4 Quintiles and the Highest Quintile of periventricular WMH volume.

	Lower 4 quintiles of peri-ventricular white matter load N= 42	**Upper quintile of peri-ventricular white matter load N=10**	**P**
	Median (IQR)	**Median (IQR)**	
MMSE	29.0 (26.0, 29.0)	28.0 (25.0, 30.0)	0.94
Total CAMCOG	95.0 (91.0, 99.0)	94.0 (89.0, 96.0)	0.44
CAMCOG memory	23.5 (21.0, 25.0)	23.0 (19.0, 24.0)	0.42
CAMCOG executive function	20.0 (18.0, 23.0)	20.5 (17.0, 21.0)	0.86
Choice reaction time (ms)	629 (583, 679)	563 (541, 669)	0.21
Simple reaction time (ms)	446 (411, 523)	439 (409, 583)	0.48
Digit vigilance time (ms)	541 (512, 592)	542 (526, 578)	0.25
Cognitive reaction time (ms)	157 (151, 224)	120 (-42.6, 206)	0.85
Power of attention (ms)	1643 (1502, 1797)	1682 (1519, 1819)	1.00

7.5.4 **White Matter Hyperintensity Volume and Depression**

Of the 53 participants who underwent MRI 51 had complete data from the Cornell depression Score. Age-adjusted partial correlation failed to show an association between WMH volume and Cornell score at follow-up (Table 7-8)

Table 7-8 Partial Correlation Examining Association between WMH volume and Performance on Cornell score at Follow-up

WMH Volumes	**Cornell Score at Follow-up**
	r (P)
Total WMH	-0.13 (0.37)
Periventricular WMH	-0.09 (0.55)
Left Frontal WMH	-0.08 (0.56)
Right Frontal WMH	-0.16 (0.27)
Left Parietal WMH	-0.11 (0.45)
Right Parietal WMH	-0.23 (0.11)
Left Occipital WMH	-0.21 (0.15)
Right Occipital WMH	-0.20 (0.17)
Left Temporal WMH	0.00 (1.00)
Right Temporal WMH	-0.14 (0.34)

Four participants had a Cornell score of 10 or more at follow-up (indicative of probable depression). There was no association between Cornell depression score ≥ 10 and WMH volume (Table 7-9).

Table 7-9 Comparison of White Matter Volume for Participants with and without Probable Depression (*depression defined as Cornell score ≥10*)

Volume of WMH as percentage of brain volume *(data log transformed for analysis but non transformed data shown here)*	**Cornell Score <10 N =47**	**Cornell score ≥10 N=4**	**P**
	Mean (SD)	**Mean (SD)**	
Total WMH	1.37 (1.34)	1.29 (1.55)	0.86
Periventricular WMH	0.96 (0.89)	1.09 (1.29)	0.90
Left Frontal WMH	0.34 (0.33)	0.27 (0.33)	0.99
Right Frontal WMH	0.32 (0.29)	0.27 (0.33)	0.65
Left Parietal WMH	0.19 (0.29)	0.19 (0.31)	1.00
Right Parietal WMH	0.19 (0.26)	0.13 (0.22)	0.41
Left Occipital WMH	0.08 (0.08)	0.09 (0.07)	0.63
Right Occipital WMH	0.06 (0.06)	0.06 (0.06)	0.48
Left Temporal WMH	0.06 (0.07)	0.06 (0.07)	0.71
Right Temporal WMH	0.06 (0.07)	0.06 (0.06)	0.83

To examine if the use of antidepressants altered this finding we expanded the definition of depression to include participants taking any antidepressant medication or scoring 10 or more on the Cornell score at follow-up. This showed an association between depression and decreased WMH in the right parietal lobe (P= 0.04). This association was not significant after adjusting for history of hypertension and cerebrovascular disease.

Table 7-10 Comparison of White Matter Volume for Participants with and without Probable Depression (*depression defined as Cornell score ≥10 and or taking antidepressants)*

Volume of WMH as percentage of brain volume *(data log transformed for analysis but non transformed data shown here)*	**Cornell Score <10 and not taking antidepressants N =43**	**Cornell score ≥10 or taking antidepressants N=8**	**P**
	Mean (SD)	**Mean (SD)**	
Total WMH	1.43 (1.38)	1.02 (1.09)	0.52
Periventricular WMH	0.99 (0.92)	0.88 (0.91)	0.86
Left Frontal WMH	0.35 (0.34)	0.28 (0.30)	0.83
Right Frontal WMH	0.33 (0.30)	0.28 (0.24)	0.78
Left Parietal WMH	0.21 (0.30)	0.12 (0.22)	0.19
Right Parietal WMH	0.20 (0.27)	0.09 (0.16)	**0.04**
Left Occipital WMH	0.09 (0.09)	0.07 (0.06)	0.54
Right Occipital WMH	0.07 (0.06)	0.05 (0.05)	0.25
Left Temporal WMH	0.07 (0.07)	0.04 (0.06)	0.63
Right Temporal WMH	0.07 (0.07)	0.04 (0.05)	0.12

7.5.5 White Matter Hyperintensity Volume and Falls

Of the 53 participants who underwent MRI, 14 reported falling in the year prior to assessment, of which six had had more than 1 fall. Fallers had a greater volume of white matter hyperintensities in all regions, but these differences were not statistically significant (Table 7-11). Similarly, comparing recurrent fallers with those who had not fallen or had fallen only once did not reveal any significant differences in white matter hyperintensity volume.

Table 7-11 Comparison of WMH Volume for Fallers and Non-fallers

Volume of WMH as percentage of brain volume ***(data log transformed for analysis but non transformed data shown here)***	**No history of Falls N = 39**	**History of ≥ 1 Fall N= 14**	**P**
Total WMH	1.25 (1.09)	1.63 (1.83)	0.92
Periventricular WMH	0.90 (0.73)	1.15 (1.25)	0.91
Left Frontal WMH	0.31 (0.27)	0.41 (0.47)	0.80
Right Frontal WMH	0.32 (0.27)	0.33 (0.34)	0.67
Left Parietal WMH	0.15 (0.22)	0.29 (0.41)	0.70
Right Parietal WMH	0.16 (0.21)	0.23 (0.35)	0.75
Left Occipital WMH	0.08 (0.06)	0.09 (0.12)	0.49
Right Occipital WMH	0.06 (0.06)	0.06 (0.05)	0.10
Left Temporal WMH	0.05 (0.06)	0.08 (0.10)	0.54
Right Temporal WMH	0.06 (0.06)	0.07 (0.08)	0.96

Negative binomial regression failed to show any significant associations between WMH volume and reported number of falls in year prior to follow-up assessment (Table 7-12)

Table 7-12 Negative Binomial Regression Examining Association between WMH Volume and Reported Number of Falls in Year Prior to Follow-up

Volume of WMH as percentage of brain volume	**IRR**	**95% CI**	**P**
Total WMH	0.94	0.30, 2.89	0.91
Periventricular WMH	1.10	0.34, 3.53	0.87
Left Frontal WMH	0.72	0.24, 2.22	0.57
Right Frontal WMH	0.57	0.18, 1.82	0.34
Left Parietal WMH	1.32	0.68, 2.55	0.42
Right Parietal WMH	0.84	0.44, 1.63	0.61
Left Occipital WMH	0.89	0.37, 2.13	0.79
Right Occipital WMH	0.57	0.25, 1.30	0.18
Left Temporal WMH	1.14	0.55, 2.36	0.72
Right Temporal WMH	1.29	0.55, 3.01	0.56

7.5.6 **White Matter Hyperintensity Volume and Gait and Balance**

Fifty-two of the participants underwent MRI scan and completed the Tinetti assessment of gait and balance. Partial correlation adjusting for age showed a significant positive association between Tinetti gait score, total WMH, periventricular, frontal and parietal WMH. Greater WMH volume in these regions was associated with better performance on the assessment of gait (Table 7-13). After adjusting for history of hypertension and cerebrovascular disease these associations were no long statistically significant. No significant associations were observed between Tinetti balance score and white matter hyperintensity volume (Table 7-13)

Table 7-13 Age-adjusted Partial Correlation between WMH Volume and Tinetti Scores.

Volume of WMH	**Age-adjusted correlation with Tinetti Gait Score**	**Age-adjusted correlation with Tinetti Balance score**
	***Pr* (P)**	***Pr* (P)**
Total WMH	0.30 (**0.03**)	0.17 (0.22)
Periventricular WMH	0.30 (**0.04**)	0.15 (0.31)
Left Frontal WMH	0.34 (**0.01**)	0.18 (0.20)
Right Frontal WMH	0.30 (**0.04**)	0.15 (0.26)
Left Parietal WMH	0.31 (**0.03**)	0.15 (0.29)
Right Parietal WMH	0.28 (**<0.05**)	0.17 (0.24)
Left Occipital WMH	0.08 (0.59)	0.24 (0.09)
Right Occipital WMH	-0.02 (0.91)	0.15 (0.29)
Left Temporal WMH	0.22 (0.12)	0.13 (0.35)
Right Temporal WMH	0.22 (0.07)	0.18 (0.22)

7.6 Results Baseline Neurocardiovascular Function and White Matter Hyperintensity Volume at Follow-up

7.6.1 Ambulatory Blood Pressure Variables at Baseline and White Matter Hyperintensity Volume at Follow-up

All 53 participants who underwent MRI at follow-up had ambulatory BP recordings with 16 readings or more readings at baseline. Of these, all had 10 or more daytime readings and 47 had five or more night-time readings. Fifty-three participants were therefore included in 24-hour and daytime analysis and 47 were included in night-time analysis and analysis of diurnal variation.

Comparing participants who underwent MRI with those who did not, did not reveal any significant differences in 24-hour ambulatory BP parameters (Table 7-14).

Table 7-14 Comparison of Baseline 24-hour Ambulatory BP Records for Participants Undergoing MRI and Those Who Did Not Undergo MRI

	No MRI N= 51	**MRI N=53**	
	Median (IQR)	**Median (IQR)**	**P**
Mean Systolic BP (mmHg)	129 (119, 136)	126 (115, 135)	0.72
Mean Diastolic BP (mmHg)	723 (66, 76)	70 (67, 80)	0.95
Systolic BP Variability	13 (11, 16)	13 (11. 14)	0.39
Diastolic BP Variability	9 (8, 10.)	9 (8, 10)	0.20

Hypertension at baseline, defined according to NICE criteria, was not associated with WMH volumes at follow-up (Table 7-15). However, mean daytime systolic BP > 150 on baseline ambulatory BP was associated with significantly greater total and periventricular white matter volumes (P= 0.019 and P= 0.035 respectively). Examining regions separately showed that the frontal regions had significantly greater volume of WMH in the systolic BP >150. The temporal, occipital and parietal lobes did not have significantly greater WMH volume (Table 7-16).

Table 7-15 Comparison of WMH Volume for Hypertensive and Normotensive Groups

Volume of WMH as percentage of brain volume *(data log transformed for analysis but non transformed data shown here)*	**No hypertension (NICE Criteria) (N= 30)**	**Hypertension (NICE Criteria) (N = 23)**	**P**
	Mean (SD)	**Mean (SD)**	
Total WMH	1.25 (1.10)	1.48 (1.57)	0.93
Periventricular WMH	0.90 (0.72)	1.05 (1.09)	0.90
Left Frontal WMH	0.32 (0.30)	0.36 (0.38)	0.95
Right Frontal WMH	0.32 (0.29)	0.32 (0.30)	0.81
Left Parietal WMH	0.16 (0.23)	0.22 (0.34)	0.84
Right Parietal WMH	0.15 (0.20)	0.22 (0.30)	0.44
Left Occipital WMH	0.07 (0.06)	0.10 (0.10)	0.86
Right Occipital WMH	0.05 (0.04)	0.07 (0.07)	0.38
Left Temporal WMH	0.05 (0.06)	0.06 (0.08)	0.94
Right Temporal WMH	0.06 (0.06)	0.07 (0.07)	0.47

Table 7-16 Comparison of WMH Volume for Participants with Mean Daytime Systolic BP >150 and Participants with Mean Daytime Systolic BP <150

Volume of WMH as percentage of brain volume ***(data log transformed for analysis but non transformed data shown here)***	**Mean daytime systolic BP <150 (N= 43)**	**Mean daytime systolic BP >150 (N = 10)**	**P**
	Mean (SD)	**Mean (SD)**	
Total WMH	1.10 (1.07)	2.42 (1.78)	**0.02**
Periventricular WMH	0.81 (0.74)	1.61 (1.21)	**0.04**
Left Frontal WMH	0.28 (0.28)	0.59 (0.44)	**0.02**
Right Frontal WMH	0.27 (0.26)	0.53 (0.32)	**0.04**
Left Parietal WMH	0.15 (0.23)	0.37 (0.42)	0.07
Right Parietal WMH	0.13 (0.19)	0.38 (0.36)	0.08
Left Occipital WMH	0.07 (0.06)	0.15 (0.13)	0.12
Right Occipital WMH	0.05 (0.04)	0.11(0.08)	0.18
Left Temporal WMH	0.05 (0.05)	0.11 (0.10)	0.08
Right Temporal WMH	0.05 (0.06)	0.10 (0.07)	0.10

Ambulatory blood pressure recordings for each time period was separately examined to determine if mean BP or BP variability were associated with WMH volume. No significant associations were identified (Table 7-17, Table 7-18 and Table 7-19). Similarly, percentage diurnal variation at baseline was not associated with WMH volume at follow-up (Table 7-20)

Table 7-17 Age-adjusted Partial Correlation Examining Association between 24 ABPM Recordings and WMH Volume

		WMH	PV WMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
24-hour											
24hr mean systolic BP (mmHg)	pr	0.18	0.15	0.23	0.17	0.10	0.06	0.12	-0.01	0.20	0.08
	P	0.20	0.30	0.11	0.23	0.47	0.69	0.38	0.97	0.16	0.60
24hr mean diastolic BP (mmHg)	pr	0.22	0.23	0.17	0.17	0.23	0.18	0.23	0.06	0.18	0.17
	P	0.12	0.10	0.22	0.22	0.11	0.22	0.11	0.69	0.20	0.23
24-hour systolic BP variability	pr	0.00	-0.02	0.04	-0.03	0.03	0.09	0.02	-0.07	0.01	-0.01
	P	0.98	0.90	0.80	0.84	0.83	0.53	0.90	0.63	0.94	0.95
24-hour systolic BP variability	pr	0.15	0.17	0.13	0.07	0.15	0.17	0.14	0.12	0.20	0.20
	P	0.29	0.24	0.35	0.60	0.31	0.24	0.34	0.42	0.16	0.15

Table 7-18 Age-adjusted Partial Correlation Examining Association between Daytime ABPM Recordings and WMH Volume

		WMH	PV WMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
Daytime											
Day mean systolic BP (mmHg)	pr	0.16	0.13	0.20	0.13	0.08	0.03	0.13	0.01	0.17	0.08
	P	0.27	0.37	0.15	0.36	0.57	0.81	0.36	0.93	0.22	0.60
Day mean diastolic BP (mmHg)	pr	0.20	0.22	0.15	0.14	0.21	0.15	0.23	0.06	0.17	0.18
	P	0.15	0.12	0.28	0.32	0.14	0.28	0.10	0.66	0.24	0.21
Day time SD SBP	pr	0.02	-0.03	0.02	0.05	0.16	0.25	-0.01	-0.09	-0.03	0.05
	P	0.91	0.86	0.87	0.72	0.26	0.07	0.95	0.52	0.85	0.74
Day time SD DBP	pr	0.06	0.05	0.08	0.12	0.12	0.16	-0.06	-0.03	0.08	0.07
	P	0.69	0.75	0.58	0.39	0.39	0.25	0.68	0.85	0.58	0.61

Table 7-19 Age-adjusted Partial Correlation Examining Association between Nigh-time ABPM Recordings and WMH Volume.

		WMH	VWMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
Night mean systolic BP (mmHg)	**pr**	0.09	0.06	0.11	0.11	0.07	0.03	0.02	-0.09	0.10	0.03
	P	0.56	0.68	0.45	0.45	0.66	0.86	0.90	0.57	0.49	0.87
Night mean diastolic BP (mmHg)	**pr**	0.10	0.10	0.05	0.12	0.18	0.15	0.07	-0.03	0.06	0.07
	P	0.51	0.53	0.74	0.44	0.25	0.31	0.62	0.86	0.72	0.65
Night-time SD SBP	**pr**	-0.01	-0.02	0.08	0.09	-0.19	-0.21	-0.06	-0.07	-0.03	-0.18
	P	0.94	0.90	0.61	0.57	0.21	0.17	0.70	0.65	0.84	0.22
Night-time SD DBP	**pr**	0.03	0.04	0.11	0.08	-0.09	-0.13	0.03	-0.02	0.07	-0.10
	P	0.83	0.81	0.45	0.59	0.57	0.38	0.86	0.91	0.64	0.50

Table 7-20 Age-adjusted Partial Correlation Examining Association between Diurnal Variation and WMH Volume.

		WMH	VWMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
Systolic diurnal	**pr**	0.02	0.03	0.08	-0.06	-0.03	-0.05	0.08	0.08	0.06	0.02
variation (mmHg)	**P**	0.89	0.84	0.60	0.71	0.84	0.77	0.58	0.62	0.69	0.89
Diastolic diurnal	**pr**	0.04	0.06	0.08	-0.03	-0.04	-0.08	0.06	0.02	0.07	0.07
variation (mmHg)	**P**	0.80	0.70	0.61	0.86	0.80	0.59	0.69	0.91	0.64	0.67

7.6.2 **Dipping Status and White Matter Hyperintensity Volume at Follow-up**

Participants were divided according to dipping status (non-dipper, normal dipper, or extreme dipper) (Figure 7-1). Because of the small sample, size non-dippers and extreme dippers were combined to form an "abnormal dipping group". White matter hyperintensity load for normal dippers and abnormal dippers were compared. Total white hyperintensities volume and white matter hyperintensity volume in the parietal lobes, left occipital lobe, and right temporal lobe were significantly greater in the abnormal dipper group than the normal dipper group. Periventricular white matter load was greater in the abnormal dipper group but this did not quite reach statistical significance (Table 7-21). As abnormal dippers were significantly older than normal dippers, [72.0 years versus 68.3 years respectively, P<0.01] these results were adjusted for age. WMH volume was no longer significantly associated with dipping status after adjusting for age.

Figure 7-1 Mean Total WMH Volume by Dipping Status

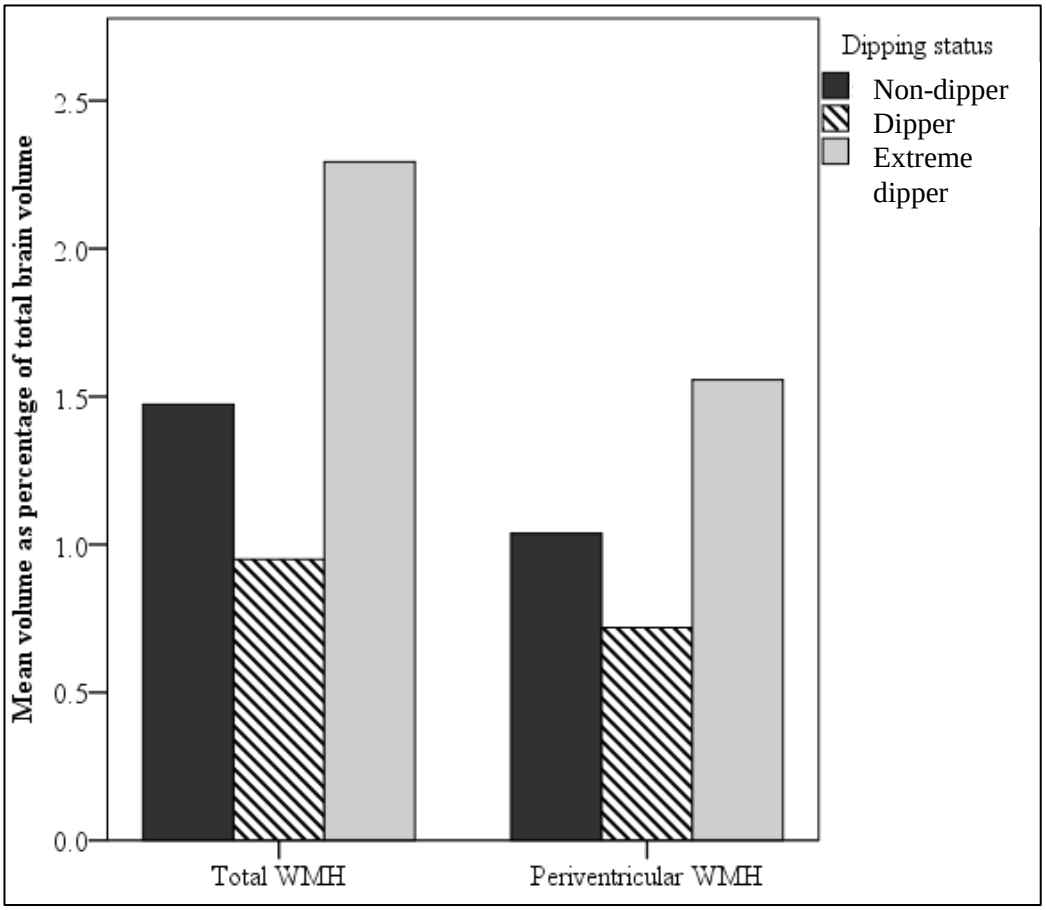


Table 7-21 Comparison of WMH Volume for Normal and Abnormal Dippers

Volume of WMH as percentage of brain volume ***(data log transformed for analysis but non transformed data shown here)***	**Normal Dipper (N = 24)**	**Abnormal Dipper (N = 6)**	**P**
	Mean (SD)	**Mean (SD)**	
Total WMH	0.94 (0.90)	1.69 (1.56)	**0.04**
Periventricular WMH	0.72 (0.67)	1.17 (1.02)	0.05
Left Frontal WMH	0.26 (0.25)	0.41 (0.40)	0.21
Right Frontal WMH	0.24 (0.22)	0.39 (0.35)	0.16
Left Parietal WMH	0.10 (0.16)	0.26 (0.33)	**0.02**
Right Parietal WMH	0.10 (0.17)	0.24 (0.29)	**0.02**
Left Occipital WMH	0.05 (0.05)	0.10 (0.09)	**0.01**
Right Occipital WMH	0.05 (0.07)	0.07 (0.04)	0.14
Left Temporal WMH	0.04 (0.05)	0.07 (0.08)	0.11
Right Temporal WMH	0.04 (0.05)	0.08 (0.07)	**0.04**

7.6.3 Response to Active Stand at Baseline and White Matter Hyperintensity Volume at Follow-up

Ninety-five follow-up participants had baseline active stand results suitable for analysis. Of these, 47 had an MRI scan. Comparing the MRI group with the group who did not undergo MRI showed identical rates of OH (81%). There were no statistically significant differences in baseline systolic or diastolic BP during active stand or degree of systolic or diastolic vasodepression between the groups (Table 7-22).

Table 7-22 Comparison of Response to Active Stand at Baseline for MRI group and Group not Undergoing MRI

	No MRI N= 48	**MRI N=47**	
	Median (IQR)	**Median (IQR)**	**P**
Baseline Systolic BP (mmHg)	141 (124, 162)	136 (123, 153)	0.43
Baseline Diastolic BP (mmHg)	62 (54, 70)	60 (53, 71)	0.75
Systolic vasodepression (mmHg)	28 (13, 41)	24 (13, 39)	0.41
Diastolic vasodepression (mmHg)	12 (8, 19)	14 (8, 20)	0.50
	Frequency (%)	**Frequency (%)**	
ANN OH	39 (81)	38 (81)	0.96
Systolic OH	33 (69)	27 (57)	0.25
Diastolic OH	33 (69)	35 (79)	0.54

Comparing total and regional white matter hyperintensity volume for the OH and no-OH group showed that the OH group consistently had higher WMH volumes but that these differences were not significantly different (Table 7-23). Similarly, examining systolic and diastolic OH separately did not reveal any statistically significant differences in white matter hyperintensity volume (Table 7-24 and Table 7-25). Further analyses were performed to test if symptoms of cerebral hypoperfusion during active stand in conjunction with OH were associated with WMH volume in any region. No statistically significant differences in volume of WMH were found between the symptomatic and asymptomatic group.

Table 7-23 WMH Volume for OH Group and Group without OH *(OH defined according to AAN definition)*.

Volume of WMH as percentage of brain volume ***(data log transformed for analysis but non transformed data shown here)***	**No OH = 9**	**OH = 38**	**P**
	Mean (SD)	**Mean (SD)**	
Total WMH	0.91 (0.41)	1.49 (1.45)	0.59
Periventricular WMH	0.67 (0.28)	1.04 (0.96)	0.66
Left Frontal WMH	0.25 (0.12)	0.37 (0.38)	0.73
Right Frontal WMH	0.27 (0.14)	0.35 (0.32)	0.97
Left Parietal WMH	0.07 (0.06)	0.22 (0.30)	0.29
Right Parietal WMH	0.09 (0.08)	0.20 (0.27)	0.42
Left Occipital WMH	0.05 (0.03)	0.08 (0.08)	0.71
Right Occipital WMH	0.05 (0.03)	0.06 (0.06)	0.24
Left Temporal WMH	0.03 (0.03)	0.07 (0.08)	0.54
Right Temporal WMH	0.03 (0.03)	0.07 (0.07)	0.13

Table 7-24 WMH Volume for Systolic OH Group and Group without Systolic OH

Volume of WMH as percentage of brain volume ***(data log transformed for analysis but non transformed data shown here)***	**No Systolic OH = 20**	**Systolic OH = 27**	**P**
	Mean (SD)	**Mean (SD)**	
Total WMH	1.27 (1.43)	1.45 (1.27)	0.43
Periventricular WMH	0.91 (0.98)	1.01 (0.82)	0.44
Left Frontal WMH	0.31 (0.30)	0.37 (0.37)	0.67
Right Frontal WMH	0.29 (0.23)	0.37 (0.34)	0.54
Left Parietal WMH	0.19 (0.35)	0.18 (0.22)	0.51
Right Parietal WMH	0.19 (0.30)	0.18 (0.22)	0.68
Left Occipital WMH	0.07 (0.10)	0.08 (0.06)	0.32
Right Occipital WMH	0.06 (0.06)	0.06 (0.06)	0.92
Left Temporal WMH	0.06 (0.08)	0.06 (0.06)	0.23
Right Temporal WMH	0.05 (0.08)	0.07 (0.06)	0.11

Table 7-25 WMH Volume for Diastolic OH Group and Group without Diastolic OH

Volume of WMH as percentage of brain volume ***(data log transformed for analysis but non transformed data shown here)***	**No Diastolic OH = 12**	**Diastolic OH = 35**	**P**
	Mean (SD)	**Mean (SD)**	
Total WMH	0.93 (0.48)	1.53 (1.49)	0.64
Periventricular WMH	0.66 (0.30)	1.07 (0.99)	0.61
Left Frontal WMH	0.27 (0.16)	0.38 (0.38)	0.88
Right Frontal WMH	0.28 (0.17)	0.35 (0.33)	0.98
Left Parietal WMH	0.07 (0.05)	0.23 (0.31)	0.27
Right Parietal WMH	0.08 (0.08)	0.21 (0.28)	0.31
Left Occipital WMH	0.05 (0.04)	0.09 (0.09)	0.15
Right Occipital WMH	0.04 (0.03)	0.06 (0.06)	0.09
Left Temporal WMH	0.03 (0.02)	0.07 (0.08)	0.51
Right Temporal WMH	0.03 (0.03)	0.07 (0.07)	0.17

Examining relationship between continuous response to active stand and white matter volume showed that greater systolic vasodepression was associated with greater volume of white matter disease in the right temporal lobe (P=0.04). A trend towards an association between greater systolic vasodepression and greater left temporal WMH volume was also observed (P = 0.06) (Table 7-26).

Multiple linear regression was performed to examine if the association between systolic vasodepression and temporal white matter volume was independent of other risk factors associated with WMH volume. After adjusting age, history of hypertension, history of cerebrovascular disease the association between systolic vasodepression was no longer an independent predictor of WMH volume in right temporal lobe (B=0.21, P=0.10).

Table 7-26 Partial Correlation between Response to Active Stand at Baseline and WMH Volume at Follow-up Adjusting for Age *(WMH volume expressed as percentage of total brain volume and log transformed for analysis)*

		WMH	PVWMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
Baseline Systolic BP (mmHg)	***pr***	0.23	0.22	0.27	0.26	0.10	0.14	0.12	0.02	0.15	0.12
	P	0.12	0.14	0.07	0.08	0.51	0.34	0.42	0.91	0.33	0.43
Baseline Diastolic BP (mmHg)	***pr***	0.15	0.19	0.13	0.13	0.08	0.11	0.21	0.17	0.15	0.11
	P	0.31	0.22	0.38	0.37	0.60	0.46	0.17	0.27	0.33	0.48
Systolic Nadir (mmHg)	***pr***	0.07	0.06	0.12	0.12	-0.05	0.03	0.04	-0.04	-0.04	-0.08
	P	0.66	0.71	0.44	0.42	0.77	0.85	0.77	0.81	0.80	0.59
Diastolic Nadir (mmHg)	***pr***	-0.04	-0.04	-0.04	-0.05	-0.03	0.00	0.05	0.00	-0.01	-0.09
	P	0.78	0.80	0.78	0.77	0.82	0.99	0.73	0.99	0.94	0.55
Systolic vasodepression (mmHg)	***pr***	0.23	0.23	0.20	0.18	0.22	0.16	0.11	0.08	0.27	0.31
	P	0.12	0.13	0.18	0.23	0.15	0.28	0.49	0.58	0.07	**0.04**
diastolic vasodepression (mmHg)	***pr***	0.23	0.26	0.21	0.22	0.14	0.13	0.16	0.19	0.18	0.25
	P	0.12	0.08	0.16	0.15	0.36	0.41	0.29	0.20	0.22	0.10

7.6.4 Response to Carotid Sinus Massage at Baseline and White Matter Hyperintensity Volume at Follow-up

Forty-four participants had valid data from CSM at baseline and underwent MR imaging at follow-up. Comparing these individuals with follow-up participants who did not undergo MRI scan did not show any significant differences in response to CSM (Table 7-27).

Table 7-27 Comparison of Response to CSM for Participants Who Underwent MRI Scan With Those who Did not Have an MRI scan

	No MRI N= 46	**MRI N=44**	
	Median (IQR)	**Median (IQR)**	**P**
Max RR interval post CSM (ms)	1568 (1168, 2423)	1460 (1131, 2298)	0.81
Max Vasodepression (mmHg)	42.7 (27.9, 49.3)	42.2 (30.7, 59.1)	0.63
Minimum Systolic Nadir (mmHg)	80.0 (68.0, 104.0)	81.0 (67.8, 101.0)	0.99
Max delta RR (ms)	628 (262, 1372)	484 (231, 1417)	0.59
	Frequency (%)	**Frequency (%)**	
CSH	11 (24)	17 (39)	0.13
Mixed CSH	6 (13)	8 (18)	0.50
Vasodepression CSH	4 (8.6)	8 (18)	0.19
Cardio inhibitory CSH	1 (2.1)	1 (2.2)	0.98

Participants with CSH had higher volumes of white matter disease than participants without CSH, but these differences were not statistically significant (Table 7-28). Comparing participants with symptomatic CSH with those without symptoms during CSM revealed that participants with symptomatic CSH had significantly greater volumes of WMH in all regions (Table 7-29).

Table 7-28 Comparison of WMH Volumes for CSH and no-CSH group

Volume of WMH as percentage of brain volume *(data log transformed for analysis but non transformed data shown here)*	**No CSH =27** **Mean (SD)**	**CSH = 17** **Mean (SD)**	**P**
Total WMH	1.07 (1.03)	1.63 (1.66)	0.30
Periventricular WMH	0.67 (0.47)	1.27 (1.23)	0.14
Left Frontal WMH	0.29 (0.29)	0.37 (0.37)	0.53
Right Frontal WMH	0.28 (0.29)	0.36 (0.30)	0.44
Left Parietal WMH	0.12 (0.19)	0.26 (0.37)	0.25
Right Parietal WMH	0.12 (0.16)	0.25 (0.33)	0.42
Left Occipital WMH	0.07 (0.06)	0.10 (0.10)	0.22
Right Occipital WMH	0.05 (0.04)	0.08 (0.07)	0.98
Left Temporal WMH	0.05 (0.06)	0.07 (0.09)	0.61
Right Temporal WMH	0.05 (0.06)	0.07 (0.07)	0.30

Table 7-29 Comparison of WMH Volumes for Group With Symptoms During CSM and Group with No Symptoms During CSM

Volume of WMH as percentage of brain volume *(data log transformed for analysis but non transformed data shown here)*	**Asymptomatic = 36** **Mean (SD**	**Symptomatic CSH = 8** **Mean (SD)**	**P**
Total WMH	1.00 (1.00)	2.59 (1.84)	**<0.01**
Periventricular WMH	0.66 (0.54)	1.99 (1.31)	**<0.01**
Left Frontal WMH	0.26 (0.26)	0.58 (0.43)	**0.03**
Right Frontal WMH	0.26 (0.26)	0.55 (0.33)	**0.04**
Left Parietal WMH	0.12 (0.20)	0.43 (0.45)	**0.01**
Right Parietal WMH	0.11 (0.18)	0.42 (0.36)	**0.01**
Left Occipital WMH	0.06 (0.06)	0.17 (0.12)	**<0.01**
Right Occipital WMH	0.05 (0.04)	0.13 (0.07)	**<0.01**
Left Temporal WMH	0.04 (0.05)	0.12 (0.11)	**0.01**
Right Temporal WMH	0.05 (0.06)	0.11 (0.07)	**0.01**

Linear regression adjusting for age, sex, and history of hypertension showed that symptomatic CSH was significantly associated with WMH volume in all regions, independent of the included covariates.

Table 7-30 Linear Regression Examining if Symptomatic CSH is an Independent Predictor of WMH Volume

Dependent variable **Volume of WMH as percentage of brain volume** ***(data log transformed for analysis but non transformed data shown here)***	**Adjusted Model R square**	**B**	**95% CI**	**P**
Total WMH	0.29	0.43	0.13, 0.73	**0.01**
Periventricular WMH	0.34	0.46	0.18, 0.73	**<0.01**
Left Frontal WMH	0.26	0.37	0.06, 0.68	**0.02**
Right Frontal WMH	0.23	0.36	0.04, 0.68	**0.03**
Left Parietal WMH	0.17	0.57	0.04, 1.10	**0.04**
Right Parietal WMH	0.19	0.63	0.07, 1.18	**0.03**
Left Occipital WMH	0.19	0.49	0.13, 0.85	**0.01**
Right Occipital WMH	0.22	0.47	0.08, 0.86	**0.02**
Left Temporal WMH	0.14	0.62	0.08, 1.15	**0.03**
Right Temporal WMH	0.11	0.53	0.06, 0.98	**0.03**
Each region examined separately. Co-variates age, sex, history of hypertension at baseline as detected by ambulatory BP and defined by NICE.				

Age-adjusted partial correlation was used to examine the association between white matter hyperintensity volume and continuous blood pressure and heart rate response to CSM. No significant associations were observed (Table 7-31).

Table 7-31 Partial Correlation between Continuous Response to CSM and WMH Volume

		WMH	PV WMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
Max RR interval post CSM (ms)	**pr**	0.04	0.10	0.03	0.10	0.02	0.01	0.06	-0.06	-0.07	0.03
	P	0.80	0.53	0.86	0.53	0.88	0.94	0.70	0.72	0.68	0.84
Max Vaso-depression (mmHg)	**pr**	0.05	0.10	0.02	0.08	0.09	0.08	0.16	-0.04	-0.01	0.03
	P	0.75	0.51	0.90	0.60	0.57	0.63	0.30	0.82	0.93	0.86
Minimum Systolic Nadir (mmHg)	**pr**	0.03	0.01	0.08	0.06	-0.15	-0.15	-0.01	0.01	0.12	-0.12
	P	0.84	0.97	0.63	0.69	0.35	0.34	0.95	0.95	0.45	0.46
Max delta RR (ms)	**pr**	0.06	0.12	0.04	0.11	0.03	0.02	0.09	-0.04	-0.05	0.04
	P	0.72	0.46	0.80	0.48	0.83	0.89	0.59	0.79	0.76	0.80
(WMH volume expressed as percentage of total brain volume and log transformed for analysis)											

7.6.5 Response to Autonomic Function Tests at Baseline and White Matter Hyperintensity Volume at Follow-up

There were no statistically significant differences in response to baseline autonomic function tests between follow-up participants who had an MRI scan and those who did not (Table 7-32).

Table 7-32 Response to Autonomic Function Tests at Baseline for Those Who Had MRI Scan and Those Who did not.

	No MRI N= 48	**MRI N=47**	
	Median (IQR)	**Median (IQR)**	**P**
30:15 ratio	1.11 (1.06, 1.18)	1.14 (1.05, 1.23)	0.45
Valsalva ratio	1.46 (1.28, 1.66)	1.48 (1.33, 1.73)	0.16
Valsalva overshoot (mmHg)	22.5 (12.3, 51.3)	30.0 (10.8, 56.0)	0.68
Response to cold pressor (mmHg)	8 .00 (4.00, 13.5)	10.0 (4.00, 17.0)	0.25
Response to isometric exercise (mmHg)	12.5 (6.00, 19.8)	12.0 (5.00, 19.8)	0.94
Response to deep breathing (BPM)	7.98 (5.23, 12.9)	7.66 (4.06, 11.3)	0.53
	Frequency (%)	**Frequency (%)**	
Ewing and Clark Abnormal	13	16	0.49

Age-adjusted partial correlation showed an association between 30:15 ratio in response to active stand and volume of white matter hyperintensities in all regions. There were no associations between heart rate response to Valsalva manoeuvre or deep breathing and white matter hyperintensity volume. Greater diastolic BP response to cold pressor test was significantly associated with greater volume of WMH in the right temporal lobe (Table 7-33). After adjusting for age, sex, history of hypertension and history of cerebrovascular disease, the association between 30:15 ratio and WMH volume in all regions remained significant but the association between BP response to cold pressor test and WMH volume in right temporal lobe did not (Table 7-34).

Table 7-33 Partial Correlation between Continuous Response to Autonomic Function Tests and WMH Volume

		WMH	VWMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
30 15 ratio [N=47]	**pr**	-0.38	-0.38	-0.34	-0.30	-0.34	-0.31	-0.38	-0.26	-0.53	-0.39
	P	**0.01**	**0.01**	**0.02**	**0.04**	**0.02**	**0.04**	**0.01**	0.08	**<0.01**	**0.01**
best Valsalva ratio [N=49]	**pr**	0.06	0.05	0.03	0.09	-0.06	0.03	0.18	-0.02	0.00	0.07
	P	0.69	0.72	0.86	0.54	0.69	0.86	0.21	0.90	0.98	0.61
Overshoot associated with best Valsalva ratio (N=49)	**pr**	0.00	0.03	0.07	0.12	-0.05	-0.04	-0.07	-0.08	-0.13	-0.14
	P	0.98	0.82	0.65	0.43	0.73	0.78	0.66	0.59	0.38	0.35
Cold pressor Difference DP (mmHg) [N=45]	**pr**	0.24	0.22	0.29	0.23	0.17	0.20	0.19	0.07	0.25	0.34
	P	0.12	0.14	0.06	0.13	0.26	0.19	0.21	0.65	0.09	**0.02**
Deep breathing average heart rate difference [N=47]	**pr**	0.05	0.04	-0.01	0.00	-0.04	0.03	0.23	0.18	0.16	0.09
	P	0.73	0.78	0.95	0.99	0.80	0.85	0.12	0.24	0.30	0.57
Isometric Exercise BP difference (mmHg) [n=45]		0.09	0.05	0.12	0.14	0.07	0.07	-0.06	-0.04	0.01	0.07
		0.56	0.74	0.42	0.37	0.65	0.66	0.70	0.76	0.93	0.63
(WMH volume expressed as percentage of total brain volume and log transformed for analysis)											

Table 7-34 Linear Regression Examining if 30:15 ratio is an Independent Predictor of WMH Volume

Dependent variable **Volume of WMH as percentage of brain volume** ***(data log transformed for analysis but non transformed data shown here)***	**Adjusted Model R square**	**B**	**95% CI**	**P**
Total WMH	0.31	-1.41	-2.42, -0.40	<**0.01**
Periventricular WMH	0.30	-1.36	-2.33, -0.39	<**0.01**
Left Frontal WMH	0.35	-1.29	-2.32, -0.27	**0.02**
Right Frontal WMH	0.26	-1.02	-2.10, 0.06	0.06
Left Parietal WMH	0.23	-2.17	-3.92, -0.42	**0.02**
Right Parietal WMH	0.18	-2.00	-3.77, -0.23	**0.03**
Left Occipital WMH	0.20	-1.80	-3.04, -0.56	<**0.01**
Right Occipital WMH	0.21	-1.55	-3.06, -0.03	<**0.05**
Left Temporal WMH	0.39	-3.27	-4.87, 1.69	<**0.01**
Right Temporal WMH	0.18	-2.02	-3.37, -0.67	<**0.01**
Each region examined separately. Co-variates age, sex, history of hypertension at baseline as detected by ambulatory BP and defined by NICE and history of cerebrovascular disease.				

7.6.6 Heart rate variability at Baseline and White Matter Hyperintensity Volume at Follow-up

Forty individuals underwent MRI and had HRV data from baseline suitable for analysis. A greater HF/LF ratio was associated with larger volumes of WMH. This was true for total volume, periventricular volume and frontal lobe volumes. After adjusting for age, sex, history of hypertension and history of cerebrovascular disease, these associations were no longer significant. Other measures of HRV were not associated with volume of white matter hyperintensities.

Figure 7-2 Age-adjusted Partial Correlation Examining Association between Heart Rate Variability and WMH Volume

		WMH	PV WMH	L frontal WMH volume	R frontal WMH volume	L parietal WMH volume	R parietal WMH volume	L occipital WMH volume	R occipital WMH volume	L temporal WMH volume	R temporal WMH volume
SDNN	**pr**	-0.02	0.04	-0.07	-0.07	-0.03	-0.05	-0.10	-0.09	0.00	0.03
	P	0.89	0.81	0.64	0.66	0.83	0.77	0.55	0.58	0.99	0.84
Total Power	**pr**	-0.05	-0.01	-0.06	-0.05	-0.07	-0.10	-0.23	-0.12	-0.06	-0.03
	P	0.76	0.95	0.69	0.73	0.65	0.51	0.15	0.45	0.70	0.84
Very low frequency	**pr**	-0.08	-0.04	-0.06	-0.06	-0.06	-0.14	-0.30	-0.19	-0.11	-0.11
	P	0.64	0.81	0.72	0.70	0.70	0.37	0.05	0.23	0.47	0.49
low frequency	**pr**	-0.11	-0.07	-0.17	-0.14	-0.11	-0.12	-0.19	-0.08	-0.06	-0.02
	P	0.48	0.64	0.29	0.37	0.48	0.47	0.24	0.63	0.71	0.91
high frequency	**pr**	0.17	0.20	0.15	0.17	0.02	0.09	0.04	0.07	0.12	0.16
	P	0.29	0.22	0.33	0.29	0.89	0.58	0.83	0.66	0.46	0.31
HF/LF Ratio	**pr**	0.30	0.28	0.39	0.37	0.12	0.15	0.08	-0.04	0.23	0.24
	P	**0.05**	**0.08**	**0.01**	**0.02**	0.45	0.35	0.61	0.82	0.14	0.12

7.7 Summary of Key Results from Chapter 7

Fifty-three individuals (51%) underwent MRI scan. Greater WMH volume was significantly associated with increasing age.

7.7.1 Clinical Association with WMH Volume

In this small cohort WMH volume was not associated with performance on any of the cognitive tests or cornell depression scale. WMH volume did not significantly differ between fallers and non-fallers. Surprisingly greater WMH volume was associated with better performance on Tinetti assessment of gait and balance.

7.7.2 Ambulatory Blood Pressure

WMH volume was greater in participants with mean systolic daytime BP> 150mmHg but there was no continous association between mean BP or BP variability and WMH volume.

On univariate analysis abnormal diurnal variation was associated with increased total and parietal WMH volume but this was no longer significant after adjusting for age.

7.7.3 Active Stand

No associations were observed between WMH volume at follow-up and response to active stand at baseline.

7.7.4 Carotid Sinus Massage

CSH was not associated with increased WMH volume. However symptomatic CSH was associated with increased WMH volume. This was independent of age, sex and history of hypertension.

7.7.5 Autonomic Function

Lower 30:15 ratio in response to standing was associated with greater volume of WMH on MRI independent of age, sex and history of cardiovascular disease. None of the other tests of cardiovascular autonomic function were independently associated with WMH volume.

7.8 **Discussion**

Fifty-one per cent of year ten follow-up participants agreed to undergo an MRI brain scan and did not have any contraindications to MRI. The cohorts undergoing imaging and not undergoing imaging were well matched in terms of performance on cognitive tests and similar in terms of past medical history. Prevalence of NCVI at baseline and response to autonomic function tests and carotid sinus massage were similar for the group who underwent MRI and those who did not.

It was the initial hypothesis that episodic systemic hypotension would cause impaired cognition, depression, gait and balance abnormalities and falls in later life as a result of cerebral hypoperfusion and resulting white matter lesion. The first half of this chapter examined if white matter hyperintensities were associated with cognition, depression, and/ or motor symptoms in this cohort at follow-up. The second half of the chapter examined if autonomic function and NCVI at baseline were associated with WMH volume at follow-up.

Age and hypertension are well-recognised risk factors for WMHs. In keeping with other studies, WMH volume in this cohort was significantly and positively associated with age and WMH volume, particularly in frontal areas, was significantly greater among individuals with systolic BP >150 mmHg at baseline.

7.8.1 **White Matter Hyperintensity Volume and Clinical Symptoms at Follow-up**

7.8.1.1 White Matter Hyperintensity Volume and Cognition

WMH volume was not associated with cognitive function in this study. Reviews of large population-based studies examining the association between WMH volume and cognition have concluded that greater WMH volume is associated with poorer cognitive function but that the clinical effect of WMH on cognition is small, particularly on measures of global cognition in community cohorts (Frisoni et al., 2007, Pantoni et al., 2007). The Framingham Offspring Study measured white matter volume in 1820 dementia-free, stroke-free older people. Participants with little or no WMH were compared with participants with large WMH volume (WMH volumes more than1 SD above the age-predicted mean). MMSE score was 0.1 point lower in the large WMH volume group than in the no / little WMH group. This difference was not statistically significant (Au et al., 2006). The authors did find that participants with large WMH

volume performed more poorly on tests of attention, concentration and executive function, which was not the case in this current study.

The lack of association between cognition and WMH in this study probably reflects the small sample size undergoing MRI, which was insufficient to detect small differences in performances on cognitive tests. This study had 80% power to detect a difference 2 or more points on the MMSE between the lower 4 quintiles of WMH volume and the upper quintile. Similarly this sample size allowed a difference of 6 points to be detected on the total CAMCOG with 80% power and differences of 40 -150 ms to be detected on the COMPASS scores. Given the apparently small effect of WMH on cognition in older, non-demented individuals, it must be acknowledged that this population size may be insufficient to detect changes in cognition resulting from WMH.

It has been suggested that there is a threshold effect between white matter hyperintensities and cognition. Many studies have shown that there is a level of WMH volume beyond which white matter disease is associated with cognitive decline, but that this threshold can vary depending on host factors (e.g. age, ethnicity, education) , and concomitant brain changes (e.g. cortical atrophy lacunar infarcts and micro bleeds) (Frisoni et al., 2007, Pantoni et al., 2007). A threshold effect was not evident in this study but this may reflect some of the population characteristics. The cohort was well educated, physically healthier than the general population and had surprisingly low rates of dementia, depression and neurodegenerative disease (Kerr, 2009, Rait et al., 2005). It is possible that these features have led to greater cognitive reserve in this study population than in the general population. Higher rates of education have been associated with cognitive reserve and have been shown to delay decline in cognition(Muniz-Terrera et al., 2011). Similarly lower rates of hypertension and diabetes were observed in the study sample compared to the population from which they were recruited from (Kerr, 2009). This may have resulted in a lower burden of WMH in this cohort than might be expected among the general population.

7.8.1.2 White Matter Hyperintensity Volume and Depression

As with cognition, this study did not show an association between depression scores and WMH volume. This is in contrast to several, larger, cross-sectional studies which have

shown an associations between depressive symptoms and WMH volume (Geerlings et al., 2012, Ikram et al., 2010, Murray et al., 2013, Firbank et al., 2012b).

Results from longitudinal studies examining the association between WMH volume and depression have been mixed (Verluis et al., 2006, Firbank et al., 2012b, Ikram et al., 2010). Follow-up of the LADIS cohort found progression of WMH volume to be associated with incident depression (Firbank et al., 2012b). However, the Prosper study, which examined 572 non-demented older people, found that presence of WMHs was not related to baseline depressive symptoms or to the development of depressive symptoms during follow-up (Verluis et al., 2006). Ikram et al found that although WMH volume was associated with the presence of depressive symptoms at baseline, there was no association between WMH grade and incident depression at follow-up (Ikram et al., 2010).

There are several reasons why this study may not have found the association between WMH and depression seen in other cross-sectional studies. Firstly this study had a small sample size and a fewer individuals than anticipated had depression. Only 8% of participants in the MRI cohort had depression. The small numbers of depressed patients in this cohort resulted in a lack of statistical power to detect small differences between depressed and non-depressed participants. The low rates of depression in this cohort may indicate sampling bias. The severity of depression suffered by participants may also account for the differences observed between our study and the LADIS study (Firbank et al., 2012b). None of the participants with a Cornell score >10 were taking antidepressants or under the care of a psychiatrist for depression, suggesting that depressive symptoms were mild in this cohort. This is in contrast to the LADIS study where only participants receiving treatment for depression (medication, psychotherapy or hospitalisation) were classed as having incident depression (Firbank et al., 2012b).

7.8.1.3 White Matter Hyperintensity Volume and Gait

Significant associations were observed between better gait and greater total, periventricular and frontal white matter hyperintensity volume in this study. However, after adjusting for covariates this was no longer significant. No associations were observed between balance and WMH volume.

Our findings are in contrast to the published literature. A systematic review of papers examining the association between WMH and gait showed that studies have consistently found greater volumes of WMH to be associated with impaired gait, specifically: decreased gait speed, shorter step length, increased double support time, and slowed gait initiation in cross-sectional studies (Zheng et al., 2011). Longitudinal studies have shown that progression of WMH volume is associated with slowing of gait speed, decreases in step length and worsening of lower limb physical function(Zheng et al., 2011, Willey et al., 2013, Kreisel et al., 2013, Callisaya et al., 2013, Moscufo et al., 2012). Three studies were identified that used the Tinetti score to assess gait, as done in this study. In the first, study poorer Tinetti gait score was associated with greater volume of periventricular but not deep WMH. In the latter two studies, greater total WMH volume was associated with poorer Tinetti score (Wakefield et al., 2010, De Laat et al., 2010, Soumaré et al., 2009).

The failure of our study to identify an association between gait and WMH may again reflect sample size. Although our sample was similar in size to the Wakefield study, their study used a balance 3x3 matrix to ensure inclusion of frailer participants (Wakefield et al., 2010). The De Latt and Soumare studies were larger than this study including 431 and 1402 participants respectively (De Laat et al., 2010, Soumaré et al., 2009). There are several versions of the Tinetti gait assessment(Kopke and Meyer, 2006) The 9 item scale (possible score 0-9) was used in this study. De Latt et al and Wakefield et al used an eight item scale, with possible score 0-12, and Soumare et al used a modified five item score. Given the similarity in the content of the scores however it seems unlikely that this accounts for the contradictory findings between our study and the published literature (Wakefield et al., 2010, De Laat et al., 2010, Soumaré et al., 2009).

7.8.1.4 White Matter Hyperintensity Volume and Balance

No association was observed between WMH volume in this study and performance on Tinetti assessment of balance. This is in keeping with the large study by Soumare that also used the Tinetti scale to measure balance (Soumaré et al., 2009). However, studies using more sensitive measures of balance have shown associations between balance and WMH volume. Using a stabilometer, Mizuta et al showed that older people with severe white matter hyperintensities were significantly more unstable (Mizuta et al., 2007) and Start et al showed that individuals unable to stand on one leg for five seconds had

significantly greater WMH volume compared to those who could complete the task (Starr et al., 2003). This suggests that, in healthy cohorts, the Tinetti balance scale may be an insensitive measure of balance.

7.8.1.5 White Matter Hyperintensity Volume and Falls

In the current study, no association was observed between WMH volume and falls, recurrent falls or number of falls in the year prior to the MRI scan. Our findings are in contrast to other studies which have found associations between severe WMH and incident falls and incident recurrent falls (Zheng et al., 2011, Srikanth et al., 2009, Blahak et al., 2009). The association between WMH and falls is thought to be mediated through impaired cognition, gait and balance. Given that WMH were not associated with cognition, gait or balance in this study it is perhaps not surprising that an association between WMH and falls was not identified in this study.

7.8.2 White Matter Hyperintensity Volume and Baseline Measure of Heart Rate and Blood Pressure Control, Autonomic Function and NCVI

7.8.2.1 White Matter Hyperintensity Volume and Hypertension

In this study, hypertension (defined as systolic BP ≥150mmHg) was associated with increased total, periventricular and frontal WMH volume. Systolic BP on ABPM, however, did not correlate with volume of white matter disease suggesting a threshold effect. While hypertension has consistently been found to be a risk factor for WMH, results from studies examining the continuous association between BP and WMH have been mixed (Sierra, 2011, Henskens et al., 2009, Goldstein et al., 2005, Yamamoto et al., 2005, Schwartz et al., 2007). A recent review showed that, several authors have, in accordance with our results, found an association between hypertension and WMH but not between continuous BP and WMH, suggesting a threshold effect rather than a "dose response" (Sierra, 2011). In contrast, Henskens et al found 24-hour, daytime and night-time BP were positively and significantly correlated with WMH volume(Henskens et al., 2009). While Yamoto et al and Goldstein et al found that higher night-time and daytime systolic and diastolic BP were associated with increased odds ratio of more severe WMH(Goldstein et al., 2005, Yamamoto et al., 2005). These differences may to some extent be explained by different populations. Schwartz et al showed that the association between ABPM results and WMH volume differs between white and black American adults (Schwartz et al., 2007). In black adults, ambulatory blood pressure measures associated with greater WMH were higher awake, asleep, and 24-hour systolic

and diastolic levels. In white adults, only higher asleep diastolic levels trended toward association with greater WMH load.

7.8.2.2 White Matter Hyperintensity Volume and Blood Pressure Variability

Greater BP variability on 24-hour ABPM has been associated with increased end organ damage (Parati et al., 2006). In this cohort we did not find an association between BP variability and WMH volume. Few studies have examined the association between 24-hour BP variability and WMH on MRI. One retrospective study examined the association between BP variability and WMH for 79 elderly patients who had undergone 24 ABPM and a CT head scan. Greater blood pressure variability was associated with greater WMH volume (Puisieux et al., 2001). Goldstein et al found increased daytime SBP variability was associated with more severe white matter disease 5 years later (Goldstein et al., 2005). BP variability increases with mean SBP and age (Parati et al., 2006). Studies examining the association between BP variability should therefore be adjusted for age and mean BP. Gómez-Angelat et al found that after adjusting for mean BP, systolic BP variability was not associated with WMH volume (Gomez-Angelats et al., 2004) suggesting the association was due to elevated BP rather than BP variability.

7.8.2.3 White Matter Hyperintensity Volume and Diurnal Variation

Abnormal dipping pattern (non-dipping or extreme dipping) was associated with greater white matter hyperintensity volume in this study. After adjusting for age however, dipping status at baseline was no longer associated with WMH volume at follow-up. Findings from cross-sectional studies examining the association between dipping status and white matter hyperintensities have been mixed. In keeping with the findings of this study, Van Boxtel et al and Henskens et al failed to show an association between dipping status and WMH volume in age-adjusted models(van Boxtel et al., 2006, Henskens et al., 2009). Schwartz et al found greater dips in BP were associated with fewer white matter lesions in white adults, but not in black adults. While Birns et al found greater nocturnal dips in BP were associated with greater white matter lesions. Finally, Yamamoto et al found non-dipping and reverse dipping (a rise in BP at night) were associated with increased odds of periventricular WMH (Yamamoto et al., 2005). These differences probably reflect differences in study populations. Studies failing to show an association between dipping and WMH or showing an adverse association between dipping and WMH have tended to include predominantly hypertensive patients

or patient groups at greater risk of hypertension (older patients /black adults). In hypertensive individuals, nocturnal falls in BP may cause BP to drop below limits of cerebral autoregulation potentially causing cerebral hypoperfusion and WMH.

7.8.2.4 White Matter Hyperintensity Volume and Orthostatic Hypotension

Volume of WMH in all regions was consistently higher in the OH groups but this was not statistically significant. After adjusting for covariates no association was found between degree of vasodepression and WMH volume. The association between OH and WMH has been examined in three previous community based studies (Longstreth et al., 1996, Gottesman et al., 2011, Havlik et al., 2002). All measured postural drop using sphygmomanometer rather than beat-to-beat monitoring. In the cardiovascular health study (n=3301), OH was associated with increased WMH grade in models adjusted for age, sex and systolic BP but not after adjusting for presence of silent cerebral infarcts (Longstreth et al., 1996). The Honolulu heart study recorded postural drop in 3734 men in 1991. MRI scans were performed in a subset of 575 men between1993–1996. OH status was not associated with white matter load (Havlik et al., 2002). In a recently published abstract regarding the Atherosclerosis Risk in Communities study (N= 983) OH was not associated with progression of WMH, but OH severity (ie the degree of vasodepression) was associated with WMH progression (OR 1.21 (95% CI 1.02-1.42) per 10 mm Hg SBP decrease) (Gottesman et al., 2011). Smaller studies have used to beat-to-beat monitoring to detect change in BP in response to standing. Colloby et al found that systolic vasodepression was significantly associated with WMH volume in bilateral temporal regions and left parietal region among patients with late-life depression, but not in age-matched controls (Colloby et al., 2011). Ballard et al found a systolic vasodepression >30 mmHg in response to CSM or active stand was associated with more severe WMH (Ballard et al., 2000).

In this study, WMH volume was greater in the CSH group for all regions, but these differences were not statistically significant. Comparing participants who had been symptomatic during CSH with those who did not report symptoms, showed significantly greater white matter hyperintensity volume in the symptomatic group than the asymptomatic group. Symptoms suggest cerebral hypoperfusion and may indicte a failure of cerebral autoregulation. Parry et al examined cerebral autoregulation response to lower body negative pressure-induced hypotension in patients with carotid sinus

syncope (CSS) and asymptomatic case controls(Parry et al., 2006). CSS patients had abnormal cerebral autoregulation. Middle cerebral artery blood flow was significantly slower in the CSS group compared to controls. Interestingly, there was a paradoxical increase in cerebrovascular resistance among the CSS group. The authors noted cerebral autoregulation at rest prior to LBNP was significantly altered in the CSS patients compared to the controls and suggested the intriguing possibility that patients with CSS are prone to relative (and paradoxical) tonic intracerebral vasoconstriction, which predisposes them to further inappropriate vasoconstriction during CSS mediated vasodepression and asystole, when vasodilatation should otherwise supervene.

Leftheriotis et al examined cerebral autoregulation in response to CSM among 11 patients with carotid sinus syndrome with a pacemaker in the OOO mode and compared to this response to CSM among 6 CSS patients with pacemakers in the DDD mode(Leftheriotis et al., 1998). In non-paced patients, CSM was associated with a 50% decrease in mean cerebral blood flow velocity. In keeping with Parry et al's findings the group also noted a transient increase in cerebrovascular resistance during CSM (although this did not reach significance). In the paced group systemic haemodynamic change and consequently cerebral haemodynamic change was reduced. The mean cerebral blood flow velocity decreased by only 30%. The authors argue that this remained above the ischemic threshold as none of the paced patients reported syncope or presyncope. Interestingly, only three patients reported symptoms when pacemaker was in the OOO mode. These studies suggest that people with symptomatic carotid sinus hypersensitivity have abnormal cerebral autoregulation in response to systemic hypotension. None of the studies compared cerebral autoregulation among the symptomatic and asymptomatic individuals with CSH.

It is interesting that degree of haemodynamic change in response to CSM was not associated with WMH volume in this study. Two other studies have examined the association between CSH and white matter hyperintensities (Kenny et al., 2004).. Kenny et al examined the association between CSH and white matter hyperintensity severity in patients with neurodegenerative dementia (43 Alzheimer's disease (AD) patients and 42 patients with dementia of Lewy body (DLB))(Kenny et al., 2004, Ballard et al., 2000). . In contrast to our findings, there was a significant association between fall in systolic blood pressure and severity of deep WMH in DLB patients. No

association between WMH and vasodepression was observed in the AD group. Dementia of Lewy body is associated with autonomic dysfunction and these patients had particularly large falls in BP in response to CSM. The authors suggested the absence of an association between vasodepression and WMH volume in AD patients reflected the less dramatic fall in systolic BP observed in these patients. Kenny et al did not record presence or absence of symptoms during CSM. Ballard et al also examined whether CSH and orthostatic hypotension were associated with WMH volume in patients with 17 AD and 13 DLB(Ballard et al., 2000). WMH were classified as present or absent. Blood pressure drop >30 mmHg (either postural hypotension on active standing or BP drop during CSM) was significantly associated with presence of basal ganglia WMH, deep WMH but not periventricular WMH. Again significance of symptoms was not evaluated in this study.

7.8.2.5 White Matter Hyperintensity Volume and Autonomic Function

In this study, decreased 30:15 ratio in response to active stand was associated with greater WMH volume. The 30:15 ratio is a measure of parasympathetic function. It decreases with age and in conditions associated with impaired autonomic function such as diabetes. In normal controls, atropine causes a decrease in 30:15 ratio indicating that it is under vagal control. It would appear that decreased vagal activity at baseline is associated with greater white matter load at follow-up. However, other autonomic function tests of vagal activity (heart rate response to Valsalva manoeuvre and heart rate response to deep breathing) were not associated with white matter volume, nor were HRV indicators of parasympathetic function.

There are few studies examining the association between autonomic function and WMH. In patients with mild cognitive impairment, reduced HRV indices of parasympathetic and sympathetic function have been associated with increased WMH severity (McLaren, 2004). Among 63 post-stroke patients, autonomic function, measured by HRV and the Ewing and Clarke autonomic battery, was not associated with WMH volume measured using the Schelten's rating scale or as a percentage of intracranial volume (McLaren, 2004).

7.8.3 **Summary**

It was the hypothesis of this study that episodic systemic hypotension would cause white matter damage and an increased prevalence of the clinical symptoms associated with white matter hyperintensities. Few associations however were identified between WMH volume and cognitive function, mood, gait, balance or falls at follow-up. Similarly, few significant correlations were identified between baseline neurocardiovascular function and WMH volume at follow-up.

There are several reasons why our findings are not as initially hypothesised. Firstly, as previously discussed, the sample size undergoing MRI was small. Secondly, it is recognised that repeated assessment of autonomic function at baseline of the follow-up would have been desirable. Repeated assessment of NCVI would have lead to more accurate classification of participants as normal or abnormal and would have identified participants who developed NCVI over the follow-up period and have thus been exposed to recurrent hypotensive episodes for a proportion of the intervening ten years. Finally, we were unable to account for the integrity of cerebral autoregulation in this study. It is possible that hypotensive episodes are only associated with white matter damage in a subgroup of individuals in whom cerebral autoregulation fails to adequately compensate for changes in systemic blood pressure. Future studies could compare white matter hyperintensity volume in patients with NCVI and impaired cerebral autoregulation with WMH volume among participants with NCVI and normal cerebral autoregulation.

Chapter 8 Neurocardiovascular Function and Ten Year All-Cause Mortality

8.1 Introduction

Autonomic dysfunction and orthostatic hypotension have been associated with increased mortality. Four large population-based studies have shown an association between orthostatic hypotension and reduced survival (Fedorowski et al., 2010, Verwoert et al., 2008, Rose et al., 2006, Masaki et al., 1998). Decreased heart rate variability has been associated with increased mortality in most community cohorts (Dekker et al., 1997, de Bruyne et al., 1999, Tsuji et al., 1994, Huikuri et al., 1998). And abnormal autonomic function, measured using bedside autonomic function tests, has been associated with increased mortality in diabetic patients (May and Arildsen, 2012, Maser et al., 2003).

In contrast to the initial hypothesis, chapters 4-7 have shown few significant associations between NCVI at baseline and cognition, depression, falls and WMH volume at ten year follow-up. One explanation for the lack of significant findings could be that NCVI is associated with increased mortality and that the individuals most severely affected at baseline have been disproportionately lost to follow-up. In this chapter, the association between response to baseline tests of neurocardiovascular function and mortality is examined.

8.2 Methods

8.2.1 Tests of Neurocardiovascular Function

Baseline test of autonomic function and NCVI have been previously described in section 2.3, page 42.

8.2.2 Survival Data

Participants' General Practice electronic medical records were reviewed in September 2012 to identify if participants were alive or their date of death if they had died. If participants were no longer registered with the general practice, the National Register of Births Deaths and Marriages up to the end of September 2012 was reviewed to confirm if they had died and verify participant's date of death.

8.2.3 **Statistics**

Time to event is defined as time between date of assessment of neurocardiovascular function and date of death or end of the study, 1st October 2012. Risk factors associated with mortality were analysed using Cox's regression analysis initially controlling only for age and sex. Subsequent models adjusted for relevant covariates. Model 2 adjusted for cardiovascular risk factors associated with increased ten year mortality and cardioactive medication. In order to adjust for baseline function, model 3 adjusted for the baseline Bristol ADL score. Finally, model 4 adjusted for baseline total CAMCOG score. Cognitive impairment is associated with increased mortality and CAMCOG score has been shown to be a strong predictor of survival (Firbank et al., 2012a, Dewey and Saz, 2001).

8.3 **Results**

8.3.1 **Characteristics of Subjects Alive at Follow-up versus Characteristics of Deceased Participants**

Three hundred and fifty one participants completed one or more test of neurocardiovascular function between 29.4.2002 and 7.10.2003. Of whom, 106 participants died, mean follow-up 99.9 months (SD 29.5).

Participants who died were significantly older at baseline, had significantly lower BMI, and significantly higher mean systolic BP. They were more likely to have diabetes, cardiovascular disease and be taking cardioactive medication at baseline. Participants who died had significantly lower MMSE and total CAMCOG scores at baseline (Table 8-1).

Table 8-1 Baseline Characteristics for Participants Who Were Alive at Follow-up versus Those Who Had Died

	Alive N=245	**Dead = 106**	**P**
	Mean (SD)	**Mean (SD)**	
Age (years)	72.0 (5.1)	77.3 (6.9)	**<0.01**
BMI (kg/m^2)	27.1 (4.0)	25.7 (3.5)	**<0.01**
Mean Systolic BP (mmHg)	133.2 (14.6)	136.7 (15.2)	**<0.05**
	Frequency (%)	**Frequency (%)**	
Sex	132 (55)	67 (63)	0.11
Diabetes	11 (4.5)	12 (11)	**0.02**
Cardiovascular disease	126 (51)	70 (66)	**0.01**
Cardiovascular medication	115 (47)	70 (66)	**<0.01**
Ever smoked	144 (59)	67 (63)	0.44
Smoking at baseline assessment	16 (6.5)	13 (12)	0.07
	Median (IQR)	**Median (IQR)**	
Pack years	3 (0 , 20)	8 (0 , 37.5)	0.10
MMSE	29 (27, 30)	28 (26.3, 29)	**<0.01**
Total CAMCOG	96 (92, 99)	93 (86, 97)	**<0.01**
Bristol ADL Score	0 (0, 1)	0 (0, 2)	**0.02**

8.3.2 **Survival and Ambulatory Blood Pressure Recordings**

8.3.2.1 24-hour recordings

Three hundred and thirty eight participants had ambulatory blood pressure recordings performed with 16 or more readings in 24-hours. Mean systolic BP was significantly higher among participants who died during the ten year follow-up. Systolic and Diastolic BP variability were also greater among participants who died during the follow-up period (Table 8-2).

Table 8-2 Comparison of 24-hour BP Variables for Participants who Died During Follow-up versus those who were Alive at the End of the Study

	Alive	**Dead**	**P**
	Mean (SD)	**Mean (SD)**	
24-hour	**N= 238**	**N= 100**	
Mean SBP (mmHg)	128.1 (13.6)	132.7 (14.9)	**0.01**
Mean DBP (mmHg)	71.9 (8.2)	72.4 (7.2)	0.60
SD SBP	13.3 (3.3)	14.7 (4.3)	**<0.01**
SD DBP	9.4 (2.2)	10.2 (2.4)	**<0.01**

8.3.2.2 Daytime

Three hundred and thirty people had daytime recordings with 10 or more readings. Mean systolic BP was higher among participants who died, but this did not quite reach significance. Systolic and diastolic BP variability were higher among participants who died during follow-up (Table 8-3).

Table 8-3 Comparison of Daytime BP Variables for Participants Who Died During Follow-up versus Those Who Were Alive at the End of the Study

	Alive	**Dead**	**P**
	Mean (SD)	**Mean (SD)**	
Daytime	**N=232**	**N=98**	
Mean SBP (mmHg)	133 (14.6)	136.6 (15.4)	**0.05**
Mean DBP (mmHg)	75.9 (9.0)	76.0 (8.1)	0.91
SD SBP (mmHg)	11.7 (3.8)	13.4 (4.5)	**<0.01**
SD DBP (mmHg)	7.9 (2.3)	8.9 (2.5)	**<0.01**

8.3.2.3 Night-time

Three hundred and ten individuals had night-time recordings with five or more readings. Mean systolic BP was significantly higher among people who died during follow-up. Blood pressure variability did not differ between groups (Table 8-4)

Table 8-4 Comparison of Night-time BP Variables for Participants Who Died during Follow-up versus Those Who Were Alive at the End of the Study

	Alive	**Dead**	**P**
	Mean (SD)	**Mean (SD)**	
Night-time	**N= 220**	**N= 90**	
Mean SBP (mmHg)	117.6 (14.5)	122.9 (17.3)	**0.01**
Mean DBP (mmHg)	64.1 (8.5)	64.3 (8.1)	0.87
SD SBP (mmHg)	8.9 (3.7)	9.6 (4.2)	0.18
SD DBP (mmHg)	7.0 (2.9)	7.1 (3.2)	0.78

8.3.2.4 24-hour BP

In the model adjusting for age and sex, there was a borderline association between mean 24-hour systolic BP and survival (HR 1.01 [95% CI 1.00, 1.03], P=0.06). Adjusting for other cardiovascular risk factors decreased the significance of this association. However, when baseline Bristol ADL score was added to the model there was a significant association between mean 24-hour systolic BP and survival (HR 1.02 [95% CI 1.00, 1.02], P=0.02) (Table 8-5).

Table 8-5 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with 24-hour Mean Systolic BP

Model 1	**B**	**HR**	**95% CI for HR**		**P**
			Lower	Upper	
Age (years)	0.11	1.12	1.08	1.15	**<0.01**
Sex	0.55	1.73	1.14	2.61	**0.01**
24-hour Mean SBP (mmHg)	0.01	1.01	1.00	1.03	0.06
Model 2					
Age (years)	0.09	1.10	1.06	1.13	**<0.01**
Sex	0.44	1.55	1.02	2.37	**0.04**
24-hour Mean SBP (mmHg)	0.01	1.01	1.00	1.02	0.11
Cardiovascular Disease	-0.25	0.78	0.38	1.59	0.50
Diabetes	0.25	1.28	0.68	2.43	0.44
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive medication	0.69	2.00	0.97	4.14	0.06
BMI (kg/m^2)	-0.07	0.93	0.88	0.99	**0.02**
Model 3					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	0.33	1.39	0.86	2.25	0.18
24-hour Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.02**
Cardiovascular Disease	0.04	1.04	0.43	2.50	0.93
Diabetes	0.63	1.88	0.93	3.81	0.08
Pack years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive medication	0.50	1.64	0.70	3.85	0.25
BMI (kg/m^2)	-0.13	0.88	0.82	0.95	**<0.01**
Bristol ADL Score	0.07	1.07	0.93	1.24	0.34
Model 4					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	0.34	1.40	0.86	2.27	0.17
24-hour Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.02**
Cardiovascular Disease	0.01	1.01	0.43	2.39	0.98
Diabetes	0.59	1.80	0.88	3.66	0.11
Pack years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive medication	0.48	1.61	0.70	3.73	0.27
BMI (kg/m^2)	-0.12	0.88	0.82	0.95	**<0.01**
Bristol ADL Score	0.04	1.04	0.89	1.22	0.61
Total CAMCOG Score	-0.02	0.98	0.94	1.01	0.22

Twenty-four hour mean diastolic BP was not associated with survival in the age and sex adjusted model or in models adjusting for baseline cardiovascular risk factors, functional status or cognitive function (Table 8-6)

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Table 8-6 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with 24-hour Mean Diastolic BP

Model 1	**B**	**HR**	**95% CI for HR**		**P**
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.16	**<0.01**
Sex	0.45	1.56	1.03	2.36	**0.04**
24-hour Mean DBP (mmHg)	0.02	1.02	0.99	1.04	0.13
Model 2					
Age (years)	0.11	1.12	1.08	1.15	**<0.01**
Sex	0.37	1.45	0.95	2.20	0.08
24-hour Mean DBP (mmHg)	0.01	1.01	0.99	1.04	0.25
Cardiovascular Disease	-0.29	0.75	0.37	1.51	0.42
Diabetes	0.32	1.38	0.74	2.59	0.32
Pack years	0.01	1.01	1.00	1.01	0.06
Cardioactive medication	0.68	1.97	0.96	4.04	0.06
Model 3					
Age (years)	0.12	1.12	1.08	1.17	**<0.01**
Sex	0.29	1.34	0.83	2.17	0.23
24-hour Mean DBP (mmHg)	0.02	1.02	0.99	1.05	0.12
Cardiovascular Disease	-0.14	0.87	0.37	2.03	0.74
Diabetes	0.70	2.01	1.03	3.89	**0.04**
Pack years	0.01	1.01	1.00	1.02	**0.03**
Cardioactive medication	0.54	1.71	0.74	3.96	0.21
Bristol ADL Score	0.10	1.11	0.97	1.27	0.13
Model 4					
Age (years)	0.11	1.12	1.08	1.16	**<0.01**
Sex	0.28	1.33	0.82	2.15	0.25
24-hour Mean DBP (mmHg)	0.02	1.02	0.99	1.05	0.11
Cardiovascular Disease	-0.16	0.86	0.37	1.98	0.72
Diabetes	0.67	1.95	1.00	3.78	**0.05**
Pack years	0.01	1.01	1.00	1.02	**0.03**
Cardioactive medication	0.50	1.64	0.72	3.78	0.24
Bristol ADL Score	0.08	1.08	0.94	1.25	0.29
Total CAMCOG Score	-0.02	0.98	0.94	1.02	0.26

In age and sex adjusted models, 24-hour SBP variability was not significantly associated with survival. Adjusting for cardiovascular risk factors did not reveal a significant association between BP variability and survival. However, models adjusting for baseline functional status, as measured by Bristol ADL and baseline cognitive function, did show a significant association between 24-hour SBP variability and survival such that increased BP variability was associated with increased risk of death.

For every one SD increase in BP variability there was a 5% increase in risk of mortality (Table 8-7).

Table 8-7 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with 24-hour Systolic BP Variability

Model 1			**95% CI for HR**		
	B	**HR**	Lower	Upper	**P**
Age (years)	0.11	1.12	1.08	1.15	<**0.01**
Sex	0.49	1.63	1.08	2.45	**0.02**
24-hour SBP Variability (mmHg)	0.02	1.02	0.98	1.07	0.27
Model 2					
Age (years)	0.09	1.10	1.06	1.14	<**0.01**
Sex	0.38	1.46	0.96	2.20	0.07
24-hour SBP Variability (mmHg)	0.02	1.02	0.98	1.07	0.37
Cardiovascular Disease	-0.24	0.79	0.39	1.60	0.51
Diabetes	0.35	1.42	0.76	2.65	0.27
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive medication	0.69	2.00	0.97	4.13	0.06
BMI (kg/m^2)	-0.07	0.94	0.88	0.99	**0.02**
Model 3					
Age (years)	0.09	1.09	1.05	1.14	<**0.01**
Sex	0.23	1.26	0.78	2.05	0.34
24-hour SBP Variability (mmHg)	0.05	1.05	1.00	1.11	**0.04**
Cardiovascular Disease	0.06	1.06	0.44	2.55	0.89
Diabetes	0.79	2.19	1.12	4.28	**0.02**
Pack years	0.01	1.01	1.00	1.02	<**0.01**
Cardioactive medication	0.43	1.53	0.65	3.60	0.33
BMI (kg/m^2)	-0.12	0.89	0.83	0.95	<**0.01**
Bristol ADL Score	0.11	1.11	0.96	1.29	0.15
Model 4					
Age (years)	0.09	1.09	1.05	1.13	<**0.01**
Sex	0.23	1.26	0.78	2.04	0.34
24-hour SBP Variability (mmHg)	0.05	1.05	1.00	1.11	<**0.05**
Cardiovascular Disease	0.04	1.04	0.44	2.47	0.93
Diabetes	0.77	2.15	1.10	4.20	**0.03**
Pack years	0.01	1.01	1.00	1.02	<**0.01**
Cardioactive medication	0.42	1.52	0.65	3.53	0.33
BMI (kg/m^2)	-0.12	0.89	0.83	0.95	<**0.01**
Bristol ADL Score	0.09	1.09	0.94	1.27	0.26
Total CAMCOG Score	-0.02	0.98	0.95	1.02	0.44

Similarly, 24-hour diastolic BP variability was not significantly associated with survival in models adjusting for age and sex or cardiovascular risk factors. However, in models adjusting for Bristol ADL score or total CAMCOG score, there was a significant association between diastolic BP variability and survival with greater BP variability being associated with increased risk of mortality (Table 8-8).

Table 8-8 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with 24-hour Diastolic BP Variability

Model 1	**B**	**HR**	**95% CI for HR**		**P**
			Lower	Upper	
Age (years)	0.11	1.11	1.08	1.15	**<0.01**
Sex	0.46	1.58	1.05	2.38	**0.03**
24-hour DBP Variability (mmHg)	0.07	1.07	0.99	1.15	0.08
Model 2					
Age (years)	0.09	1.10	1.06	1.13	**<0.01**
Sex	0.34	1.41	0.93	2.13	0.11
24-hour DBP Variability (mmHg)	0.07	1.07	0.99	1.16	0.07
Cardiovascular Disease	-0.25	0.78	0.38	1.57	0.48
Diabetes	0.33	1.38	0.74	2.59	0.31
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive medication	0.72	2.06	1.01	4.22	**0.05**
BMI (kg/m^2)	-0.07	0.93	0.88	0.99	**0.02**
Model 3					
Age (years)	0.09	1.09	1.05	1.13	**<0.01**
Sex	0.18	1.20	0.74	1.94	0.47
24-hour DBP Variability (mmHg)	0.12	1.13	1.04	1.23	**0.01**
Cardiovascular Disease	-0.01	0.99	0.42	2.31	0.98
Diabetes	0.80	2.22	1.15	4.30	**0.02**
Pack years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive medication	0.53	1.71	0.75	3.88	0.20
BMI (kg/m^2)	-0.13	0.88	0.82	0.94	**<0.01**
Bristol ADL Score	0.13	1.14	0.99	1.32	0.08
Model 4					
Age (years)	0.08	1.09	1.05	1.13	**<0.01**
Sex	0.18	1.20	0.74	1.94	0.47
24-hour DBP Variability (mmHg)	0.12	1.13	1.03	1.23	**0.01**
Cardiovascular Disease	-0.04	0.96	0.41	2.22	0.92
Diabetes	0.77	2.17	1.12	4.19	**0.02**
Pack years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive medication	0.53	1.70	0.76	3.83	0.20
BMI (kg/m^2)	-0.13	0.88	0.82	0.94	**<0.01**
Bristol ADL Score	0.11	1.12	0.96	1.30	0.15
Total CAMCOG Score	-0.02	0.98	0.95	1.02	0.43

8.3.2.5 Daytime

Mean daytime SBP and DBP were not associated with survival in age and sex adjusted models. Adding cardiovascular risk factors to the model did not reveal any significant

associations between mean daytime blood pressures and survival. Adding Bristol ADL score to the model (in order to adjust for baseline functional status) did reveal significant association between both daytime mean SBP and mean DBP and survival, with greater mean BP being associated with increased risk of death due to all causes. The same was true for models including baseline CAMCOG score (Table 8-9 Table 8-10).

Both systolic and diastolic BP variability were associated with survival in age and sex adjusted models. After adjusting for cardiovascular risk factors, the association between systolic BP variability and survival was no longer significant; however, greater diastolic daytime BP variability remained associated with poorer outcome. In addition to adjusting for cardiovascular risk factors, baseline Bristol ADL score and baseline total CAMCOG score were entered into the models. Systolic BP variability was significantly associated with survival in models adjusting for baseline Bristol ADL score, but not in the model adjusting for cognition (Table 8-11). Diastolic BPV was associated with survival in all models (Table 8-12).

Table 8-9 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Daytime Mean Systolic BP

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.11	1.12	1.08	1.15	**<0.01**
Sex	0.49	1.64	1.08	2.48	**0.02**
daytime Mean SBP (mmHg)	0.01	1.01	1.00	1.02	0.22
Model 2					
Age (years)	0.09	1.10	1.06	1.13	**<0.01**
Sex	0.39	1.47	0.96	2.24	0.07
daytime Mean SBP (mmHg)	0.01	1.01	1.00	1.02	0.18
Cardiovascular Disease	-0.27	0.77	0.38	1.57	0.47
Diabetes	0.32	1.38	0.74	2.59	0.31
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive medication	0.71	2.03	0.98	4.20	0.06
BMI (kg/m^2)	-0.06	0.94	0.89	1.00	**0.04**
Model 3					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	0.27	1.31	0.80	2.13	0.28
daytime Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.01**
Cardiovascular Disease	0.03	1.03	0.43	2.47	0.95
Diabetes	0.69	2.00	0.99	4.04	**0.05**
Pack years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive medication	0.51	1.67	0.71	3.92	0.24
BMI (kg/m^2)	-0.12	0.89	0.82	0.95	**<0.01**
Bristol ADL Score	0.08	1.09	0.93	1.27	0.28
Model 4					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	0.27	1.31	0.80	2.13	0.28
daytime Mean SBP (mmHg)	0.02	1.02	1.01	1.03	**0.01**
Cardiovascular Disease	0.00	1.00	0.42	2.37	1.00
Diabetes	0.66	1.94	0.96	3.91	0.07
Pack years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive medication	0.49	1.63	0.70	3.79	0.26
BMI (kg/m^2)	-0.12	0.89	0.83	0.95	**<0.01**
Bristol ADL Score	0.05	1.05	0.89	1.24	0.54
Total CAMCOG Score	-0.02	0.98	0.94	1.01	0.22

Table 8-10 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Daytime Mean Diastolic BP

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.12	1.12	1.09	1.16	**<0.01**
Sex	0.43	1.53	1.01	2.33	**0.05**
Daytime Mean DBP (mmHg)	0.01	1.01	0.99	1.04	0.23
Model 2					
Age (years)	0.10	1.11	1.07	1.14	**<0.01**
Sex	0.31	1.36	0.89	2.07	0.16
Daytime Mean DBP (mmHg)	0.02	1.02	0.99	1.04	0.13
Cardiovascular Disease	-0.24	0.79	0.39	1.59	0.51
Diabetes	0.33	1.39	0.74	2.60	0.31
Pack years	0.01	1.01	1.00	1.02	**0.03**
Cardioactive medication	0.74	2.09	1.02	4.28	**0.05**
BMI (kg/m^2)	-0.06	0.94	0.88	0.99	**0.03**
Model 3					
Age (years)	0.11	1.11	1.07	1.15	**<0.01**
Sex	0.10	1.11	0.67	1.82	0.68
Daytime Mean DBP (mmHg)	0.03	1.03	1.01	1.06	**0.01**
Cardiovascular Disease	0.02	1.02	0.43	2.44	0.96
Diabetes	0.81	2.25	1.14	4.43	**0.02**
Pack years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive medication	0.61	1.84	0.79	4.29	0.16
BMI (kg/m^2)	-0.13	0.88	0.82	0.94	**<0.01**
Bristol ADL Score	0.11	1.12	0.96	1.30	0.15
Model 4					
Age (years)	0.10	1.11	1.06	1.15	**<0.01**
Sex	0.10	1.11	0.68	1.82	0.69
Daytime Mean DBP (mmHg)	0.03	1.03	1.01	1.06	**0.01**
Cardiovascular Disease	-0.01	0.99	0.42	2.33	0.98
Diabetes	0.78	2.18	1.11	4.30	**0.02**
Pack years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive medication	0.59	1.81	0.79	4.17	0.16
BMI (kg/m^2)	-0.13	0.88	0.82	0.94	**<0.01**
Bristol ADL Score	0.08	1.09	0.93	1.28	0.30
Total CAMCOG Score	-0.02	0.98	0.94	1.02	0.27

Table 8-11 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Daytime Systolic BP Variability

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.11	1.11	1.08	1.15	**<0.01**
Sex	0.49	1.64	1.08	2.47	**0.02**
Daytime SBP Variability (mmHg)	0.05	1.05	1.00	1.10	**0.04**
Model 2					
Age (years)	0.10	1.10	1.07	1.14	**<0.01**
Sex	0.37	1.45	0.96	2.20	0.08
Daytime SBP Variability (mmHg)	0.04	1.04	0.99	1.09	0.09
Cardiovascular Disease	-0.25	0.78	0.38	1.60	0.50
Diabetes	0.40	1.50	0.80	2.80	0.21
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive medication	0.62	1.85	0.89	3.87	0.10
BMI (kg/m^2)	-0.05	0.95	0.89	1.00	0.07
Model 3					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	0.21	1.23	0.75	2.01	0.41
Daytime SBP Variability (mmHg)	0.06	1.06	1.00	1.11	**0.04**
Cardiovascular Disease	0.05	1.05	0.43	2.54	0.92
Diabetes	0.87	2.40	1.23	4.67	**0.01**
Pack years	0.01	1.01	1.01	1.02	**<0.01**
Cardioactive medication	0.36	1.43	0.60	3.42	0.42
BMI (kg/m^2)	-0.10	0.90	0.84	0.97	**<0.01**
Bristol ADL Score	0.08	1.08	0.93	1.26	0.33
Model 4					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	0.20	1.22	0.75	2.00	0.42
Daytime SBP Variability (mmHg)	0.05	1.05	1.00	1.11	0.07
Cardiovascular Disease	0.03	1.03	0.43	2.48	0.94
Diabetes	0.86	2.36	1.21	4.61	**0.01**
Pack years	0.01	1.01	1.01	1.02	**<0.01**
Cardioactive medication	0.36	1.43	0.60	3.39	0.42
BMI (kg/m^2)	-0.10	0.90	0.84	0.97	**<0.01**
Bristol ADL Score	0.06	1.07	0.91	1.25	0.44
Total CAMCOG Score	-0.01	0.99	0.95	1.03	0.57

Table 8-12 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Daytime Diastolic BP Variability

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.11	1.11	1.08	1.15	**<0.01**
Sex	0.47	1.60	1.06	2.42	**0.03**
Daytime DBP Variability (mmHg)	0.10	1.11	1.02	1.20	**0.02**
Model 2					
Age (years)	0.09	1.10	1.06	1.13	**<0.01**
Sex	0.37	1.44	0.95	2.19	0.08
Daytime DBP Variability (mmHg)	0.09	1.09	1.01	1.19	**0.03**
Cardiovascular Disease	-0.28	0.76	0.38	1.52	0.43
Diabetes	0.29	1.33	0.71	2.50	0.37
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive medication	0.70	2.02	1.00	4.08	**0.05**
BMI (kg/m^2)	-0.06	0.94	0.89	1.00	**0.05**
Model 3					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	0.16	1.18	0.72	1.92	0.51
Daytime DBP Variability (mmHg)	0.12	1.13	1.03	1.23	**0.01**
Cardiovascular Disease	-0.01	0.99	0.42	2.32	0.98
Diabetes	0.84	2.31	1.20	4.47	**0.01**
Pack years	0.01	1.01	1.01	1.02	**<0.01**
Cardioactive medication	0.52	1.69	0.74	3.82	0.21
BMI (kg/m^2)	-0.12	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.09	1.09	0.94	1.27	0.26
Model 4					
Age (years)	0.10	1.11	1.07	1.15	**<0.01**
Sex	0.31	1.36	0.84	2.20	0.21
Daytime DBP Variability (mmHg)	0.11	1.12	1.02	1.23	**0.02**
Cardiovascular Disease	-0.19	0.82	0.36	1.89	0.65
Diabetes	0.80	2.23	1.17	4.26	**0.02**
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive medication	0.46	1.58	0.70	3.53	0.27
Bristol ADL Score	0.08	1.08	0.92	1.27	0.35
Total CAMCOG Score	-0.02	0.98	0.95	1.02	0.42

8.3.2.6 Night-time

Night-time mean SBP was associated with survival in age and sex adjusted models but not in models adjusting for cardiovascular risk factors, baseline functional status, or baseline cognitive function (Table 8-13). Night-time mean DBP and SBP variability

were not associated with survival in any model (Table 8-14 and Table 8-15). Nocturnal DBP variability showed a significant association with survival in the age and sex adjusted model (Table 8-16). The association between DBP variability and survival was not quite significant in models adjusting for cardiovascular risk factors, but did reach statistical significance in models adjusting for Bristol ADL score and CAMCOG total score

Table 8-13 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Nocturnal Mean Systolic BP

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.11	1.12	1.08	1.15	**<0.01**
Sex	0.56	1.76	1.13	2.73	**0.01**
Nocturnal Mean SBP (mmHg)	0.01	1.01	1.00	1.03	**0.04**
Model 2					
Age (years)	0.10	1.10	1.07	1.14	**<0.01**
Sex	0.46	1.58	1.01	2.47	**0.05**
Nocturnal Mean SBP (mmHg)	0.01	1.01	1.00	1.02	0.18
Cardiovascular Disease	-0.33	0.72	0.35	1.49	0.38
Diabetes	0.25	1.28	0.65	2.54	0.48
Pack years	0.01	1.01	1.00	1.02	**0.04**
Cardioactive medication	0.77	2.15	1.02	4.54	**0.05**
BMI (kg/m^2)	-0.07	0.94	0.88	0.99	**0.03**
Model 3					
Age (years)	0.10	1.11	1.06	1.15	**<0.01**
Sex	0.38	1.46	0.88	2.41	0.14
Nocturnal Mean SBP (mmHg)	0.01	1.01	1.00	1.02	0.19
Cardiovascular Disease	0.01	1.01	0.42	2.42	0.98
Diabetes	0.74	2.09	1.02	4.29	**0.05**
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive medication	0.41	1.51	0.64	3.54	0.34
BMI (kg/m^2)	-0.11	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.09	1.09	0.93	1.28	0.29
Model 4					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	0.37	1.45	0.88	2.40	0.15
Nocturnal Mean SBP (mmHg)	0.01	1.01	1.00	1.02	0.16
Cardiovascular Disease	-0.02	0.98	0.41	2.32	0.96
Diabetes	0.70	2.02	0.98	4.16	0.06
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive medication	0.40	1.49	0.64	3.46	0.35
BMI (kg/m^2)	-0.11	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.06	1.06	0.90	1.26	0.50
Total CAMCOG Score	-0.02	0.98	0.94	1.02	0.33

Table 8-14 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Nocturnal Mean Diastolic BP

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.12	1.12	1.09	1.16	**<0.01**
Sex	0.49	1.63	1.06	2.52	**0.03**
Nocturnal Mean DBP (mmHg)	0.01	1.01	0.99	1.04	0.26
Model 2					
Age (years)	0.10	1.11	1.07	1.14	**<0.01**
Sex	0.40	1.49	0.96	2.32	0.07
Nocturnal Mean DBP (mmHg)	0.01	1.01	0.99	1.03	0.44
Cardiovascular Disease	-0.30	0.74	0.36	1.52	0.41
Diabetes	0.32	1.37	0.71	2.68	0.35
Pack years	0.01	1.01	1.00	1.02	**0.04**
Cardioactive medication	0.79	2.20	1.05	4.61	**0.04**
BMI (kg/m^2)	-0.07	0.94	0.88	0.99	**0.03**
Model 3					
Age (years)	0.10	1.11	1.07	1.16	**<0.01**
Sex	0.31	1.36	0.82	2.27	0.23
Nocturnal Mean DBP (mmHg)	0.01	1.01	0.99	1.04	0.32
Cardiovascular Disease	0.02	1.02	0.43	2.43	0.97
Diabetes	0.80	2.24	1.11	4.52	**0.03**
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive medication	0.45	1.57	0.68	3.65	0.29
BMI (kg/m^2)	-0.11	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.10	1.11	0.95	1.29	0.18
Model 4					
Age (years)	0.10	1.11	1.06	1.15	**<0.01**
Sex	0.30	1.35	0.81	2.25	0.25
Nocturnal Mean DBP (mmHg)	0.02	1.02	0.99	1.04	0.29
Cardiovascular Disease	-0.01	0.99	0.42	2.34	0.98
Diabetes	0.78	2.18	1.08	4.41	**0.03**
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive medication	0.44	1.55	0.68	3.57	0.30
BMI (kg/m^2)	-0.11	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.08	1.08	0.92	1.28	0.33
Total CAMCOG Score	-0.02	0.98	0.94	1.02	0.36

Table 8-15 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Nocturnal Systolic BP Variability

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.11	1.12	1.09	1.15	**<0.01**
Sex	0.52	1.68	1.09	2.60	**0.02**
Nocturnal SBP Variability (mmHg)	0.02	1.02	0.97	1.07	0.51
Model 2					
Age (years)	0.10	1.10	1.07	1.14	**<0.01**
Sex	0.40	1.49	0.96	2.32	0.07
Nocturnal SBP Variability (mmHg)	0.00	1.00	0.95	1.05	0.89
Cardiovascular Disease	-0.33	0.72	0.35	1.48	0.38
Diabetes	0.36	1.44	0.74	2.81	0.29
Pack years	0.01	1.01	1.00	1.02	**0.03**
Cardioactive medication	0.81	2.25	1.07	4.72	**0.03**
BMI (kg/m^2)	-0.07	0.93	0.88	0.99	**0.03**
Model 3					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	0.37	1.45	0.87	2.41	0.15
Nocturnal SBP Variability (mmHg)	0.02	1.02	0.97	1.08	0.41
Cardiovascular Disease	-0.01	0.99	0.42	2.34	0.97
Diabetes	0.77	2.15	1.06	4.38	**0.03**
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive medication	0.44	1.55	0.67	3.57	0.31
BMI (kg/m^2)	-0.11	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.13	1.14	0.98	1.32	0.09
Model 4					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	0.36	1.44	0.86	2.38	0.16
Nocturnal SBP Variability (mmHg)	0.02	1.02	0.97	1.08	0.46
Cardiovascular Disease	-0.04	0.96	0.41	2.26	0.92
Diabetes	0.75	2.11	1.04	4.30	**0.04**
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive medication	0.43	1.54	0.67	3.52	0.31
BMI (kg/m^2)	-0.11	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.11	1.12	0.96	1.30	0.17
Total CAMCOG Score	-0.02	0.98	0.95	1.02	0.45

Table 8-16 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Nocturnal Diastolic BP Variability

Model 1	**B**	**HR**	**95.0% CI**		**P**
			Lower	Upper	
Age (years)	0.11	1.12	1.08	1.15	**<0.01**
Sex	0.51	1.67	1.09	2.57	**0.02**
Daytime DBP Variability (mmHg)	0.09	1.09	1.00	1.19	**0.05**
Model 2					
Age (years)	0.10	1.10	1.07	1.14	**<0.01**
Sex	0.41	1.51	0.98	2.34	0.06
Daytime DBP Variability (mmHg)	0.07	1.08	0.99	1.17	0.09
Cardiovascular Disease	-0.34	0.71	0.35	1.46	0.36
Diabetes	0.28	1.32	0.68	2.57	0.42
Pack years	0.01	1.01	1.00	1.02	**0.03**
Cardioactive medication	0.81	2.25	1.09	4.67	**0.03**
BMI (kg/m^2)	-0.07	0.94	0.88	0.99	**0.03**
Model 3					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	0.31	1.37	0.82	2.26	0.23
Daytime DBP Variability (mmHg)	0.10	1.10	1.01	1.21	**0.04**
Cardiovascular Disease	-0.06	0.94	0.40	2.20	0.89
Diabetes	0.78	2.18	1.09	4.36	**0.03**
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive medication	0.50	1.65	0.73	3.75	0.23
BMI (kg/m^2)	-0.11	0.90	0.83	0.96	**<0.01**
Bristol ADL Score	0.12	1.13	0.98	1.31	0.10
Model 4					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	0.31	1.36	0.82	2.25	0.23
Daytime DBP Variability (mmHg)	0.09	1.10	1.00	1.21	**0.05**
Cardiovascular Disease	-0.08	0.93	0.40	2.15	0.86
Diabetes	0.77	2.16	1.08	4.31	**0.03**
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive medication	0.50	1.65	0.73	3.72	0.23
BMI (kg/m^2)	-0.11	0.90	0.84	0.96	**<0.01**
Bristol ADL Score	0.11	1.12	0.96	1.31	0.16
Total CAMCOG Score	-0.01	0.99	0.95	1.03	0.64

8.3.2.7 Hypertension

Cox regression analysis was also used to establish if hypertension on baseline ambulatory blood pressure (defined according to NICE criteria) was associated with survival. Hypertension was not associated in the model adjusting only for age and sex or

cardiovascular factors. However, after adjusting for baseline functional and cognitive status, hypertension was associated with increased mortality (Table 8-17).

Table 8-17 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Hypertension

Model 1	**B**	**HR**	**95.0% CI**		**P**
			Lower	Upper	
Age (years)	0.11	1.12	1.09	1.53	**<0.01**
Sex	0.02	1.652	1.08	2.45	**0.02**
Hypertension on ambulatory BP	0.30	1.36	0.91	2.02	0.14
Model 2					
Age (years)	0.10	1.10	1.07	1.14	**<0.01**
Sex	0.37	1.44	0.95	2.19	0.09
Hypertension on ambulatory BP	0.29	1.34	0.89	2.10	0.16
Cardiovascular Disease	-0.28	0.76	0.37	1.55	0.45
Diabetes	0.30	1.35	0.72	2.54	0.35
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive medication	0.68	1.98	0.96	4.11	0.07
BMI (kg/m^2)	-0.06	0.94	0.89	1.00	0.06
Model 3					
Age (years)	0.10	1.11	1.07	1.15	**<0.01**
Sex	0.24	1.27	0.78	2.07	0.33
Hypertension on ambulatory BP	0.66	1.94	1.22	3.09	**0.01**
Cardiovascular Disease	0.01	1.01	0.42	2.43	0.98
Diabetes	0.78	2.18	1.08	4.38	**0.03**
Pack years	0.01	1.01	1.01	1.02	**<0.01**
Cardioactive medication	0.43	1.54	0.65	3.65	0.32
BMI (kg/m^2)	-0.11	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.08	1.08	0.93	1.26	0.30
Model 4					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	0.24	1.27	0.78	2.06	0.34
Hypertension on ambulatory BP	0.67	1.96	1.23	3.12	**<0.01**
Cardiovascular Disease	-0.02	0.98	0.41	2.32	0.96
Diabetes	0.75	2.13	1.06	4.27	**0.03**
Pack years	0.01	1.01	1.01	1.02	**<0.01**
Cardioactive medication	0.42	1.52	0.65	3.54	0.33
BMI (kg/m^2)	-0.11	0.89	0.83	0.96	**<0.01**
Bristol ADL Score	0.05	1.05	0.89	1.23	0.58
Total CAMCOG Score	-0.03	0.97	0.94	1.01	0.18

8.3.3 **Survival and Blood Pressure Response to Active Stand**

Baseline active stand results were available for 297 participants. Of these, 74 participants had died during the follow-up period. Comparing participants who were alive at the end of the follow-up period with those who had died did not reveal any significant difference in rates of orthostatic hypotension as defined by AAN, or systolic or diastolic OH examined separately. Similarly, there were no significant differences in terms of nadir reached during stand. Systolic vasodepression was greater in participants who died compared to those who were alive at end of follow-up, but this did not quite reach statistical significance (P=0.07). Degree of diastolic vasodepression did not differ between the groups (Table 8-18).

Table 8-18 Response to Active Stand for Participants Who Were Alive at End of Follow-up versus Those Who Had Died

	Alive N= 223	**Dead N = 74**	**P**
	Frequency (%)	**Frequency (%)**	
Orthostatic Hypotension	182 (81.6)	30 (40.5)	0.92
Systolic Hypotension	147 (65.9)	45 (60.8)	0.43
Diastolic Hypotension	161 (72.2)	49 (66.2)	0.33
	Mean (SD)	**Mean (SD)**	
Systolic Vasodepression (mmHg)	26.5 (16.4)	23.9 (19.4)	0.25
Diastolic Vasodepression (mmHg)	14.5 (8.7)	15.1 (12.2)	0.65
Systolic Nadir (mmHg)	115.2 (26.7)	121.7 (25.0)	0.07
Diastolic Nadir (mmHg)	46.9 (13.1)	48.0 (13.9)	0.54

Cox regression models were used to determine if OH was associated with survival. OH defined by the AAN was not associated with survival in models adjusting for age at baseline and sex. Further models adjusting for cardiovascular risk factors, baseline functional status and baseline cognitive function also failed to show an association between OH and survival (Table 8-19). Analysis was repeated to explore if examining systolic and diastolic OH separately showed any associations with survival. None were observed in the age and sex adjusted model, or in subsequent models adjusting for cardiovascular risks, functional ability and cognitive function (Table 8-20 & Table 8-21). Finally, Cox regression models were repeated to examine if symptomatic

orthostatic hypotension was associated with survival. Symptomatic OH was not a significant predictor of survival in any of the models.

Table 8-19 Cox Regression Models. Relative of All-Cause Mortality According Associated With Orthostatic Hypotension as Defined by ANN.

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	**Upper**	
Age (years)	0.12	1.12	1.09	1.16	**<0.01**
Sex	-0.48	0.62	0.38	1.00	**0.05**
OH (AAN definition)	0.03	1.03	0.57	1.84	0.93
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.43	0.65	0.40	1.06	0.08
OH (AAN definition)	0.12	1.13	0.61	2.11	0.70
CVD	0.37	1.45	0.60	3.51	0.41
Diabetes	-0.36	0.70	0.32	1.50	0.35
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.67	0.51	0.21	1.26	0.15
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.10
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.02**
Model 3					
Age (years)	0.11	1.12	1.07	1.16	**<0.01**
Sex	-0.19	0.83	0.49	1.41	0.49
OH (AAN definition)	-0.13	0.88	0.42	1.84	0.74
CVD	0.04	1.04	0.38	2.86	0.94
Diabetes	-0.74	0.48	0.20	1.14	0.09
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.50	0.61	0.22	1.64	0.32
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.06	1.06	0.89	1.26	0.54
Model 4					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.22	0.80	0.47	1.36	0.42
OH (AAN definition)	-0.19	0.82	0.39	1.73	0.61
CVD	0.04	1.04	0.39	2.80	0.93
Diabetes	-0.72	0.49	0.20	1.17	0.11
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.44	0.65	0.24	1.72	0.38
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.00	1.00	0.82	1.21	0.97
CAMCOG total score	-0.04	0.96	0.92	1.00	**0.05**

Table 8-20 Cox Regression Models. Relative of All-Cause Mortality Associated with Systolic Orthostatic Hypotension.

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	**Upper**	
Age (years)	0.12	1.13	1.09	1.16	**<0.01**
Sex	-0.47	0.62	0.39	1.00	**0.05**
Systolic OH	-0.29	0.75	0.47	1.19	0.22
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.44	0.64	0.40	1.05	0.08
Systolic OH	-0.29	0.75	0.46	1.21	0.23
CVD	0.33	1.39	0.57	3.38	0.46
Diabetes	-0.36	0.70	0.32	1.52	0.37
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.65	0.52	0.21	1.29	0.16
BMI (kg/m^2)	-0.06	0.94	0.87	1.01	0.09
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.02**
Model 3					
Age (years)	0.11	1.12	1.07	1.16	**<0.01**
Sex	-0.19	0.83	0.49	1.41	0.49
Systolic OH	-0.05	0.95	0.55	1.64	0.86
CVD	0.02	1.02	0.37	2.81	0.98
Diabetes	-0.74	0.48	0.20	1.14	0.10
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.49	0.62	0.23	1.67	0.34
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.06	1.06	0.89	1.27	0.52
Model 4					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.21	0.81	0.47	1.37	0.43
Systolic OH	-0.03	0.97	0.56	1.67	0.90
CVD	0.02	1.02	0.38	2.77	0.96
Diabetes	-0.72	0.49	0.20	1.17	0.11
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.42	0.66	0.24	1.76	0.40
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.00	1.00	0.82	1.21	0.99
CAMCOG total score	-0.04	0.96	0.92	1.00	0.06

Table 8-21 Cox Regression Models. Relative of All-Cause Mortality Associated with Diastolic Orthostatic Hypotension.

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	**Upper**	
Age (years)	0.12	1.12	1.09	1.16	**<0.01**
Sex	-0.46	0.63	0.39	1.01	0.06
Diastolic OH	-0.18	0.83	0.51	1.36	0.46
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.42	0.66	0.40	1.07	0.09
Diastolic OH	-0.20	0.82	0.50	1.35	0.43
CVD	0.39	1.48	0.61	3.60	0.39
Diabetes	-0.39	0.67	0.31	1.46	0.32
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.66	0.52	0.21	1.27	0.15
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.10
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.02**
Model 3					
Age (years)	0.11	1.12	1.07	1.16	**<0.01**
Sex	-0.17	0.84	0.50	1.42	0.52
Diastolic OH	-0.10	0.91	0.52	1.58	0.73
CVD	0.03	1.03	0.38	2.84	0.95
Diabetes	-0.76	0.47	0.20	1.12	0.09
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.48	0.62	0.23	1.68	0.35
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.06	1.06	0.89	1.27	0.51
Model 4					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.21	0.81	0.48	1.38	0.45
Diastolic OH	-0.09	0.91	0.52	1.60	0.75
CVD	0.04	1.04	0.38	2.81	0.94
Diabetes	-0.74	0.48	0.20	1.15	0.10
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.42	0.66	0.24	1.77	0.41
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.00	1.00	0.83	1.22	0.98
CAMCOG total score	-0.04	0.96	0.92	1.00	0.06

To explore if degree of vasodepression or BP nadir reached during stand were associated with survival, BP responses as a continuous variable were entered into the models. Systolic vasodepression, diastolic vasodepression, systolic nadir, and diastolic nadir were entered into separate models controlling for age and sex. None of these variables were associated with survival (Table 8-22, Table 8-23, Table 8-24 & Table 8-25). The models were then adjusted for cardiovascular risk factors, baseline physical function, and baseline cognitive function. There were no associations between survival and any of the continuous BP responses to active stand in these models (Table 8-22, Table 8-23, Table 8-24 and Table 8-25).

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Table 8-22 Cox Regression Models. Hazard Ratio of All-Cause Mortality According to Systolic Vasodepression

	B	HR	95% CI		P
			Lower	Upper	
Model 1					
Age (years) (years)	0.12	1.13	1.09	1.16	**<0.01**
Sex	-0.46	0.63	0.39	1.01	0.06
Systolic Vasodepression (mmHg)	-0.01	0.99	0.97	1.00	0.14
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.43	0.65	0.40	1.06	0.08
Systolic Vasodepression (mmHg)	-0.01	0.99	0.97	1.00	0.10
CVD	0.32	1.38	0.57	3.34	0.47
Diabetes	-0.35	0.71	0.33	1.53	0.38
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.66	0.52	0.21	1.27	0.15
BMI (kg /m^2)	-0.07	0.93	0.87	1.00	0.07
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.02**
Model 3					
Age (years)	0.11	1.11	1.07	1.16	**<0.01**
Sex	-0.21	0.81	0.48	1.38	0.43
Systolic Vasodepression (mmHg)	-0.01	0.99	0.98	1.01	0.29
CVD	0.00	1.00	0.36	2.73	1.00
Diabetes	-0.69	0.50	0.21	1.21	0.13
Pack years	0.01	1.01	1.00	1.02	**0.03**
Cardioactive Medication	-0.48	0.62	0.23	1.67	0.34
BMI (kg /m^2)	-0.11	0.90	0.83	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.07	1.07	0.89	1.28	0.47
Model 4					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.23	0.79	0.47	1.35	0.39
Systolic Vasodepression (mmHg)	-0.01	0.99	0.98	1.01	0.31
CVD	0.02	1.02	0.38	2.74	0.97
Diabetes	-0.68	0.51	0.21	1.23	0.13
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.42	0.66	0.25	1.77	0.41
BMI (kg /m^2)	-0.11	0.90	0.83	0.97	**<0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.01	1.01	0.83	1.22	0.95
CAMCOG total score	-0.04	0.96	0.92	1.00	0.06

Table 8-23 Cox Regression Models. Hazard Ratio of All-Cause Mortality According to Diastolic Vasodepression

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	**Upper**	
Age (years)	0.12	1.12	1.09	1.16	**<0.01**
Sex	-0.49	0.62	0.38	0.99	**0.05**
Diastolic Vasodepression (mmHg)	0.00	1.00	0.98	1.03	0.80
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.44	0.65	0.40	1.05	0.08
Diastolic Vasodepression (mmHg)	0.00	1.00	0.98	1.02	0.97
CVD	0.38	1.46	0.60	3.56	0.40
Diabetes	-0.36	0.70	0.33	1.51	0.36
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.67	0.51	0.21	1.26	0.14
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.11
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.03**
Model 3					
Age (years)	0.11	1.12	1.07	1.16	**<0.01**
Sex	-0.17	0.84	0.50	1.43	0.53
Diastolic Vasodepression (mmHg)	0.01	1.01	0.98	1.04	0.46
CVD	-0.03	0.97	0.35	2.69	0.96
Diabetes	-0.76	0.47	0.20	1.12	0.09
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.48	0.62	0.23	1.66	0.34
BMI (kg/m^2)	-0.10	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.05	1.05	0.88	1.26	0.58
Model 4					
Age (years)	0.10	1.11	1.06	1.15	**<0.01**
Sex	-0.20	0.82	0.48	1.39	0.46
Diastolic Vasodepression (mmHg)	0.01	1.01	0.98	1.04	0.47
CVD	-0.04	0.96	0.35	2.61	0.93
Diabetes	-0.74	0.48	0.20	1.14	0.10
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.40	0.67	0.25	1.79	0.43
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	-0.01	0.99	0.82	1.20	0.94
CAMCOG total score	-0.04	0.96	0.92	1.00	0.06

Table 8-24 Cox Regression Models. Hazard Ratio of All-Cause Mortality According to Systolic Nadir

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	**Upper**	
Age (years)	0.11	1.12	1.08	1.16	**<0.01**
Sex	-0.50	0.61	0.38	0.97	**0.04**
Systolic nadir (mmHg)	0.01	1.01	1.00	1.01	0.21
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.44	0.64	0.40	1.05	0.08
Systolic nadir (mmHg)	0.00	1.00	0.99	1.01	0.71
CVD	0.37	1.45	0.60	3.52	0.41
Diabetes	-0.35	0.70	0.33	1.51	0.37
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.67	0.51	0.21	1.26	0.15
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.11
Mean SBP (mmHg)	0.01	1.01	1.00	1.03	0.06
Model 3					
Age (years)	0.11	1.12	1.07	1.16	**<0.01**
Sex	-0.18	0.83	0.49	1.41	0.50
Systolic nadir (mmHg)	0.00	1.00	0.99	1.01	0.97
CVD	0.03	1.03	0.37	2.82	0.96
Diabetes	-0.74	0.48	0.20	1.15	0.10
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.49	0.61	0.22	1.66	0.33
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.06	1.06	0.89	1.27	0.53
Model 4					
Age (years)	0.10	1.11	1.06	1.15	**<0.01**
Sex	-0.20	0.81	0.48	1.38	0.45
Systolic nadir (mmHg)	0.00	1.00	0.99	1.01	0.69
CVD	0.04	1.04	0.39	2.77	0.94
Diabetes	-0.75	0.47	0.20	1.14	0.10
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.43	0.65	0.24	1.73	0.39
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.05	**<0.01**
Bristol ADL Score	-0.01	0.99	0.82	1.21	0.94
CAMCOG total score	-0.04	0.96	0.92	1.00	**0.05**

Table 8-25 Cox Regression Models. Hazard Ratio of All-Cause Mortality According to Diastolic Nadir

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	**Upper**	
Age (years)	0.12	1.12	1.09	1.16	**<0.01**
Sex	-0.48	0.62	0.38	0.99	**0.05**
Diastolic nadir (mmHg)	0.01	1.01	0.99	1.03	0.34
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.43	0.65	0.40	1.05	0.08
Diastolic nadir (mmHg)	0.01	1.01	0.99	1.02	0.47
CVD	0.35	1.42	0.58	3.47	0.44
Diabetes	-0.40	0.67	0.31	1.45	0.31
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.65	0.52	0.21	1.30	0.16
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.10
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	0.04
Model 3					
Age (years)	0.11	1.12	1.07	1.16	**<0.01**
Sex	-0.18	0.84	0.49	1.41	0.51
Diastolic nadir (mmHg)	0.01	1.01	0.99	1.03	0.54
CVD	0.01	1.01	0.36	2.79	0.99
Diabetes	-0.74	0.48	0.20	1.13	0.09
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.47	0.62	0.23	1.71	0.36
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.06	1.07	0.89	1.28	0.49
Model 4					
Age (years)	0.10	1.11	1.06	1.15	**<0.01**
Sex	-0.21	0.81	0.48	1.38	0.44
Diastolic nadir (mmHg)	0.00	1.00	0.98	1.02	0.79
CVD	0.02	1.02	0.38	2.77	0.97
Diabetes	-0.72	0.49	0.20	1.16	0.10
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.42	0.66	0.24	1.78	0.41
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.00	1.00	0.83	1.22	0.97
CAMCOG total score	-0.04	0.96	0.92	1.00	0.07

As previously discussed orthostatic hypotension, diagnosed using a sphygmomanometer has been associated with increased mortality. To establish if the AAN criteria for OH are too sensitive when using beat-to-beat monitoring, new thresholds for OH were defined based on haemodynamic response observed in a subgroup that had no history of falls syncope or dizziness and had an MMSE≥24 at baseline. The 95th percentiles for systolic and diastolic vasodepression were 49mmHg and 33mmHg respectively. Twenty-six participants had orthostatic hypotension using these thresholds.

In age and sex adjusted models there was a borderline association between OH defined by modified criteria and survival. After adjusting for cardiovascular risk factors and medication OH defined according to modified criteria was no longer a significant predictor of survival (Table 8-26).

Table 8-26 Cox Regression Models. Hazard Ratio of All-Cause Mortality According Modified Criteria for OH

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	**Upper**	
Age (years)	0.13	1.13	1.09	1.17	**<0.01**
Sex	0.42	1.53	0.95	2.45	0.08
Modified OH criteria	0.58	1.79	0.91	3.49	0.09
Model 2					
Age (years)	0.10	1.11	1.07	1.15	**<0.01**
Sex	0.29	1.34	0.83	2.18	0.24
Modified OH criteria	0.47	1.60	0.81	3.18	0.18
CVD	0.52	1.68	0.79	3.60	0.18
Diabetes	-0.20	0.82	0.38	1.80	0.62
Pack years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	-0.80	0.45	0.21	0.96	**0.04**
BMI (kg/m^2)	-0.07	0.94	0.87	1.01	0.07
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.01**
Model 3					
Age (years)	0.12	1.12	1.08	1.17	**<0.01**
Sex	0.14	1.15	0.68	1.95	0.60
Modified OH criteria	0.58	1.79	0.86	3.71	0.12
CVD	0.23	1.26	0.54	2.94	0.60
Diabetes	-0.76	0.47	0.20	1.10	0.08
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.62	0.54	0.24	1.21	0.14
BMI (kg/m^2)	-0.10	0.90	0.83	0.98	**0.02**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.06	1.06	0.89	1.26	0.49
Model 4					
Age (years)	0.11	1.11	1.07	1.16	**<0.01**
Sex	0.17	1.19	0.70	2.02	0.52
Modified OH criteria	0.56	1.75	0.85	3.64	0.13
CVD	0.24	1.27	0.55	2.92	0.58
Diabetes	-0.72	0.49	0.20	1.15	0.10
Pack years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.58	0.56	0.25	1.25	0.16
BMI (kg/m^2)	-0.10	0.90	0.83	0.98	**0.02**
Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.01	1.01	0.84	1.22	0.88
CAMCOG total score	-0.04	0.96	0.93	1.00	0.07

8.3.4 **Survival and Response to Carotid Sinus Massage**

To assess if CSH was more common among participants who had died before October 2012 than in those who were alive at the end of follow-up, prevalence of CSH between the two groups in 2002 was compared. Mixed CSH was significantly more common among participants who died before October 2012 (Table 8-27).

Continuous response to CSM was compared for the two groups. Systolic vasodepression post carotid sinus massage was significantly greater, and systolic nadir was significantly lower among participants who died prior to end of follow-up. Delta RR post CSM was longer for participants who died, but this did not quite reach statistical significance (Table 8-27).

Table 8-27 Response to CSM among Participants who Died During Follow-up with Prevalence among Participants alive in October 2012

	Alive N=201	**Dead N=71**	**P**
CSH (any)	72 (38.5)	34 (47.9)	0.07
Cardio inhibitory	5 (2.5)	1 (1.4)	0.51
Vasodepressor	31 (15.4)	11 (15.5)	0.99
Mixed	37 (18.4)	21 (29.6)	**0.05**
	Median (IQR)	**Median (IQR)**	
RR post CSM (ms)	1670 (1215, 2728)	1815(1316, 3882)	0.17
Max Delta RR (ms)	693 (284, 1762)	1012 (338, 3018)	0.08
Systolic Nadir (mmHg)	82.0 (66.5, 101.5)	73.0 (62.0, 94.0)	**0.03**
Max systolic vasodepression (mmHg)	42.1 (30.7, 57.7)	48.7 (35.2, 66.4)	**0.01**

Carotid sinus hypersensitivity was not associated with survival in age and sex adjusted Cox regression models or in models adjusted for cardiovascular risk factors, baseline functional status, or baseline cognitive function (Table 8-28).

Table 8-28 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Carotid Sinus Hypersensitivity.

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.17	**<0.01**
Sex	-0.63	0.53	0.32	0.88	**0.01**
CSH	0.28	1.32	0.83	2.11	0.24
Model 2					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.56	0.57	0.34	0.97	**0.04**
CSH	0.20	1.22	0.76	1.98	0.41
CVD	-0.42	0.65	0.29	1.49	0.31
Diabetes	0.35	1.41	0.63	3.17	0.40
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.63	1.88	0.82	4.30	0.14
BMI (kg/m^2)	-0.08	0.93	0.86	0.99	**0.03**
Mean SBP (mmHg)	0.00	1.00	0.99	1.02	0.56
Model 3					
Age (years)	0.13	1.14	1.09	1.19	**<0.01**
Sex	-0.40	0.67	0.37	1.20	0.18
CSH	0.25	1.28	0.76	2.18	0.35
CVD	-0.04	0.96	0.39	2.38	0.94
Diabetes	0.95	2.57	1.11	5.95	**0.03**
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.42	1.52	0.62	3.76	0.36
BMI (kg/m^2)	-0.12	0.89	0.82	0.96	**<0.01**
Mean SBP (mmHg)	0.02	1.02	1.00	1.04	**0.02**
Bristol ADL score	-0.01	0.99	0.91	1.08	0.86
Model 4					
Age (years)	0.11	1.12	1.07	1.18	**<0.01**
Sex	-0.42	0.66	0.37	1.17	0.15
CSH	0.28	1.32	0.78	2.24	0.31
CVD	-0.05	0.95	0.40	2.29	0.91
Diabetes	0.91	2.49	1.08	5.76	**0.03**
Pack years	0.01	1.01	1.00	1.03	**0.03**
Cardioactive medication	0.34	1.41	0.58	3.44	0.45
BMI (kg/m^2)	-0.12	0.88	0.82	0.96	**<0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL score	-0.06	0.94	0.85	1.05	0.27
CAMCOG total score	-0.04	0.96	0.92	1.00	**0.05**

To establish if the different subgroups of CSH were associated with survival, the models were run with mixed, vasodepressor and cardioinhibitory CSH entered separately. No associations were seen between CSH group and survival in either age and sex adjusted models, or in the models adjusting for cardiovascular risk factors, baseline functional status, or baseline cognitive function (Table 8-29).

To examine if continuous BP or HR response to CSM were better predictors of survival than categorical variables, Cox regression models were run with HR and BP response entered into the model. Heart rate and BP response to CSM were not associated with survival in either age and sex adjusted models, or in models adjusting for cardiovascular risk factors, baseline functional status or baseline cognitive function (Table 8-30, Table 8-31).

Table 8-29 Cox Regression Models. Hazard Ratio of All-Cause Mortality According to CSH group

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.17	**<0.01**
Sex	-0.61	0.54	0.33	0.89	**0.02**
CSH group	0.13	1.13	0.95	1.35	0.16
Model 2					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.54	0.58	0.34	0.99	**0.05**
CSH group	0.10	1.11	0.93	1.33	0.26
CVD	-0.42	0.66	0.29	1.50	0.32
Diabetes	0.35	1.42	0.63	3.16	0.40
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.63	1.87	0.82	4.29	0.14
BMI (kg/m^2)	-0.08	0.93	0.86	0.99	**0.03**
Mean SBP (mmHg)	0.00	1.00	0.99	1.02	0.54
Model 3					
Age (years)	0.13	1.14	1.09	1.19	**<0.01**
Sex	-0.37	0.69	0.38	1.23	0.21
CSH group	0.14	1.15	0.94	1.41	0.17
CVD	-0.05	0.95	0.38	2.37	0.92
Diabetes	0.93	2.54	1.10	5.86	**0.03**
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.43	1.54	0.62	3.84	0.35
BMI (kg/m^2)	-0.12	0.89	0.82	0.96	**<0.01**
Mean SBP (mmHg)	0.02	1.02	1.00	1.04	**0.02**
Bristol ADL score	-0.01	0.99	0.91	1.08	0.80
Model 4					
Age (years)	0.12	1.12	1.07	1.18	**<0.01**
Sex	-0.40	0.67	0.38	1.20	0.18
CSH group	0.16	1.17	0.95	1.43	0.13
CVD	-0.05	0.95	0.39	2.31	0.91
Diabetes	0.90	2.45	1.06	5.67	**0.04**
Pack years	0.01	1.01	1.00	1.03	**0.03**
Cardioactive medication	0.35	1.42	0.58	3.49	0.44
BMI (kg/m^2)	-0.13	0.88	0.82	0.95	**<0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL score	-0.06	0.94	0.85	1.04	0.23
CAMCOG total score	-0.04	0.96	0.92	1.00	**0.04**

Table 8-30 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Maximum RR response to CSM

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.17	**<0.01**
Sex	-0.58	0.56	0.33	0.93	**0.03**
Maximum RR (ms)	0.00	1.00	1.00	1.00	0.27
Model 2					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.53	0.59	0.34	1.01	**0.05**
Maximum RR (ms)	0.00	1.00	1.00	1.00	0.32
CVD	-0.43	0.65	0.29	1.47	0.30
Diabetes	0.31	1.37	0.61	3.06	0.45
Pack years	0.01	1.01	1.00	1.02	0.06
Cardioactive medication	0.64	1.89	0.83	4.31	0.13
BMI (kg/m^2)	-0.08	0.92	0.86	0.99	**0.02**
Mean SBP	0.01	1.01	0.99	1.02	0.41
Model 3					
Age (years)	0.13	1.14	1.09	1.19	**<0.01**
Sex	-0.34	0.71	0.39	1.29	0.27
Maximum RR (ms)	0.00	1.00	1.00	1.00	0.10
CVD	-0.05	0.95	0.39	2.34	0.92
Diabetes	0.92	2.51	1.08	5.82	**0.03**
Pack years	0.01	1.01	1.00	1.02	0.06
Cardioactive medication	0.43	1.53	0.62	3.77	0.35
BMI (kg/m^2)	-0.13	0.88	0.81	0.95	**<0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL score	0.00	1.00	0.92	1.08	0.93
Model 4					
Age (years)	0.12	1.12	1.07	1.18	**<0.01**
Sex	-0.37	0.69	0.39	1.25	0.22
Maximum RR (ms)	0.00	1.00	1.00	1.00	0.07
CVD	-0.05	0.95	0.40	2.27	0.90
Diabetes	0.90	2.45	1.06	5.69	**0.04**
Pack years	0.01	1.01	1.00	1.02	**0.04**
Cardioactive medication	0.36	1.43	0.59	3.48	0.43
BMI (kg/m^2)	-0.14	0.87	0.81	0.95	**<0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.05	**<0.01**
Bristol ADL score	-0.06	0.95	0.85	1.05	0.29
CAMCOG total score	-0.04	0.96	0.92	1.00	**0.04**

Table 8-31 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Maximum Vasodepression Response to CSM.

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.12	1.12	1.08	1.16	**<0.01**
Sex	-0.61	0.54	0.33	0.89	**0.02**
Maximum vasodepression (mmHg)	0.01	1.01	0.99	1.02	0.30
Model 2					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	-0.55	0.57	0.34	0.98	**0.04**
Maximum vasodepression (mmHg)	0.00	1.00	0.99	1.02	0.50
CVD	-0.44	0.64	0.28	1.45	0.29
Diabetes	0.35	1.42	0.63	3.19	0.40
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.64	1.89	0.83	4.30	0.13
BMI (kg/m^2)	-0.08	0.92	0.86	0.99	**0.03**
Mean SBP	0.00	1.00	0.99	1.02	0.57
Model 3					
Age (years)	0.13	1.13	1.08	1.19	**<0.01**
Sex	-0.35	0.70	0.39	1.27	0.24
Maximum vasodepression (mmHg)	0.01	1.01	1.00	1.02	0.19
CVD	-0.08	0.92	0.37	2.28	0.86
Diabetes	0.96	2.62	1.14	6.05	**0.02**
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.43	1.54	0.63	3.80	0.35
BMI (kg/m^2)	-0.12	0.89	0.82	0.96	**<0.01**
Mean SBP (mmHg)	0.02	1.02	1.00	1.04	**0.02**
Bristol ADL score	-0.01	0.99	0.91	1.08	0.82
Model 4					
Age (years)	0.11	1.12	1.07	1.17	**<0.01**
Sex	-0.38	0.68	0.38	1.23	0.20
Maximum vasodepression (mmHg)	0.01	1.01	1.00	1.02	0.18
CVD	-0.10	0.91	0.38	2.19	0.83
Diabetes	0.95	2.57	1.11	5.94	**0.03**
Pack years	0.01	1.01	1.00	1.03	**0.03**
Cardioactive medication	0.36	1.44	0.59	3.50	0.42
BMI (kg/m^2)	-0.13	0.88	0.81	0.95	**<0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL score	-0.06	0.94	0.85	1.04	0.26
CAMCOG total score	-0.04	0.96	0.92	1.00	0.05

The criteria for CSH were arbitrarily defined in young men. To establish if the criteria for CSH are too sensitive when using beat-to-beat monitoring, new thresholds for CSH were defined based on haemodynamic response observed in a subgroup that had no history of falls syncope or dizziness at baseline and had an MMSE≥24 at baseline. The 95th percentile for systolic vasodepression was 76.6 mmHg and the 95th percentile for RR interval post CSM was 7.3 seconds. These thresholds were used to define CSH modified criteria.

Twenty-three individuals had CSH defined according to modified criteria. In age and sex adjusted models there was a significant association between CSH defined according to modified criteria and mortality [HR 2.37, P=0.02] (Figure 8-1). This remained significant after adjusting for baseline cardiovascular risk factors and functional status (Table 8-32).

Figure 8-1 Survival Curve Comparing Survival Among Participants With and Without CSH Defined According to Modified Criteria. Graph Shows Data Adjusted for Age and Sex.

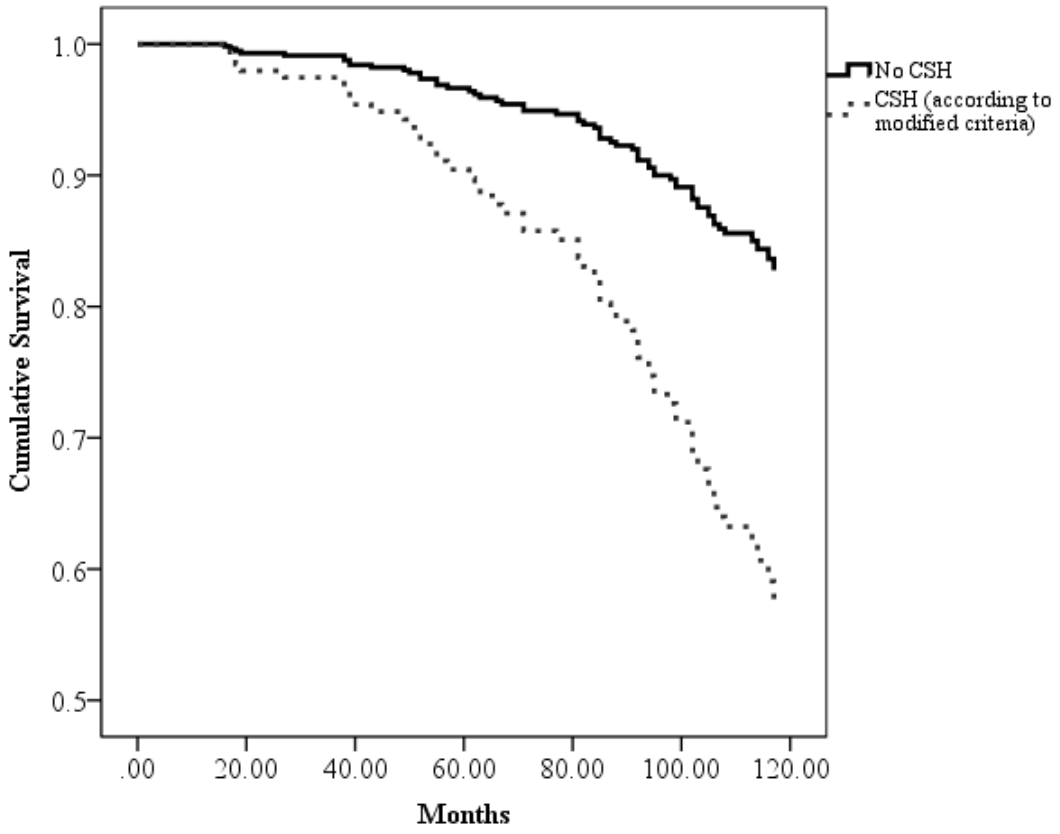

Table 8-32 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with CSH Defined According to Modified Criteria

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.13	1.14	1.10	1.19	**<0.01**
Sex	0.56	1.75	1.02	3.00	**0.04**
CSH defined by modified criteria	0.86	2.37	1.16	4.87	**0.02**
Model 2					
Age (years)	0.11	1.12	1.07	1.17	**<0.01**
Sex	0.51	1.66	0.94	2.92	0.08
CSH defined by modified criteria	0.82	2.26	1.09	4.70	**0.03**
CVD	-0.44	0.65	0.30	1.41	0.27
Diabetes	0.12	1.13	0.46	2.78	0.79
Pack years	0.01	1.01	1.00	1.02	0.13
Cardioactive medication	0.64	1.89	0.86	4.16	0.11
BMI (kg/m^2)	-0.10	0.91	0.84	0.98	**0.01**
Mean SBP	0.01	1.01	1.00	1.03	0.13
Model 3					
Age (years)	0.15	1.16	1.10	1.22	**<0.01**
Sex	0.32	1.38	0.73	2.60	0.32
CSH defined by modified criteria	1.02	2.78	1.18	6.52	**0.02**
CVD	0.04	1.04	0.42	2.55	0.93
Diabetes	1.10	3.01	1.16	7.78	**0.02**
Pack years	0.01	1.01	1.00	1.03	0.09
Cardioactive medication	0.31	1.37	0.58	3.25	0.48
BMI (kg/m^2)	-0.14	0.87	0.79	0.95	**<0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.05	**<0.01**
Bristol ADL score	-0.14	0.87	0.67	1.13	0.30
Model 4					
Age (years)	0.13	1.14	1.08	1.20	**<0.01**
Sex	0.40	1.50	0.80	2.82	0.21
CSH defined by modified criteria	1.01	2.76	1.18	6.43	**0.02**
CVD	0.05	1.05	0.43	2.59	0.91
Diabetes	1.14	3.13	1.20	8.14	**0.02**
Pack years	0.01	1.01	1.00	1.03	0.06
Cardioactive medication	0.23	1.25	0.53	2.99	0.61
BMI (kg/m^2)	-0.16	0.85	0.78	0.94	**<0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.05	**<0.01**
Bristol ADL score	-0.26	0.77	0.58	1.04	0.09
CAMCOG total score	-0.06	0.94	0.90	0.99	**<0.01**

8.3.5 **Survival and Response to Autonomic Function Tests**

Three hundred and twenty-one had data from at least one autonomic function test (AFT) suitable for analysis. Of these, 231 had adequate data from all five AFT. Comparing participants who died during follow-up with those who were alive at the end of follow-up showed that the Valsalva ratio was significantly smaller in the group who had died. Statistically significant differences were not seen in response to the other AFT.

Response to Autonomic Function tests among Participants who died During Follow-up versus those who were Alive at the End of the Study

	Alive N=223	**Dead N= 74**	**P**
	Mean (SD)	**Mean (SD)**	
Best Valsalva Ratio	1.51 (0.29)	1.39 (0.24)	**<0.01**
Heart rate response to deep breathing	7.86 (4.45)	8.48 (6.36)	0.37
30: 15 Ratio	1.15 (0.09)	1.15 (0.29)	0.90
Active sit difference in DBP (mmHg)	12.4 (13.1)	13.1 (12.3)	0.70
Valsalva BP overshoot (mmHg)	27.3 (24.7)	21.2 (24.9)	0.12
DBP rise with cold pressor (mmHg)	9.82 (9.1)	8.4 (11.3)	0.30

8.3.5.1 Normal v. Abnormal Autonomic Function

Two hundred and fifty two individuals had sufficient tests to classify their function as normal or abnormal by modified Ewing criteria. Cox regression was used to establish if abnormal autonomic function at baseline was associated with survival.

After adjusting for age and sex, abnormal autonomic function was not associated with survival. Further models adjusting in turn for cardiovascular risk factors, baseline functional status and baseline cognitive function did not show any association between abnormal autonomic function and survival (Table 8-33).

Table 8-33 Cox Regression Models. Hazard Ratio of All-Cause Mortality According Associated with Abnormal Autonomic Function at Baseline.

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.05	1.06	1.02	1.09	**<0.01**
Sex	-0.35	0.71	0.44	1.15	0.16
Abnormal autonomic function	-0.15	0.86	0.53	1.41	0.56
Model 2					
Age (years)	0.05	1.05	1.02	1.09	**<0.01**
Sex	-0.35	0.71	0.42	1.18	0.19
Abnormal autonomic function	-0.06	0.94	0.56	1.59	0.83
CVD	-0.46	0.63	0.25	1.55	0.31
Diabetes	0.23	1.25	0.58	2.71	0.57
Pack Years	0.01	1.01	1.00	1.02	**0.04**
Cardioactive Medication	0.14	1.15	0.46	2.86	0.76
BMI (kg/m^2)	-0.03	0.97	0.90	1.04	0.38
Mean SBP (mmHg)	0.01	1.01	0.99	1.02	0.22
Model 3					
Age (years)	0.07	1.07	1.03	1.12	**<0.01**
Sex	-0.27	0.77	0.44	1.35	0.36
Abnormal autonomic function	-0.33	0.72	0.41	1.25	0.25
CVD	-0.39	0.68	0.20	2.25	0.52
Diabetes	0.14	1.15	0.48	2.78	0.75
Pack Years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	0.05	1.05	0.33	3.34	0.93
BMI (kg/m^2)	-0.06	0.94	0.86	1.02	0.15
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL Score	0.02	1.02	0.87	1.20	0.80
Model 4					
Age (years)	0.06	1.06	1.02	1.11	**<0.01**
Sex	-0.29	0.75	0.42	1.31	0.31
Abnormal autonomic function	-0.42	0.66	0.37	1.15	0.14
CVD	-0.45	0.64	0.19	2.11	0.46
Diabetes	0.11	1.12	0.46	2.71	0.80
Pack Years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	-0.01	0.99	0.31	3.15	0.99
BMI (kg/m^2)	-0.07	0.94	0.86	1.02	0.14
Mean SBP (mmHg)	0.03	1.03	1.01	1.05	**<0.01**
Bristol ADL Score	-0.04	0.96	0.80	1.15	0.65
CAMCOG total score	-0.04	0.96	0.92	1.01	0.11

Cox regression models were formulated to examine if responses to individual autonomic function tests were associated with survival at ten years.

8.3.5.2 Stand 30:15 ratio

Two-hundred participants underwent active stand and had heart rate recordings adequate for analysis. The 30:15 ratio was not associated with survival in the age and sex adjusted model. Adjusting for cardiovascular risk factors, functional status at baseline or baseline cognition did not reveal any association between 30:15 ratio and survival (Table 8-34).

8.3.5.3 Active sit

Adequate BP recordings in response to isometric exercise were available for 297 participants. Rise in diastolic BP in response to isometric exercise was not associated with survival in age and sex adjusted models or subsequent models (Table 8-35).

8.3.5.4 Heart Rate and BP response to Valsalva Manoeuvre

Three hundred participants had results from one or more Valsalva manoeuvres suitable for analysis. There was a borderline association between Valsalva ratio and survival in the age and sex adjusted model P= 0.07 (Table 8-36). In models adjusted for cardiovascular risk factors, functional status at baseline and baseline cognitive function, this relationship was not apparent (Table 8-36).

Cox regression did not reveal a significant association between Valsalva phase four systolic BP overshoot and survival in any of the models (Table 8-37).

8.3.5.5 Cold Pressor Test

Two hundred and eighty three participants completed the cold pressor test and had recordings suitable for analysis. Diastolic BP rise with cold pressor was not associated with survival in age and sex adjusted models or subsequent models (Table 8-38).

8.3.5.6 Deep Breathing

Recordings suitable to determine heart rate response to deep breathing were available for 289 participants. Heart rate response to deep breathing was not associated with survival in any of the models (Table 8-39).

Table 8-34 Cox Regression Models. Hazard Ratio of All-Cause Mortality According to Active Stand 30:15 ratio

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.12	1.12	1.09	1.16	**<0.01**
Sex	-0.48	0.62	0.39	1.00	**0.05**
30:15 ratio	0.36	1.43	0.39	5.26	0.59
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.43	0.65	0.40	1.06	0.08
30:15 ratio	0.28	1.33	0.46	3.85	0.61
CVD	-0.38	0.68	0.28	1.65	0.40
Diabetes	0.38	1.47	0.68	3.18	0.33
Pack Years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	0.67	1.96	0.80	4.80	0.14
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.11
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.03**
Model 3					
Age (years)	0.11	1.12	1.07	1.17	**<0.01**
Sex	-0.17	0.84	0.50	1.43	0.53
30:15 ratio	0.46	1.59	0.55	4.56	0.39
CVD	-0.04	0.96	0.35	2.64	0.94
Diabetes	0.78	2.17	0.91	5.21	0.08
Pack Years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	0.49	1.63	0.60	4.43	0.34
BMI (kg/m^2)	-0.11	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.06	1.06	0.89	1.27	0.49
Model 4					
Age (years)	0.10	1.11	1.06	1.15	**<0.01**
Sex	-0.20	0.82	0.48	1.39	0.45
30:15 ratio	0.39	1.47	0.49	4.44	0.49
CVD	-0.04	0.96	0.36	2.60	0.94
Diabetes	0.75	2.11	0.88	5.09	0.10
Pack Years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	0.42	1.53	0.57	4.10	0.40
BMI (kg/m^2)	-0.10	0.90	0.83	0.98	**0.01**
Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.01	1.01	0.83	1.22	0.96
CAMCOG total score	-0.04	0.96	0.92	1.00	0.07

Table 8-35 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Response to Active Sit.

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.12	1.12	1.09	1.16	**<0.01**
Sex	-0.44	0.64	0.40	1.03	0.07
DBP rise with isometric exercise (mmHg)	0.01	1.01	0.99	1.02	0.43
Model 2					
Age (years)	0.10	1.10	1.07	1.14	**<0.01**
Sex	-0.38	0.69	0.42	1.11	0.13
DBP rise with isometric exercise (mmHg)	0.01	1.01	0.99	1.02	0.43
CVD	-0.28	0.76	0.31	1.84	0.54
Diabetes	0.05	1.05	0.44	2.50	0.92
Pack Years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	0.66	1.93	0.79	4.72	0.15
BMI (kg/m^2)	-0.06	0.95	0.88	1.01	0.12
Mean SBP (mmHg)	0.01	1.01	1.00	1.03	0.14
Model 3					
Age (years)	0.11	1.12	1.08	1.17	**<0.01**
Sex	-0.14	0.87	0.52	1.48	0.61
DBP rise with isometric exercise (mmHg)	0.00	1.00	0.98	1.02	0.98
CVD	0.23	1.26	0.47	3.39	0.64
Diabetes	0.53	1.70	0.68	4.23	0.26
Pack Years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive Medication	0.44	1.55	0.59	4.08	0.38
BMI (kg/m^2)	-0.11	0.90	0.82	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.03**
Bristol ADL Score	0.03	1.03	0.96	1.11	0.45
Model 4					
Age (years)	0.11	1.11	1.07	1.16	**<0.01**
Sex	-0.16	0.85	0.50	1.45	0.56
DBP rise with isometric exercise (mmHg)	0.00	1.00	0.98	1.02	0.82
CVD	0.19	1.22	0.45	3.26	0.70
Diabetes	0.49	1.63	0.65	4.08	0.29
Pack Years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive Medication	0.42	1.52	0.58	4.03	0.40
BMI (kg/m^2)	-0.11	0.90	0.83	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.03**
Bristol ADL Score	0.00	1.00	0.92	1.10	0.96
CAMCOG total score	-0.02	0.98	0.93	1.02	0.28

Table 8-36 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Response to Valsalva Manoeuvre (Valsalva Ratio).

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.10	1.10	1.07	1.14	**<0.01**
Sex	-0.46	0.63	0.40	1.01	**0.05**
Valsalva ratio	-0.90	0.41	0.16	1.06	0.07
Model 2					
Age (years)	0.09	1.09	1.05	1.13	**<0.01**
Sex	-0.40	0.67	0.42	1.08	0.10
Valsalva ratio	-0.79	0.45	0.16	1.27	0.13
CVD	-0.50	0.61	0.24	1.52	0.29
Diabetes	0.13	1.14	0.50	2.58	0.75
Pack Years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	0.57	1.77	0.71	4.41	0.22
BMI (kg/m^2)	-0.05	0.95	0.89	1.02	0.15
Mean SBP (mmHg)	0.01	1.01	1.00	1.03	0.06
Model 3					
Age (years)	0.09	1.10	1.05	1.14	<0.01
Sex	-0.19	0.83	0.50	1.39	0.48
Valsalva ratio	-0.85	0.43	0.13	1.35	0.15
CVD	-0.01	0.99	0.38	2.64	0.99
Diabetes	0.53	1.70	0.73	4.01	0.22
Pack Years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	0.29	1.33	0.51	3.47	0.56
BMI (kg/m^2)	-0.10	0.90	0.83	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.02	1.02	0.94	1.10	0.66
Model 4					
Age (years)	0.09	1.09	1.04	1.13	**<0.01**
Sex	-0.20	0.82	0.49	1.37	0.45
Valsalva ratio	-0.79	0.45	0.14	1.42	0.17
CVD	-0.05	0.95	0.36	2.51	0.92
Diabetes	0.49	1.64	0.69	3.87	0.26
Pack Years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive Medication	0.28	1.32	0.51	3.42	0.57
BMI (kg/m^2)	-0.11	0.90	0.83	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	-0.02	0.98	0.90	1.08	0.73
CAMCOG total score	-0.03	0.97	0.93	1.01	0.17

Table 8-37 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Response to Valsalva Manoeuvre (Valsalva Overshoot)

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.11	1.11	1.08	1.15	**<0.01**
Sex	-0.43	0.65	0.41	1.04	0.07
Valsalva overshoot (mmHg)	0.00	1.00	0.99	1.01	0.98
Model 2					
Age (years)	0.09	1.10	1.06	1.14	**<0.01**
Sex	-0.38	0.69	0.42	1.11	0.12
Valsalva overshoot (mmHg)	0.00	1.00	0.99	1.01	0.69
CVD	-0.36	0.70	0.29	1.70	0.43
Diabetes	0.26	1.30	0.57	2.93	0.53
Pack Years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive Medication	0.61	1.84	0.76	4.48	0.18
BMI (kg/m^2)	-0.05	0.95	0.89	1.02	0.14
Mean SBP (mmHg)	0.01	1.01	1.00	1.03	0.09
Model 3					
Age (years)	0.10	1.11	1.06	1.15	**<0.01**
Sex	-0.19	0.83	0.50	1.38	0.47
Valsalva overshoot (mmHg)	0.00	1.00	0.99	1.02	0.57
CVD	0.12	1.12	0.43	2.91	0.81
Diabetes	0.68	1.97	0.84	4.61	0.12
Pack Years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	0.38	1.46	0.57	3.78	0.43
BMI (kg/m^2)	-0.10	0.90	0.83	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL Score	0.03	1.03	0.96	1.11	0.40
Model 4					
Age (years)	0.09	1.10	1.05	1.14	**<0.01**
Sex	-0.21	0.81	0.48	1.36	0.43
Valsalva overshoot (mmHg)	0.00	1.00	0.99	1.02	0.54
CVD	0.07	1.07	0.41	2.77	0.89
Diabetes	0.64	1.89	0.80	4.45	0.15
Pack Years	0.01	1.01	1.00	1.02	**<0.01**
Cardioactive Medication	0.36	1.43	0.55	3.69	0.46
BMI (kg/m^2)	-0.11	0.90	0.83	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**<0.01**
Bristol ADL Score	0.00	1.00	0.91	1.09	0.92
CAMCOG total score	-0.03	0.97	0.93	1.01	0.13

Table 8-38 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Response to Cold Pressor Test

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.12	1.12	1.08	1.16	**<0.01**
Sex	-0.42	0.66	0.41	1.06	0.09
DBP rise with cold pressor (mmHg)	-0.01	0.99	0.96	1.01	0.31
Model 2					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	-0.33	0.72	0.44	1.17	0.19
DBP rise with cold pressor	-0.02	0.98	0.96	1.01	0.15
CVD	0.00	1.00	0.41	2.45	0.99
Diabetes	0.62	1.86	0.82	4.21	0.14
Pack Years	0.01	1.01	1.00	1.02	**0.02**
Cardioactive Medication	0.41	1.51	0.61	3.72	0.37
BMI (kg/m^2)	-0.07	0.93	0.87	1.00	**0.04**
Mean SBP (mmHg)	0.01	1.01	1.00	1.03	0.13
Model 3					
Age (years)	0.11	1.11	1.07	1.16	**<0.01**
Sex	-0.14	0.87	0.51	1.46	0.59
DBP rise with cold pressor (mmHg)	-0.01	0.99	0.96	1.02	0.42
CVD	0.20	1.23	0.47	3.21	0.68
Diabetes	0.60	1.82	0.77	4.28	0.17
Pack Years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	0.32	1.38	0.53	3.58	0.51
BMI (kg/m^2)	-0.10	0.91	0.84	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL Score	0.02	1.02	0.94	1.10	0.64
Model 3					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.17	0.85	0.50	1.43	0.54
DBP rise with cold pressor	-0.01	0.99	0.96	1.01	0.37
CVD	0.16	1.17	0.45	3.05	0.74
Diabetes	0.55	1.74	0.74	4.12	0.21
Pack Years	0.01	1.01	1.00	1.02	**0.01**
Cardioactive Medication	0.32	1.37	0.53	3.55	0.51
BMI (kg/m^2)	-0.10	0.90	0.84	0.98	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL Score	-0.01	0.99	0.90	1.09	0.85
CAMCOG total score	-0.03	0.98	0.93	1.02	0.26

Table 8-39 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Heart Rate Response to Deep Breathing.

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.11	1.12	1.08	1.16	**<0.01**
Sex	-0.37	0.69	0.43	1.11	0.13
Heart rate response to deep breathing	0.02	1.02	0.99	1.06	0.22
Model 2					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	-0.34	0.71	0.44	1.17	0.18
Heart rate response to deep breathing	0.03	1.03	0.99	1.07	0.18
CVD	-0.28	0.76	0.30	1.89	0.55
Diabetes	0.31	1.37	0.61	3.08	0.45
Pack Years	0.01	1.01	1.01	1.02	**<0.01**
Cardioactive Medication	0.48	1.62	0.66	3.95	0.29
BMI (kg/m^2)	-0.06	0.94	0.87	1.01	0.09
Mean SBP(mmHg)	0.01	1.01	1.00	1.03	0.16
Model 3					
Age (years)	0.11	1.11	1.07	1.16	**<0.01**
Sex	-0.10	0.90	0.53	1.54	0.71
Heart rate response to deep breathing	0.02	1.02	0.97	1.07	0.38
CVD	0.20	1.22	0.45	3.31	0.70
Diabetes	0.78	2.18	0.92	5.19	0.08
Pack Years	0.02	1.02	1.01	1.03	**<0.01**
Cardioactive Medication	0.20	1.22	0.47	3.19	0.68
BMI (kg/m^2)	-0.11	0.90	0.83	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL Score	0.02	1.03	0.95	1.10	0.50
Model 4					
Age (years)	0.10	1.11	1.06	1.16	**<0.01**
Sex	-0.12	0.89	0.52	1.52	0.67
Heart rate response to deep breathing	0.02	1.02	0.97	1.06	0.52
CVD	0.17	1.19	0.44	3.25	0.73
Diabetes	0.75	2.13	0.89	5.07	0.09
Pack Years	0.02	1.02	1.01	1.03	**<0.01**
Cardioactive Medication	0.16	1.18	0.45	3.11	0.74
BMI (kg/m^2)	-0.11	0.90	0.83	0.97	**0.01**
Mean SBP (mmHg)	0.02	1.02	1.01	1.04	**0.01**
Bristol ADL Score	0.00	1.00	0.91	1.09	0.94
CAMCOG total score	-0.03	0.97	0.93	1.02	0.24

8.3.6 **Survival and Heart Rate Variability**

Two hundred and eighty participants underwent heart rate variability recordings and had recordings with less than 10% interpolated or ectopic beats. Of these participants, 72 died during follow-up. Participants who died had significantly lower total power and LF HRV at baseline. Other measures of HRV did not significantly differ between those alive at end of follow-up and those who had died.

Table 8-40 Heart Rate Variability among Participants who Died During Follow-up versus Participants alive in October 2012

	Alive	**Dead**	**P**
	208	**72**	
	Median (IQR)	**Median (IQR)**	
SDNN	27.4 (19.1, 36.3)	24.2 (17.9, 31.9)	0.10
Total Power	438.9 (218.3, 972.5)	330.0 (134.9, 698.7)	**<0.05**
VLF	152.0 (83.7, 343.0)	120.7 (58.6, 319.4)	0.10
Low frequency	172.3 (73.2, 350.0)	107.3 (49.4, 274.3)	**0.03**
High frequency	72.5 (32.7, 155.3)	50.3 (19.3, 150.8)	0.09
HF/ LF	0.39 (0.23, 0.77)	0.48 (0.24, 0.96)	0.49

None of the markers of heart rate variability were related to survival in age and sex adjusted models (Table 8-41, Table 8-42, Table 8-43, Table 8-44 and Table 8-45). Further adjusting models for cardiovascular risk factors, baseline functional status and cognitive function did not reveal any significant relationships between heart rate variability and survival (Table 8-41, Table 8-42, Table 8-43, Table 8-44 and Table 8-45).

Table 8-41 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Total Power

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.17	**<0.01**
Sex	0.45	1.57	0.97	2.55	0.07
Total power	0.00	1.00	1.00	1.00	0.42
Model 2					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	0.43	1.53	0.92	2.55	0.10
Total power	0.00	1.00	1.00	1.00	0.28
Cardiovascular Disease	-0.67	0.51	0.22	1.19	0.12
Diabetes	0.21	1.24	0.57	2.69	0.59
Pack years	0.01	1.01	1.00	1.02	**0.04**
Cardioactive medication	0.92	2.52	1.06	5.96	**0.04**
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.09
daytime Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.03**
Model 3					
Age (years)	0.12	1.13	1.08	1.19	**<0.01**
Sex	0.23	1.26	0.73	2.18	0.40
Total power	0.00	1.00	1.00	1.00	0.09
Cardiovascular Disease	-0.15	0.86	0.33	2.26	0.76
Diabetes	0.63	1.87	0.80	4.35	0.15
Pack years	0.01	1.01	1.00	1.02	**0.06**
Cardioactive medication	0.66	1.94	0.72	5.21	0.19
BMI (kg/m^2)	-0.12	0.89	0.82	0.97	**0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.02	1.02	0.94	1.10	0.65
Model 4					
Age (years)	0.11	1.12	1.06	1.17	**<0.01**
Sex	0.27	1.31	0.76	2.27	0.33
Total power	0.00	1.00	1.00	1.00	0.09
Cardiovascular Disease	-0.14	0.87	0.34	2.20	0.76
Diabetes	0.60	1.82	0.78	4.22	0.16
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.61	1.84	0.71	4.80	0.21
BMI (kg/m^2)	-0.12	0.89	0.82	0.96	**<0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	-0.02	0.98	0.90	1.07	0.71
Total CAMCOG Score	-0.03	0.97	0.93	1.01	0.14

Table 8-42 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Very Low Frequency

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.17	**<0.01**
Sex	0.44	1.55	0.95	2.52	0.08
Very Low Frequency	0.00	1.00	1.00	1.00	0.70
Model 2					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	0.41	1.51	0.90	2.52	0.12
Very Low Frequency	0.00	1.00	1.00	1.00	0.54
Cardiovascular Disease	-0.66	0.52	0.22	1.20	0.12
Diabetes	0.23	1.26	0.58	2.73	0.56
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.93	2.52	1.07	5.97	**0.04**
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.10
daytime Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.03**
Model 3					
Age (years)	0.12	1.13	1.08	1.19	**<0.01**
Sex	0.24	1.27	0.73	2.20	0.39
Very Low Frequency	0.00	1.00	1.00	1.00	0.20
Cardiovascular Disease	-0.15	0.86	0.33	2.26	0.76
Diabetes	0.61	1.84	0.79	4.25	0.16
Pack years	0.01	1.01	1.00	1.02	0.07
Cardioactive medication	0.67	1.95	0.73	5.23	0.19
BMI (kg/m^2)	-0.11	0.89	0.82	0.97	**0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.02	1.02	0.95	1.10	0.62
Model 4					
Age (years)	0.11	1.12	1.07	1.18	**<0.01**
Sex	0.28	1.33	0.76	2.30	0.32
Very Low Frequency	0.00	1.00	1.00	1.00	0.18
Cardiovascular Disease	-0.14	0.87	0.34	2.19	0.76
Diabetes	0.58	1.78	0.77	4.12	0.18
Pack years	0.01	1.01	1.00	1.02	0.06
Cardioactive medication	0.62	1.86	0.71	4.83	0.21
BMI (kg/m^2)	-0.12	0.89	0.82	0.97	**0.01**
daytime Mean SBP	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	-0.02	0.98	0.90	1.07	0.72
Total CAMCOG Score	-0.03	0.97	0.93	1.01	0.12

Table 8-43 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with Low Frequency HRV

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.17	**<0.01**
Sex	0.47	1.59	0.98	2.58	0.06
Low Frequency	0.00	1.00	1.00	1.00	0.29
Model 2					
Age (years)	0.10	1.10	1.06	1.14	**<0.01**
Sex	0.44	1.55	0.93	2.56	0.09
Low Frequency	0.00	1.00	1.00	1.00	0.20
Cardiovascular Disease	-0.65	0.52	0.23	1.20	0.13
Diabetes	0.20	1.22	0.56	2.66	0.61
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.91	2.48	1.05	5.87	**0.04**
BMI (kg/m^2)	-0.06	0.94	0.88	1.01	0.08
daytime Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.03**
Model 3					
Age (years)	0.12	1.13	1.08	1.18	**<0.01**
Sex	0.23	1.26	0.73	2.17	0.40
Low Frequency	0.00	1.00	1.00	1.00	0.12
Cardiovascular Disease	-0.16	0.85	0.32	2.26	0.75
Diabetes	0.61	1.84	0.79	4.26	0.16
Pack years	0.01	1.01	1.00	1.02	0.06
Cardioactive medication	0.66	1.94	0.72	5.26	0.19
BMI (kg/m^2)	-0.11	0.89	0.82	0.97	**0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.02	1.02	0.95	1.10	0.62
Model 4					
Age (years)	0.11	1.12	1.06	1.17	**<0.01**
Sex	0.27	1.32	0.76	2.28	0.33
Low Frequency	0.00	1.00	1.00	1.00	0.11
Cardiovascular Disease	-0.16	0.86	0.34	2.18	0.74
Diabetes	0.58	1.78	0.77	4.12	0.18
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	0.61	1.83	0.70	4.81	0.22
BMI (kg/m^2)	-0.12	0.89	0.82	0.97	**0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	-0.02	0.98	0.90	1.08	0.71
Total CAMCOG Score	-0.03	0.97	0.93	1.01	0.12

Table 8-44 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with High Frequency Heart Rate Variability

Model 1	B	HR	95% CI		P
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.17	**<0.01**
Sex	-0.42	0.66	0.41	1.06	0.09
High Frequency	0.00	1.00	1.00	1.00	0.54
Model 2					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.38	0.68	0.41	1.13	0.14
High Frequency	0.00	1.00	1.00	1.00	0.38
Cardiovascular Disease	-0.67	0.51	0.22	1.19	0.12
Diabetes	0.24	1.27	0.58	2.76	0.55
Pack years	0.01	1.01	1.00	1.02	**0.04**
Cardioactive medication	0.92	2.51	1.06	5.93	**0.04**
BMI (kg/m^2)	-0.06	0.95	0.88	1.01	0.11
daytime Mean SBP (mmHg)	0.02	1.02	1.00	1.03	**0.04**
Model 3					
Age (years)	0.13	1.13	1.08	1.19	**<0.01**
Sex	-0.15	0.86	0.50	1.48	0.59
High Frequency	0.00	1.00	1.00	1.00	0.17
Cardiovascular Disease	0.16	1.17	0.44	3.08	0.75
Diabetes	-0.70	0.50	0.21	1.18	0.11
Pack years	0.01	1.01	1.00	1.02	0.06
Cardioactive medication	-0.69	0.50	0.19	1.35	0.17
BMI (kg/m^2)	-0.11	0.89	0.82	0.97	**0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.04	**<0.01**
Bristol ADL Score	0.02	1.02	0.95	1.09	0.63
Model 4					
Age (years)	0.11	1.12	1.07	1.18	**<0.01**
Sex	-0.18	0.83	0.48	1.44	0.51
High Frequency	0.00	1.00	1.00	1.00	0.19
Cardiovascular Disease	0.16	1.17	0.46	2.99	0.74
Diabetes	-0.68	0.51	0.21	1.19	0.12
Pack years	0.01	1.01	1.00	1.02	**0.05**
Cardioactive medication	-0.63	0.53	0.20	1.39	0.20
BMI (kg/m^2)	-0.12	0.89	0.82	0.97	**0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.05	**<0.01**
Bristol ADL Score	-0.01	0.99	0.90	1.08	0.77
Total CAMCOG Score	-0.03	0.97	0.93	1.01	0.18

Table 8-45 Cox Regression Models. Hazard Ratio of All-Cause Mortality Associated with HFLF ratio

Model 1	**B**	**HR**	**95% CI**		**P**
			Lower	Upper	
Age (years)	0.12	1.13	1.09	1.17	**<0.01**
Sex	-0.40	0.67	0.41	1.08	0.10
HF:LF	-0.10	0.91	0.70	1.18	0.48
Model 2					
Age (years)	0.10	1.10	1.06	1.15	**<0.01**
Sex	-0.35	0.70	0.43	1.17	0.17
HF:LF	-0.13	0.87	0.67	1.14	0.33
Cardiovascular Disease	0.73	2.08	0.88	4.94	0.10
Diabetes	-0.24	0.79	0.36	1.71	0.54
Pack years	0.01	1.01	1.00	1.02	**0.04**
Cardioactive medication	-1.02	0.36	0.15	0.88	**0.03**
BMI (kg/m^2)	-0.05	0.95	0.89	1.02	0.13
daytime Mean SBP (mmHg)	0.01	1.01	1.00	1.03	**0.04**
Model 3					
Age (years)	0.13	1.14	1.08	1.19	**<0.01**
Sex	-0.08	0.92	0.53	1.60	0.77
HF:LF	-0.33	0.72	0.50	1.04	0.08
Cardiovascular Disease	0.26	1.29	0.47	3.58	0.62
Diabetes	-0.75	0.47	0.20	1.11	0.09
Pack years	0.01	1.01	1.00	1.02	0.10
Cardioactive medication	-0.90	0.41	0.14	1.16	0.09
BMI (kg/m^2)	-0.11	0.90	0.82	0.97	**0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.05	**<0.01**
Bristol ADL Score	0.02	1.02	0.95	1.10	0.53
Model 4					
Age (years)	0.12	1.12	1.07	1.18	**<0.01**
Sex	-0.12	0.89	0.51	1.55	0.68
HF:LF	-0.33	0.72	0.49	1.05	0.08
Cardiovascular Disease	0.25	1.29	0.48	3.46	0.62
Diabetes	-0.75	0.47	0.20	1.11	0.09
Pack years	0.01	1.01	1.00	1.02	0.10
Cardioactive medication	-0.84	0.43	0.16	1.21	0.11
BMI (kg/m^2)	-0.11	0.89	0.82	0.97	**0.01**
daytime Mean SBP (mmHg)	0.03	1.03	1.01	1.05	**<0.01**
Bristol ADL Score	-0.01	0.99	0.91	1.08	0.83
Total CAMCOG Score	-0.03	0.97	0.93	1.01	0.15

8.4 **Discussion**

8.4.1 **Hypertension**

Hypertension is considered a risk factor for all-cause mortality in all age groups (Lewington et al., 2002). In this cohort, hypertension was not associated with mortality in age and sex adjusted models, or in models adjusting for cardiovascular risk factors. The addition of a term controlling for baseline functional status however did reveal a significant association between hypertension and increased mortality. Similar results were found when 24-hour and daytime mean systolic BP and mean daytime diastolic BP were entered into the models as a continuous variable.

Two studies by Oden et al have also shown an interaction between functional status, hypertension, and mortality among older individual (Odden et al., 2012a, Odden et al., 2012b). The first study accessed functional status by self-reported walking speed. The relationship between systolic BP and mortality varied according to reported walking speed. In high-functioning older adults, elevated systolic BP was a risk factor for all-cause mortality but not in adults with slower walking speed(Odden et al., 2012a). In the second study, time to walk 20m was recorded in 2097 adults aged 65 years and older. Among fast walkers, elevated systolic BP >140 mmHg was associated with increased mortality (Odden et al., 2012b). Among slow walkers, neither systolic nor diastolic BP were associated with mortality. Further analysis stratified participants by age (above 75 years and below 75 years). Elevated systolic BP remained associated with increased mortality among fast walkers aged 75 years and older, but not among fast walkers less than 75 years, suggesting that the interaction between functional status and hypertension may increase with age. Finally, the group examined the association between BP and mortality among the 243 older people unable to complete the 20m walk due to frailty. In this group, higher systolic BP was associated with reduced mortality, supporting the hypothesis that in frail older people hypertension may be beneficial. Although hypertension is generally considered a risk factor for all-cause mortality in all ages these data suggest that frailty may play an important role in modifying the relationship.

Further evidence to suggest that hypertension is associated with all-cause mortality among fitter very elderly patients comes from the HYVETT study which showed antihypertensive treatment is associated with reduced all-cause mortality in the

elderly(Beckett et al., 2012). However, owing to the inclusion criteria, participants in these trials were healthier than the general older population and it remains unclear if antihypertensive treatment reduces mortality in frail older people.

8.4.2 **Blood Pressure variability**

In this study, 24-hour systolic and diastolic BP variability and daytime systolic BP variability were not associated with mortality in models adjusting for age, sex, and cardiovascular risk factors. However, as occurred with hypertension, they were associated with mortality when baseline functional status was added to the model. Greater daytime diastolic BP variability was associated with increased mortality in all models. Night-time blood pressure variability was not associated with mortality.

A recently published study from the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome examined the association between BP variability and mortality in 8938 participants from 11 countries across 3 continents (Hansen et al., 2010). Mean age of participants was 53 years, median follow-up 11.3 years. Measures of variability included SD24 (BP variability over 24-hour), SDdn (SD day night - the mean of day and night SD) and the average real 24-hour variability (24 ARV - the average of the absolute differences of consecutive measurements). In fully adjusted models, greater systolic SDdn and 24 ARV were associated with increased all-cause mortality, as were diastolic SD24, SDdn and 24 ARV. In keeping with the findings of the current study, Hansen et al found Diastolic BP variability tended to be a stronger predictor of outcome than systolic BP variability (Hansen et al., 2010). In the PAMELA study, systolic BP variability was not associated with mortality in adjusted models, whereas daytime and night-time diastolic BP variability were associated with mortality in adjusted models (Sega et al., 2005).

8.4.3 **Orthostatic hypotension**

In this study, orthostatic hypotension defined according to standard criteria was not associated with ten year mortality. Nor were systolic or diastolic OH when examined separately. Similarly, systolic and diastolic vasodepression in response to standing were not associated with mortality.

These results are in contrast to several large population-based studies examining the association between OH and all-cause mortality. The Malmo, Rotterdam, ARIC and

Honolulu heart studies have between them included over 50 000 middle aged and elderly participants (Fedorowski et al., 2010, Verwoert et al., 2008, Rose et al., 2006, Masaki et al., 1998). Follow-up periods ranged from 4 – 24 years. In each case, these studies showed an association between OH defined according to AAN criteria and increased adjusted all-cause mortality. Furthermore, the Malmo and Honolulu studies showed an association between degree of vasodepression and mortality (Fedorowski et al., 2010, Masaki et al., 1998).

It is important to note that all these studies used a sphygmomanometer to record BP in the lying and standing position at predefined interval (number of recordings and interval between recordings differed between studies). There are no studies reporting mortality in association with OH diagnosed using beat-to-beat BP. As has been previously discussed, beat-to-beat monitoring is a more sensitive way of diagnosing OH. Methods using a sphygmomanometer to record BP intermittently risk overlooking short-lived drops in BP or missing the BP nadir and therefore underestimate the prevalence of OH. As a result, these methods are only likely to detect more severe, prolonged drops in BP. In this study, prevalence of OH according to AAN criteria was 71%. This is in keeping with other population-based studies that have found a high prevalence of OH using beat-to-beat monitoring and the AAN definition (Romero-Ortuno et al., 2011b). Using intermittent sphygmomanometer recordings, the Malmo, Rotterdam, ARIC and Honolulu studies have reported the prevalence of OH to be 6.2%, 17.8%, 5.0%, and 6.9% respectively. It is likely that when using beat-to-beat monitoring the AAN criteria are too sensitive. OH, defined according modified criteria derived using beat-to-beat responses from baseline normal subsample was not associated with survival. Further analysis examining if symptomatic OH was associated with increased mortality also failed to reveal any significant association between symptomatic OH and survival in this cohort

8.4.4 **CSH**

In this study, CSH defined according to standard criteria was not associated with mortality. Similarly, mortality was not associated with Maximum RR interval post CSM or maximum vasodepression post CSM. Our findings are in keeping with two other studies reporting an association between CSH and mortality. Hampton et al examined mortality among1504 patients with CSH identified from a single syncope centre. Standardised mortality rates (SMRs) were compared with regional age-matched SMR

data from the Office of National Statistics. There was no difference between CSH patients and the general population in SMRs for all causes (Hampton et al., 2011). Comparable results were reported in a similar smaller study by Brignole et al (Brignole et al., 1992). CSH defined according to modified criteria, derived from the asymptomatic baseline population, was, however, associated with increased risk or mortality. This finding remained significant after adjusting for cardiovascular risk factors and use of cardioactive medication and suggests that the current criteria used to define CSH may be too sensitive to predict mortality in this age groups when using beat-to-beat monitoring. This study is the first to assess the association between asymptomatic CSH and mortality within a community population in which the prevalence of asymptomatic CSH is accurately documented.

8.4.5 **Response to Autonomic Function Tests**

Response to autonomic function tests was not associated with survival in this study when examined as composite variable "abnormal" or "normal". Nor were there any associations between continuous response to each individual test and survival. There are no population-based studies examining the association between responses to Ewing's battery of autonomic function tests and survival. A meta-analysis examining the association between performance on autonomic function tests and mortality in diabetic patients found that cardiovascular autonomic neuropathy is associated with increased mortality in patients with diabetes. Stronger associations were observed when 2 or more tests were used to define autonomic neuropathy(Maser et al., 2003). A recent study showed that, among 136 diabetic patients, autonomic function tests are a better predictor of mortality than heart rate variability(May and Arildsen, 2012).

8.4.6 **Heart Rate Variability**

None of the markers of heart rate variability recorded in this study were related to mortality at ten years. The Rotterdam, Zutphen, Bronx Ageing Heart and Leiden 85+ studies calculated time domain HRV measures from 12 lead ECG (de Bruyne et al., 1999, Dekker et al., 1997, Bernstein et al., 1997, van Bemmel et al., 2006). Participants were followed-up for between 4 and 5 years in these studies. The Zutphen study found that low HRV was associated with increased mortality (Dekker et al., 1997). The Rotterdam study divided participants into quartiles according to HRV(de Bruyne et al., 1999). Membership of the lowest and highest quartile was associated with increased mortality compared to participants in quartile 3. In contrast, the Leiden 85+ and Bronx

Ageing Heart studies showed no association between HRV and mortality (Bernstein et al., 1997, van Bemmel et al., 2006). Participants were older in the later studies (Bernstein et al., 1997, van Bemmel et al., 2006).

In the ARIC study, time domain measures of HRV were made from a 2 minute ECG recording(Dekker et al., 2000). Participants in the lowest tertile of HRV had the highest mortality. Reduced HRV, calculated from longer recordings made using ambulatory heart rate monitors, has also been associated with increased mortality (Tsuji et al., 1994, Huikuri et al., 1998). The Framingham study recorded HRV for 2 hours. Reduced SDNN, total power, HF, LF and VLF were all associated with increased mortality, while Huikuri et al found SDNN <120ms is associated with increased mortality (Tsuji et al., 1994, Huikuri et al., 1998).

8.4.7 **Summary**

Using conventional definitions of OH and CSH, NCVI was not associated with increased risk of death. However, a modified definition of CSH, possibly more appropriate to older populations, and the use of beat-to-beat monitoring did show an association between severe CSH and increased risk of mortality. Neither autonomic function measured using Ewing and Clark's battery nor heart rate variability were associated with survival in this population. This is in contrast to several previous studies (Tsuji et al., 1994, Huikuri et al., 1998, Dekker et al., 1997, de Bruyne et al., 1999). Data on cause of death were not available. Examination of cause specific mortality may have revealed associations between autonomic dysfunction and death due to specific conditions that have been overlooked in this study. Previous studies have shown associations between altered autonomic function and cardiovascular mortality, fatal stroke and neurological mortality but not with deaths due to cancer.

The association between autonomic function, NCVI, and risk of mortality in this study was examined to establish if individuals with more severe NCVI had been lost to follow-up due to excess mortality. With the exception of severe CSH, baseline NCVI and autonomic dysfunction do not appear to have been associated with reduced survival in this cohort.

Chapter 9 Concluding Remarks and Areas for Future Research

The current study has shown few longitudinal associations between neurocardiovascular or autonomic function at baseline and cognitive function, depression, gait, balance and falls at ten years follow-up. These findings are in contrast to our hypothesis and cross-sectional studies but are in keeping with the small body of literature examining the longitudinal associations between blood pressure control, cognition, depression, and falls.

The study's findings raise questions about the direction of the relationship between NCVI, cognitive impairment, depression, and motor function; raising the possibility that NCVI may be a symptom of progressive neurodegenerative disease rather than a precipitating or exacerbating factor. Histopathological studies have shown involvement of the autonomic nervous system in a number of neurodegenerative disease associated with impaired cognition, depression and motor decline (Jellinger, 2011, Korczyn and Gurevich, 2010, Allan et al., 2007). Furthermore areas of the central nervous system influential in the control of autonomic nervous system are affected early in a number of dementing diseases (Korczyn and Gurevich, 2010, Allan et al., 2007). It is therefore possible that the associations between NCVI, cognition, and mood that have been observed in cross-sectional studies are a feature of simultaneous neurodegeneration of the autonomic and central nervous systems. All participants taking part in this study have been approached by the Newcastle Brain Tissue Resource. Consenting participants have agreed to post-mortem, whole brain donation, and donation of samples of cardiac tissue, peripheral nervous system tissue and tissue from the spinal column. In time, these samples may help to identify underlying pathological changes responsible for observed cross-sectional clinical associations of NCVI. Alternatively, the lack of association between NCVI and cognition, mood or gait at ten years may reflect diagnostic criteria used to define CSH and OH. At baseline, 82% of participants met the AAN criteria for OH and 39% met the criteria for CSH (Kerr, 2009). The criteria for OH and CSH were developed prior to the widespread use of beat-to-beat monitoring and the diagnostic cut-offs were arbitrarily defined based on studies in young men (Krediet et al., 2011). Use of modified criteria for CSH, defined according to age-specific normal ranges, did show an adverse association between CSH at baseline and

survival at ten years. Further studies are needed to examine if these modified criteria are associated with adverse outcome in other populations.

Since this follow-up study began, the criteria for the diagnosis of OH have been modified (Freeman et al., 2011). Both initial OH and late OH are now described in the AAN 2011 criteria. Initial OH is defined as a 40 mmHg decrease in systolic blood pressure and/or a 20 mmHg decrease in diastolic blood pressure within 15 seconds of standing accompanied by symptoms of cerebral hypoperfusion. In this cohort 76.5% of participants reached systolic nadir within 15 seconds of standing, of these 24% had a decrease in systolic BP of ≥ 40mmHg. Similarly, 92% of participants reached diastolic nadir within 15 seconds of standing of which 20% had a decrease in diastolic BP of ≥ 20mmHg. In contrast to the definition of classical OH, the guidelines suggest, symptoms indicative of cerebral hypoperfusion are required to make the diagnosis of in initial OH. There were some indications in this study that symptomatic NCVI may be important. Symptomatic orthostatic hypotension was associated with longer choice reaction time, greater decline in CAMCOG memory score and recurrent falls. Symptomatic CSH was associated with greater white matter hyperintensity volume. Although these associations did not always stand-up to multivariable analysis, and should be interpreted with caution given the extent of multiple testing, there are good reasons why symptoms may be important in identifying individuals at greater risk of adverse effects from NCVI.

Symptoms in conjunction with NCVI are thought to indicate cerebral hypoperfusion. In order for cerebral hypoperfusion to occur there must be a drop in systemic BP below the lower limit of cerebral autoregulation and / or a failure of cerebral autoregulation. As haemodynamic response to CSM and active stand did not significantly differ between symptomatic and asymptomatic individuals, failure of cerebral autoregulation may play a greater role in determining presence of symptoms than degree of vasodepression (Kerr, 2009). One small study has shown greater decline in cerebral blood flow among symptomatic patients with OH compared to asymptomatic individuals with similar changes in systolic blood pressure during head-up-tilt (Khandelwal et al., 2011). Cerebral autoregulation in response to syncope is poorly understood. Although systemic hypoperfusion may be expected to cause a reduction in cerebral vascular resistance, several studies have shown a paradoxical increase in cerebral vascular resistance just

before syncope (Franco Folino, 2007). Some authors suggest this increased cerebrovascular resistance is secondary to hypercapnea induced by hyperventilation, while others have suggested the autonomic nervous system innervating the cerebral arterioles may play a role (Lagi et al., 2001). Ideally, future studies should establish cerebral autoregulation in participants and compare outcomes across four groups;

1. Peripheral haemodynamic response diagnostic of NCVI with normal cerebral perfusion maintained.
2. Peripheral haemodynamic response diagnostic of NCVI with impaired cerebral autoregulation
3. Peripheral haemodynamic response not diagnostic of NCVI with normal cerebral perfusion maintained.
4. Peripheral haemodynamic response not diagnostic of NCVI with impaired cerebral autoregulation

9.1 Limitations and Areas for Furture Research

It must be acknowledged that the study sample size was small. This study relied on the use of an existing well characterised cohort and there were therefore limited opportunities to expand the number of individuals participating in the study. In an attempt to make the study as accessible as possible to frailer individuals, all follow-up assessments (except MRI scan) were conducted in participants' homes. Participants living in residential or nursing care at follow-up were also invited to take part.

Nevertheless, participants recruited to follow-up were younger, more independent with activities of daily living and scored better on assessments of gait, balance, and cognitive function at baseline than participants lost to follow-up, suggesting that frailer individuals elected not to participate in the follow-up study. Similar difficulties were encountered at baseline where participants were more likely to be younger than non-participants, were more likely to be male, and were less likely to have ischaemic heart disease or be using cardioactive, and psychoactive medication. As frailer older individuals were lost to follow-up in larger numbers at each stage, individuals studied here are the fitter survivors. Furthermore most individuals in this cohort had asymptomatic NCVI and the findings from this study cannot be assumed to apply to older frailer individual, individuals presenting to clinical services with symptomatic

NCVI. Notably, comparison with other cohort studies conducted in populations of a similar age showed rates of cognitive impairment and depression were considerably lower in this study than in other similar UK studies suggesting selection bias has been a problem in this study. (Luppa et al., 2012, Rait et al., 2005).

Added to this there has been significant attrition. Only a third of participants enrolled in the study in 2001 took part in the ten year follow-up study. This meant only 99 individuals underwent full cognitive assessment at follow-up and only 53 were able to undergo MRI. This was particularly problematic when analysing the impact of NCVI on incident cognitive impairment and depression as only very small numbers incident cognitive impairment or depression over the follow-up period and the study lacked power to examine the assocations with incident disease.

The statistically significant associations found in this study should be interpreted with caution given the extensive statistical calculations performed. One possible option to reduce potential Type 1 error would have been to perform a Bonferroni correction. A decision was made not to use this or similar methods because it was felt that in this small sample the power would have become unacceptably low and there would have been serious risk of Type 2 error. It was therefore decided that a narrative approach would be taken where all data were presented at P value <0.05 and the overall data examined for patterns that may suggest an association between hypotension and the potential sequel examined here including cognitive decline, falls and WMH. This study can therefore support hypothesis generation for future studies and identify areas for focus for upcoming larger studies such as the Tilda Study.Tilda is a larger, longitudinal, study that aims to establish the long-term associations between NCVI, cognition, mood, gait and balance is now under way in Ireland (Cronin et al., 2013). Over 8000 participants have completed the baseline assessment of the TILDA study. The large sample size of TILDA means that it will have greater statistical power to detect small differences in outcomes between groups and it will be interesting to see in what way the results of the current study and TILDA differ.

Finally, much of the support for the hypothesis that hypotension causes cognitive decline, motor impairment and depression comes from cross sectional magnetic resonance imaging studies. Unfortunately MRI was only included in the final phase of

this study. It was therefore not possible to examine the association between NCVI and WMH progression. To truly understand the direction of the relationship between hypotensive syndromes, white matter hyperintensities and related clinical symptoms, studies are needed that make repeated contemporaneous measures of neurocardiovascular function, WMH volume and clinical outcome. Such studies should include measures of cerebral auto regulation.

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Appendix: Posters and Presentations Resulting From Study

McDonald, C. Firbank, M. Lewis, I. Pearce, M. Kerr, S.J. Blamire, A. Newton. J.L **Symptoms suggestive of cerebral hypoperfusion during carotid sinus massage but not magnitude of peripheral haemodynamic change, are associated with white matter lesions in later life.** Accepted for poster presentation at the International Stroke Conference, San Diego, USA, and February 2014. Awarded Young Investigators Award.

McDonald, C. Pearce, M.S. Newton, J.L. Kerr, S.R.J **Masked Hypertension is Common and Is Associated with Significant Mortality.** Platform presentation at British Geriatric Society Conference, Harrogate UK October 2013

McDonald, C. Pearce, M.S. Newton, J.L. Kerr, S.R.J **Symptoms but not Vasodepression During Active Stand Associate With Falling.** Poster presentation at British Geriatric Society Conference, Harrogate UK October 2013

McDonald, C. Pearce, M.S. Newton, J.L. Kerr, S.R.J. **Blood Pressure Variability Increases with Age Over a 10 Year Follow-Up and is Associated with Baseline Variability**. Poster presentation at American Society of Hypertension Annual Meeting, San Francisco USA, May 2013

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