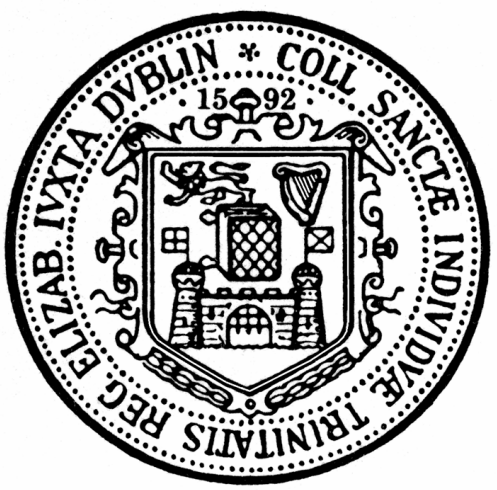

University of Dublin, Trinity College School of Medicine

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Implications of Cardiovascular Ageing for Cerebral Perfusion and Cognitive Performance

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2022

Supervisor: Professor Rose Anne Kenny

Declaration

I declare that no part of the material contained in this thesis has been submitted as part of a degree in Trinity College Dublin or any other institution. All work contained in this thesis was performed by me, including hypothesis formation, literature review, statistical analysis, interpretation and manuscript preparation, under the direction of my supervisor, Professor Rose Anne Kenny.

Data from The Irish Longitudinal Study on Ageing (TILDA) was used to undertake the studies included in this thesis. TILDA is under the governance of Professor Rose Anne Kenny. TILDA bioengineers including Dr Ciaran Finucane, Dr Hugh Nolan, and Louise Newman performed data processing of the neurocardiovascular signals obtained during health assessments. I undertook clinical interpretation of electrocardiogram (ECG) data with assistance from Dr Susan O'Callaghan.

Following acceptance of my PhD submission, I agree that the library may lend or copy this thesis on request.

Signed:

Acknowledgements

First, I would like to acknowledge my supervisor Professor Rose Anne Kenny for her guidance, expertise, and support throughout my PhD.

I would like to thank Dr Katy Tobin for the statistical guidance and support she provided in the work submitted in this thesis.

I would also like to acknowledge my friends and colleagues Dr Susan O'Callaghan, Dr Robert Briggs and Dr Paul Claffey, both for their assistance with the work contained in this thesis, and for the constant moral support they provided.

I would like to thank all of the staff working in the Falls and Syncope unit in St James's Hospital for their support throughout.

I would like to thank my parents, Walter and Nuala McNicholas, for their support while undertaking this work and over the many years of my education.

Finally, I would like to thank my husband, Adrian Bushell, for his moral support and for his patience.

Dissemination of Thesis

Peer Reviewed Publications:

(1) McNicholas T, Tobin K, O'Callaghan S, Kenny RA. ***Is orthostatic hypotension more common in individuals with atrial fibrillation?—Findings from The Irish Longitudinal Study on Ageing (TILDA).*** Age and ageing. 2017 Nov 1;46(6):1006-10.

(2) McNicholas T, Tobin K, Carey D, O'Callaghan S, Kenny RA***. Is baseline orthostatic hypotension associated with a decline in global cognitive performance at 4-Year Follow-Up? data from TILDA (the Irish longitudinal study on ageing).*** Journal of the American Heart Association. 2018 Oct 2;7(19):e008976.

(3) McNicholas T, Tobin K, O'Callaghan S, Kenny RA; ***Global cognitive performance at 4 year follow-up in individuals with atrial fibrillation – findings from The Irish Longitudinal Study on Ageing.*** - Age and Ageing. July 2021

Papers under review:

(1) McNicholas T, Briggs R, Tobin K, Claffey P, Newman L, Finucane C, Kenny RA; ***Relationship between Symptoms of Orthostatic Intolerance, Orthostatic Hypotension, and Cerebral Haemodynamics in adults – Data from The Irish Longitudinal Study on Ageing (TILDA).***

(2) McNicholas T, Briggs R, O'Callaghan S, Newman L, Claffey P, Tobin K, Kenny RA; ***Cerebral haemodynamics during orthostatic challenge in people with Atrial Fibrillation in the TILDA population study*.**

Conference Presentations:

(1) Irish Gerontological Society Annual Scientific Meeting, Cork Ireland, 2019 (Oral):

Atrial Fibrillation and Frontal Lobe Perfusion

(2) European Society of Cardiology Congress, Munich Germany 2018 (Poster):

Cerebral perfusion in Atrial Fibrillation

(3) British and Irish Hypertension Society Annual Scientific Meeting, Cambridge, England 2018 (Poster – winner of Best Poster prize):

Symptoms of orthostatic intolerance and cerebral perfusion-Data from The Irish Longitudinal Study on Ageing (TILDA)

(4) Irish Gerontological Society Annual Scientific Meeting, Wexford, Ireland 2018 (Poster):

Atrial Fibrillation and Cognition at Four Year Follow-Up – Data from The Irish Longitudinal Study on Ageing (TILDA)

(5) Irish Gerontological Society Annual Scientific Meeting, Galway, Ireland 2017 (Oral):

Is Orthostatic Hypotension at Baseline Associated with a Decline in Cognitive Function at Four Year Follow-up?

(6) Heart Rhythm Congress, Birmingham, England 2017 (Oral):

Orthostatic Hypotension and Atrial Fibrillation

Summary of thesis

The aim of this thesis is to examine how manifestations of cardiovascular ageing affect cerebral perfusion and cognitive function in Irish adults. Five quantitative studies are presented in this thesis, which use data from The Irish Longitudinal Study on Ageing (TILDA), a large population representative cohort study of Irish adults over the age of 50. The thesis focuses on two commonly observed manifestations of cardiovascular ageing – Orthostatic Hypotension (OH) and Atrial Fibrillation (AF). Cerebral flow and cognitive function in Orthostatic Hypotension and Atrial Fibrillation are also examined.

Both Orthostatic Hypotension and Atrial Fibrillation have been implicated as risk factors for cognitive impairment and dementia, and this thesis examines these associations in an Irish population. In addition, this thesis aims to add to the understanding of the mechanisms by which such conditions may impact on brain health – that is by examining their impact on cerebral hypoperfusion.

In this thesis, individuals with AF are found to be more likely to have OH. In addition, OH is found to be associated with cognitive decline in an Irish population, and cerebral haemodynamics in response to orthostasis are also impaired in OH. While AF was not found to be robustly associated with cognitive decline, it was found to impair cerebral haemodynamics in response to orthostasis. We hypothesise that the Autonomic Nervous System (ANS) may play a role in the link between OH and AF. Both are common in ageing, and abnormalities of autonomic function have been demonstrated in ageing. In addition, the autonomic nervous system plays a key role in cerebral autoregulation. Both OH and AF are commonly linked to cognitive decline, and we hypothesise that impaired cerebral

perfusion in response to standing demonstrated in this thesis may contribute to this association.

Chapter Summaries:

Background and Literature Review

Chapter 1 provides a background and review of the literature pertaining to the Autonomic Nervous System and its role in the cardiovascular system, with a particular focus on its role in Orthostatic Hypotension and Atrial Fibrillation, as well as its role in Cerebral Autoregulation (CA). **Chapter 2** reviews the available literature assessing whether OH and AF are risk factors for cognitive impairment and dementia and discusses the proposed mechanisms for these associations. **Chapter 3** introduces The Irish Longitudinal Study on Ageing, and describes the methods used in this study.

Quantitative Studies

Chapter 4 describes the first study of this thesis, "Is Orthostatic Hypotension more common in Individuals with Atrial Fibrillation – Findings from The Irish Longitudinal Study on Ageing". This study investigates whether Irish adults with AF are more likely to have OH, hypothesising that the role of the autonomic nervous system may link the two.

The second study of this thesis is presented in **Chapter 5** – "Is Baseline Orthostatic Hypotension associated with a decline in global cognitive performance at 4-year follow-up? Data from the Irish Longitudinal Study on Ageing". This is a longitudinal study that assess whether participants with OH have a more rapid decline in global cognition at follow-up, assessed using the Montreal Cognitive Assessment (MOCA). In **Chapter 6**, the third study of this thesis assesses one potential mechanism for this association, by examining cerebral flow in participants with OH., This study is entitled "Relationship between Symptoms of

Orthostatic Intolerance, Orthostatic Hypotension, and Cerebral Haemodynamics in adults – Data from The Irish Longitudinal Study on Ageing (TILDA)."

The fourth study of this thesis is presented in **Chapter 7** – "Global cognitive performance at 4 year follow-up in individuals with Atrial Fibrillation – findings from The Irish Longitudinal Study on Ageing". This study examines longitudinal changes in global cognition, assessed using the MOCA, in Irish adults. The final study, "Cerebral haemodynamics during orthostatic challenge in people with Atrial Fibrillation in the TILDA population study", is presented in **Chapter 8.** This final study examines one potential mechanism by which AF could be associated with a risk of cognitive impairment and dementia – that is, cerebral hypoperfusion.

Discussion and Conclusions

Chapter 9 summarises the findings of this thesis, and how it contributes to existing literature. Limitations of the thesis are also presented, as well as future directions that could build on the work presented in this thesis

Abbreviations

AF – Atrial Fibrillation

AD – Alzheimer's Dementia

ANS – Autonomic Nervous System

APOE – Apolipoprotein E

AV – Atrioventricular

BP – Blood Pressure

BRS - Baroreflex Sensitivity

CA - Cerebral Autoregulation

CA2+ -Calcium

CAMCOG – Cambridge Cognition Examination

CAMDEX - Cambridge Examination for Mental Disorders of the Elderly

CAPI - Computer-aided Personal Interview

CBF – Cerebral Blood Flow

CERAD - Consortium to Establish a Registry for Alzheimer's Disease

CHF - Congestive heart failure

COWA - Controlled Oral Word Association Test

CRT – Choice Reaction Time

CSM – Carotid Sinus Massage

DLB – Dementia with Lewy Bodies

DBP – Diastolic Blood Pressure

DSM - Diagnostic and Statistical Manual of Mental Disorders

DSST - Digit Symbol Substitution Test

DWRT - Delayed Word Recall Test

ECG – Electrocardiogram

EDRF - Endothelium derived relaxing factor

ESRI - Economic and Social Research Institute of Ireland

FTD – Frontotemporal Dementia

GMS - Geriatric Mental State Examination

HDSR - Hasegawa Dementia Scale Revised

HF – High Frequency

HR – Heart rate

HRV – Heart Rate Variability

HTN – Hypertension

HUTT – Head-up Tilt Test

LF – Low Frequency

MAP – Mean Arterial Pressure

MCI – Mild Cognitive Impairment

MOCA -Montreal Cognitive Assessment

MRI – Magnetic Resonance Imaging

NIAAA - National Institute on Aging—Alzheimer's Association

NINCDS-ADRDA - National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association

NINDS/CSN - National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network

NTS - Nucleus tractus solitarius

OH- Orthostatic Hypotension

OI – Orthostatic Intolerance

PaCO2 – Partial Pressure of Carbon Dioxide

PSNS – Parasympathetic Nervous System

PWV - Pulse Wave Velocity

RVLM – Rostro-ventrolateral medulla

SA – Sinoatrial

SART - Sustained Attention to Response Task

SBP – Systolic Blood Pressure

SCQ – Self-completion Questionnaire

SDNN – Standard Deviation of R-R Intervals

SNS – Sympathetic Nervous System

TCD – Transcranial Doppler

TILDA - The Irish Longitudinal Study on Ageing

TMT – Trail Making Test

VaD – Vascular Dementia

VCPS - Visuospatial Cognitive Performance Score

WFT – Word Fluency Test

WML – White Matter Legion

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Chapter 1: Introduction

This chapter introduces the Autonomic Nervous System (ANS), with a focus on cardiovascular autonomic control, and discusses the role of the ANS in cardiovascular disease and the impact of ageing on the ANS. It also describes the pathophysiology of Atrial Fibrillation (AF) and Orthostatic Hypotension (OH) and discusses the role of the ANS in both. Finally, the concept of cerebral autoregulation (CA) and brain health in ageing are discussed.

1.1 Introduction to The Autonomic Nervous System

The ANS is a complex system of interconnected neurons responsible for control of visceral functions, maintaining homeostasis and adapting to changing conditions. The ANS is largely an involuntary system, with diffuse pathways innervating organ systems. The ANS is responsible for the innervation of all organs and tissues, except skeletal muscle [1], and hence it is involved in almost all disease. It consists of both central and peripheral networks. The peripheral ANS is the point of sensory input and autonomic output and is divided into the sympathetic (SNS) and parasympathetic arms (PSNS). The central ANS consists of a complex arrangement of afferent and efferent interconnections in many brainstem and cortical areas [2], receiving an array of sensory afferents and participating in an integrated response to internal and external stimuli, via efferent neurons of the ANS controlling smooth muscle cells, cardiac muscle cells and glands. Figure 1.1 provides a schematic representation of the sympathetic and parasympathetic divisions of the ANS, and the structures innervated by each division.

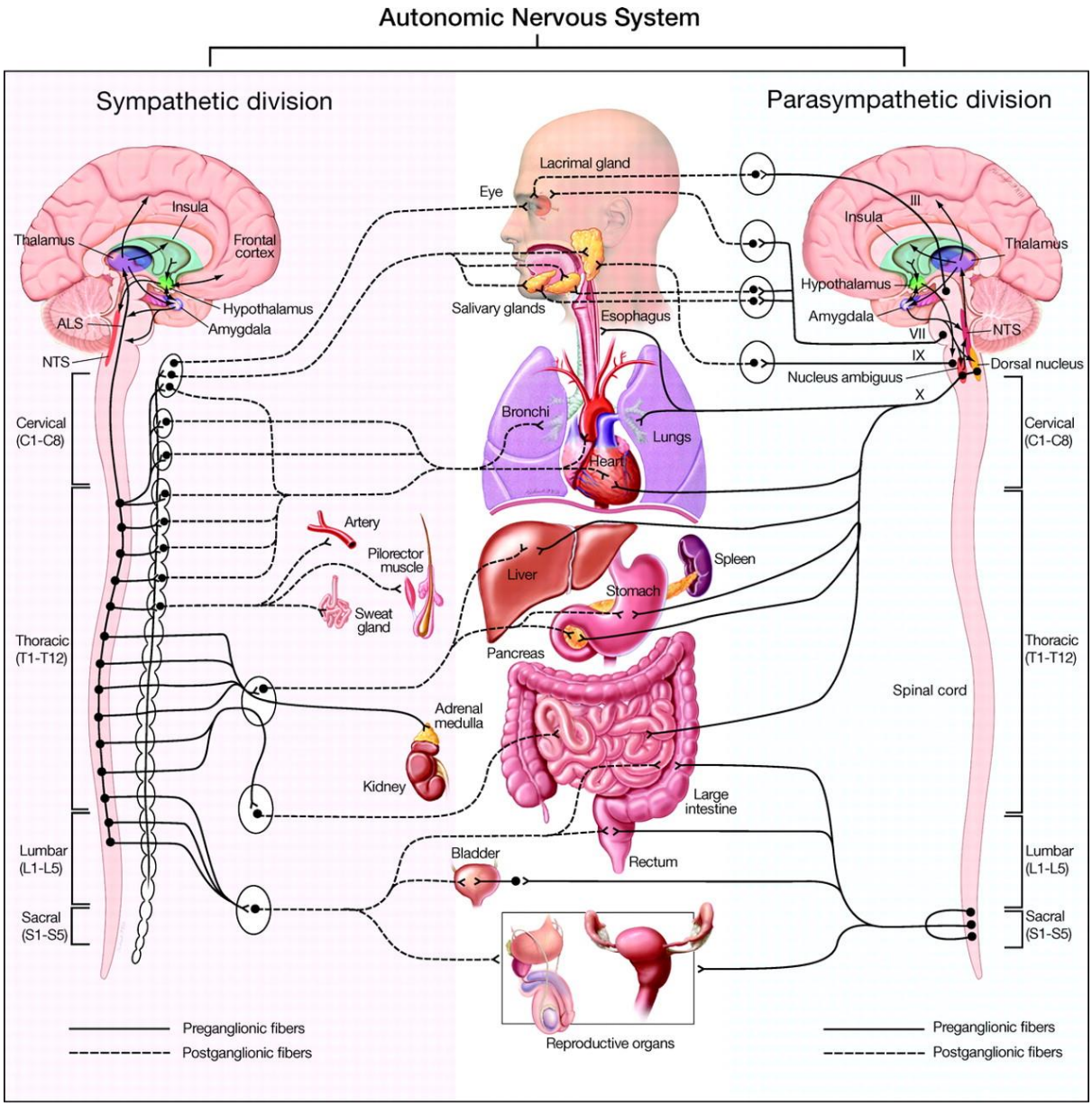

Figure 1.1 Schematic representation of the Autonomic Nervous System – sympathetic and parasympathetic divisions and anatomical structure innervated by each [3].

III, VII, IX, and X represent cranial nerves. ALS = anterolateral system; NTS = nucleus tractus solitarius.

1.1.2 The Peripheral Autonomic Nervous System

The peripheral ANS is functionally and anatomically divided into the SNS and the PSNS (Figure 1.1). Both the SNS and PSNS have pre-ganglionic neurons located in the brainstem or spinal cord and an autonomic ganglion that innervates the target organ. Sympathetic pre-ganglionic neuron cell bodies are confined to the first thoracic segments through to the first lumbar spinal segments (T1 to L3); hence it is known as the thoracolumbar division. Similarly, the parasympathetic nervous system is known as the craniosacral division because of the location of its pre-ganglionic neurons (cranial nerves III, VII, IX, X, mid brain, pons, medulla and the sacral spinal cord). The SNS pre-ganglionic neurons use acetylcholine for neurotransmission, while post-ganglionic neurons transmit noradrenaline (except sweat glands which transmit acetylcholine). The primary neurotransmitter of the PSNS is acetylcholine, acting via muscarinic receptors.

The SNS is known as the “fight or flight” response and acts in response to stressful situations and prepares the body for emergency by increasing heart rate (HR) and blood pressure (BP), as well as decreasing blood flow to digestive organs. The PSNS, known as the “rest and digest” system, acts to conserve and restore energy by exerting opposing functions, decreasing HR and BP, and activating digestive organs. Functions of the SNS and PSNS are summarised in Table 1. Because of its involvement in a variety of visceral functions, patients with autonomic dysfunction can present with a number of symptoms, which should be considered in assessing patients presenting with symptoms suggesting autonomic dysfunction, for example orthostatic dizziness [4].

Target Organ	Sympathetic Response	Parasympathetic Response
The Eye	Pupillary dilation	Pupillary constriction Light accommodation
Salivary and lacrimal glands	Inhibition	Stimulation
Heart	Accelerates SA node and ectopic activity Increases contractility	Decreases SA node Decreases contractility
Blood vessels	Contracts skin and splanchnic vessels Relaxes skeletal muscle vessels	Releases EDRF in endothelium
Bronchial smooth muscle	Relaxes	Contracts
Gut smooth muscle	Inhibits smooth muscle Sphincter contracts Bladder wall relaxes Bladder neck contracts	Stimulates smooth muscle Sphincter relaxes Bladder wall contracts Bladder neck relaxes
Skin	Pilomotor smooth muscle contracts Increases thermoregulatory sweat glands Increases apocrine sweat gland	
Exocrine functions	Stimulation of adrenaline, glucagon, renin and thyroxine	Simulation of gastrin, insulin, cholecystokinin, and pancreatic polypeptide
Metabolic functions	Liver – gluconeogenesis and glycogenolysis Fat cells – lipolysis	

	Kidneys – renin release

Table 1.1. Summary of function of SNS and PSNS by target organ
SA – Sinoatrial; EDRF – Endothelium derived relaxing factor;

1.1.3 The Central Autonomic Nervous System

The Central ANS consists of a group of extensively interconnected areas including the insular and medial prefrontal cortices, the amygdala, hypothalamus, periaqueductal grey matter, the pons, the nucleus of the tractus solitaries (NTS) and the medullary intermediate reticular zone [5]. The central ANS receives visceral and somatosensory information and is involved in visceromotor, neuroendocrine, complex motor and pain-modulating control mechanisms that are essential for adaptation, as well as for survival.

The central ANS can be split into hypothalamic and extra-hypothalamic nuclei [6]. In the hypothalamus, the most important nucleus of the central ANS is the paraventricular nucleus (PVN), which has direct influence over both sympathetic and parasympathetic outflow and receives inputs from the caudalis nucleus (sympathetic) and nucleus tractus solitarius (NTS) (parasympathetic) [6].

Extra-hypothalamic structures of the central ANS include those that control sympathetic outflow and parasympathetic outflow. Sympathetic outflow is controlled by the locus ceruleus, the rostral and caudal ventrolateral medulla, the pontine and medullary raphe nuclei, while parasympathetic outflow is controlled by the central nucleus of the amygdala, the dorsal motor nucleus of the vagus, the nucleus ambiguous, the periaqueductal gray nucleus and parabrachial nucleus [6]. Additionally, limbic cortices including the cingulate, orbitofrontal, insular and rhinal cortices influence both sympathetic and parasympathetic outflow. The major pathway connecting the hypothalamus with other central ANS structures is the dorsal longitudinal fasciculus (DLF), which originates from the PVN.

1.1.4 ANS control of the cardiovascular system

Cardiovascular diseases are the leading cause of death worldwide [7]. A number of well-known risk factors exist for cardiovascular disease, such as cholesterol levels and smoking,

however, understanding how other factors, such as cardiovascular autonomic control, contribute is important in comprehending the development and progression of most cardiac disease, including hypertension, heart failure, arrhythmias, and myocardial infarction [8]. Increased sympathetic activity and reduced parasympathetic activity are noted in a number of cardiovascular disorders, and carry a poor prognosis, with increased risk of arrhythmias [9] and sudden death [10].

The cardiac ANS is divided into the extrinsic and intrinsic systems. The intrinsic cardiac sensory neurons are located throughout both atria and ventricles organised into ganglionated plexi, concentrated in the sinoatrial node, as well as the outflow tracts of the ventricles [11]. Cardiac motor neurons are classified as cholinergic (parasympathetic) and adrenergic (sympathetic) and exert opposing effects. The appropriate balance (autonomic tone) between the two is fundamental to the pathophysiology of cardiovascular disease [9]. The pre-ganglionic plexus of cholinergic neurons is located primarily in the ventral lateral region of the nucleus ambiguous, with a small area located in the medullary dorsal motor nucleus of the medulla oblongata and the intermediate zone between these two medullary nuclei [12]. Parasympathetic efferent post-ganglionic neurons are found in individual atrial or ventricular ganglionated plexi and receive input from both vagal trunks, therefore cholinergic motor control of the heart is widely distributed.

Adrenergic pre-ganglionic neurons are located in the inter-mediolateral cell column of the spinal cord (C7 – T6), with post-ganglionic neuronal somata located in superior cervical, middle cervical, mediastinal and stellate ganglia [13]. Post-ganglionic neurons from these post-ganglionic somata synapse in the atrial and ventricular myocardium, releasing noradrenaline at their nerve endings as well as other neurotransmitters, to increase chronotropy, inotropy and vasoconstriction [13].

The organisation of the cardiac ANS is complex (Figure 1.2). Regulation of cardiac function is dependent on medullary centres – the nucleus of the solitary tract (NTS) and the rostro-ventrolateral medulla (RVLM). The NTS receives afferents from the baroreceptors and the visceral sensorial information from cranial nerves (including the vagal nerve). The RVLM is mainly composed of excitatory neurons that are responsible for the generation of the sympathetic response. [14] These regions generate reflexes that play a role in cardiac adaptation, however supra-medullary regions also play a role. The insular cortex is critical in controlling autonomic tone, and stroke patients with insular damage are prone to sudden cardiac death and autonomic alterations [15, 16]. The prefrontal cortex is also involved in the regulation of cardiovascular functions, as well as the hypothalamus – through the posterolateral hypothalamus and paraventricular nucleus.

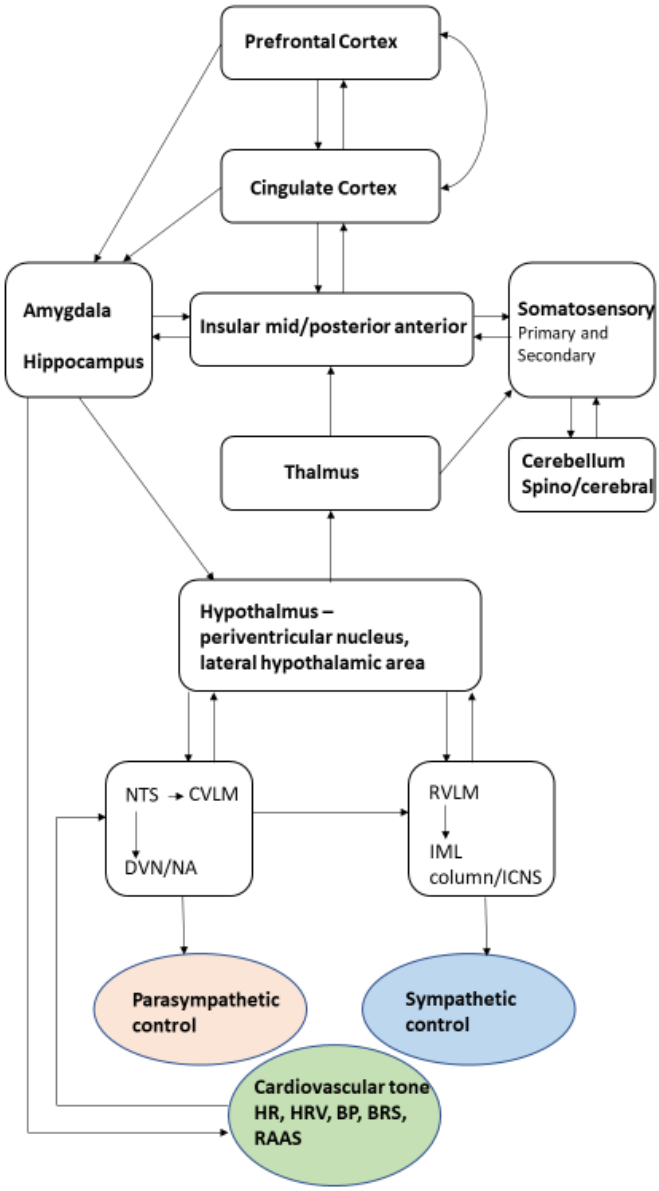

Figure 1.2 Cardiac autonomic nervous system
NTS - Nucleus tractus solitarius; CVLM - Caudal ventrolateral medulla; RVLM - Rostral ventrolateral medulla; DVN - Dorsal motor nucleus of the vagus; NA – Nucleus ambiguous; IML – Intermediolateral column; ICNS – Intrinsic cardiac nervous system.

Autonomic dysfunction plays a role in several cardiovascular diseases [17]. The ANS regulates events, allowing for appropriate HR and BP responses, as well as vaso-regulatory responses. Dysfunction or dysregulation of these responses contributes to cardiovascular disease, including hypertension, ischaemic heart disease, arrythmias, and congestive heart failure

[17]. As discussed, the SNS increases HR, as well as myocardial contractility and peripheral resistance, while the PSNS slows down HR and has a limited action on cardiac contractility. Generally, enhanced sympathetic activity is proarrhythmogenic, while the vagus nerve exerts a protective effect [18]. Cardiac autonomic dysfunction has been linked with ventricular rhythms and sudden death [9, 19].

In heart failure, left ventricular dysfunction leads to a compensatory sympathetic overactivation, which is reflected in increased resting heart rate and plasma norepinephrine levels [20], which have been associated with an increased risk of mortality in heart failure [21]. The ANS has also been implicated in pathophysiological mechanism underlying hypertension (HTN). A sympathetic dominance is observed in HTN [22, 23], leading to elevations in BP driven by increased HR and cardiac output, and with more sustained elevations in BP, to increased systemic vascular resistance.

Heart rate variability (HRV) is commonly used to assess cardiac autonomic function, as it is a simple and non-invasive technique [24]. It measures variability of R-R intervals (time period between two successive R waves) on an ECG. Power spectral analysis of HRV allows assessment of autonomic tone. The parasympathetic system applies its action on the heart quickly via ACh release, mainly affecting the high frequency (HF) component of HRV [24]. The sympathetic component acts over a longer period via noradrenaline and is reflected in both low (LF) and high frequency components of the HRV spectrum. The LF/HF ratio is a proxy to sympatho-vagal balance [25]. The total power of the spectrum is reflected by the standard deviation of the RR intervals (SDNN) [25]. During sympathetic activation, there is a reduction in SDNN, whereas the opposite is true during parasympathetic activation. When HRV decreases, there is a decreased ability to modulate BP via the ANS.

1.1.5 ANS and Ageing

Ageing is associated with several abnormalities in ANS function that can impair an older person's ability to adapt to the stresses of everyday life [26]. In older adults, autonomic function is relatively maintained at rest, but ability to adapt to change is often impaired [27]. Age-related changes in sympathetic nerve activity include an increase in plasma noradrenaline concentrations, and an increase in the discharge rates of muscle sympathetic nerve fibres, as measured by micro-neuropathy [27]. An age-related increase in vascular resistance has also been observed [26]. It has also been observed that the vagal component of HRV decreases with age [28], and that HR changes in response to acetylcholine receptor blocking agents are blunted [27, 29]. In addition, ageing is associated with a reduction in cardiovagal baroreflex sensitivity, manifesting as a blunted response to hypotensive stimuli such as upright posture, and a blunted bradycardic response to hypertensive stimuli [26].

1.2 Cerebral Autoregulation

Cerebral Autoregulation (CA) refers to the ability to regulate and maintain adequate cerebral blood flow (CBF) during changes in systemic BP. The brain is highly metabolically active, with the volume of blood required by the human brain representing 20% of cardiac output [30]. Therefore, precise regulation of CBF is critical to maintain a constant supply of nutrients and oxygen to the brain [31]. Control of CBF involves a number of overlapping mechanisms including the partial pressure of arterial carbon dioxide (PaCO2), mean arterial pressure (MAP), cerebral metabolism and the ANS [31].

In 1959 Lassen et al. [32] proposed a plot of average BP and total CBF, suggesting a large plateau across which CBF remains constant within the MAP range of 60 to 150mmHg. More recent work by Tan et al. [33] suggests a smaller plateau, with a more pressure-passive CBF than previously reported (Figure 1.3). This more recent work proposes that the brain defends more effectively against hypertensive episodes than hypotension. When CA responses are impaired, the brain can be exposed to cerebral hypoperfusion, which has been associated white matter hyperintensities [34] and cerebral atrophy [35, 36].

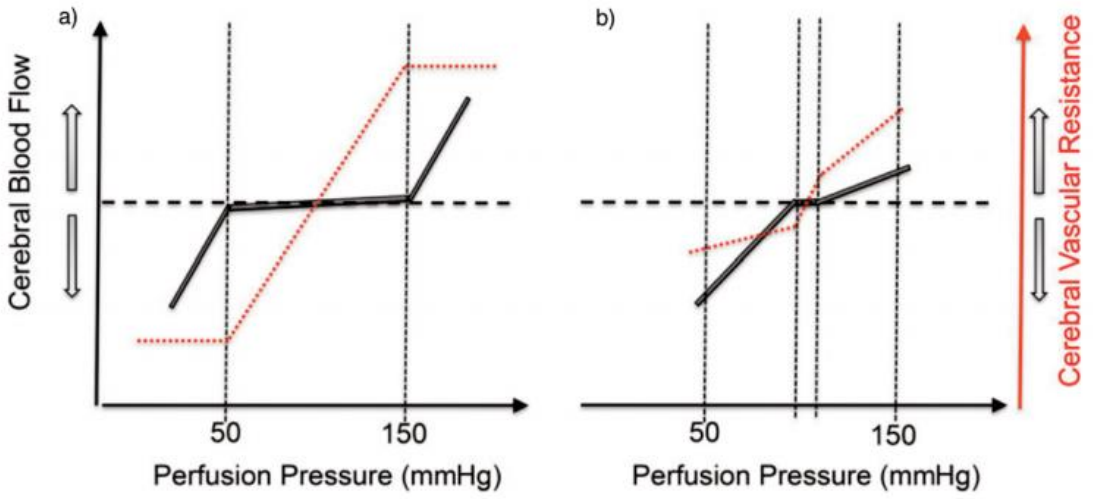

Figure 1.3 Representation of the (a) classical and (b) contemporary relationship between MAP and CBF[31]

MAP – Mean arterial pressure; CBF – Cerebral blood flow

1.3 Atrial Fibrillation

Atrial Fibrillation (AF) is the most common sustained arrythmia, and its prevalence increases with age. AF is a significant Public Health problem, with estimates suggesting an AF prevalence of 3% in adults older than 20, with a steep increase in prevalence with age, and in conditions such as hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus and chronic kidney disease [37, 38]. The prevalence of AF is constantly rising, even after adjusting for age and the presence of structural heart disease [39].

AF is associated with an increased morbidity and mortality, including a 4-5 fold increased risk of stroke, and a threefold increase risk of heart failure [40, 41]. It has also been associated with functional impairment and reduced quality of life [42, 43]. The risk of stroke in Atrial Fibrillation is well established, however more recently, AF has been associated with cognitive impairment [44] and falls [45]. It is proposed that cerebral hypoperfusion in Atrial Fibrillation contributes to this risk.

In a normal heart the sinoatrial (SA) node, located at the junction of the superior vena cava and the right atrium, acts as the dominant pacemaker. The SA node initiates an electrical impulse that travels through the right and left atria, causing them to contract and pump blood into the ventricles. This electrical impulse is transmitted to the ventricles via the atrioventricular (AV) node, leading to synchronisation between contraction of the atria and ventricles. In AF, these regular impulses that are initiated by the SA node become overwhelmed by rapid electrical discharges from ectopic foci or re-entrant pathways, leading to un-coordinated, chaotic electrical activity in the atria. Such ectopic foci occur most frequently around the pulmonary veins. AF is diagnosed by surface electrocardiogram (ECG), with absence of discrete p-waves and an irregularly irregular ventricular rate (Figure 1.4).

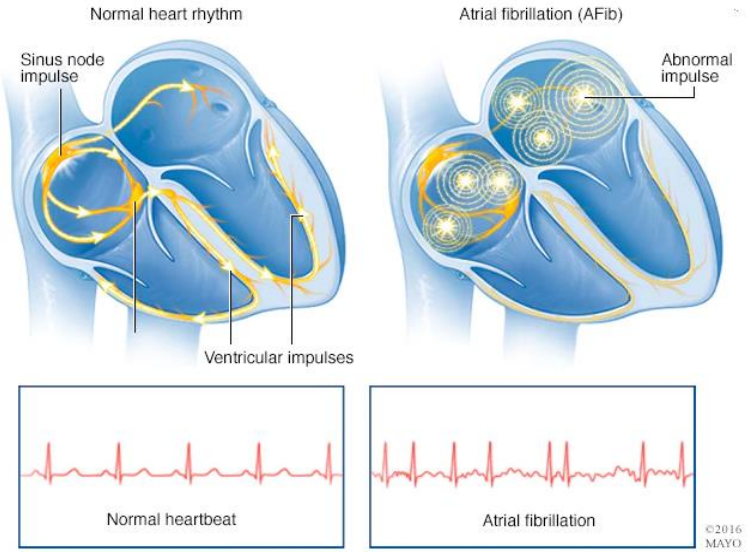

Figure 1.4. Initiation of AF by ectopic foci, and ECG findings

Clinical presentations of AF include paroxysmal AF, persistent AF and permanent AF. In paroxysmal AF, AF episodes terminate spontaneously within seven days. Persistent AF requires termination by pharmacological or DC cardioversion, and in permanent AF restoration of normal sinus rhythm is not possible or thought to be inadvisable [46]. It is thought that the natural history of AF involves evolution from paroxysmal AF to persistent AF, to permanent AF as a result of atrial remodelling that is caused by the arrhythmia itself or progression of underlying heart disease [47]. AF-related electrical remodelling,, resulting from altered expression or function of cardiac ion channels favours the development of functional re-entry substrates, which are reversible on AF termination and contribute to persistent AF [46]. As atrial disease progresses to irreversible structural changes, AF disease becomes permanent [46].

The pathogenesis of AF involves an interaction between initiating triggers, and abnormal atrial tissue substrate that can maintain the arrhythmia [39]. Its pathogenesis is complex, with multiple mechanisms playing a role in its initiation and maintenance, including the ANS. The

prevailing hypothesis of AF initiation is that rapid firing of ectopic foci initiates propagating re-entrant waves in a vulnerable atrial substrate [48]. The importance of the trigger may decrease as AF progresses, as atrial modelling the AF substrate progresses, and AF becomes more stable. Ablation of ectopic foci located at the pulmonary veins in patients with paroxysmal AF may lead to reduced AF burden [49]. While a trigger is required in paroxysmal AF, a vulnerable atrial substrate is also required. Electrical remodelling that occurs in AF alters ion channel expression and function in a way that promotes AF [46]. Because Calcium (Ca2+) enters atrial cells with each action potential, rapid atrial rates increase Ca2+ loading and initiate auto-protective mechanisms that reduce Ca2+ entry and decrease Ca2+ loading by reducing action potential duration [46]. This stabilises atrial re-entry rotors and increases AF vulnerability. Alterations in Ca2+ handling also promote diastolic Ca2+ release and ectopic activity [46]. Structural remodelling, particularly fibrosis is also important in AF. Fibrosis causes progression of AF to permanent forms, and AF itself may promote structural remodelling that contributes to the development of permanent AF [46].

Autonomic nervous system factors are important in AF [50]. In 1978 Coumel et al. described a group of patients with AF of vagal origin, manifested by the absence of structural heart disease and nocturnal onset of AF preceded by a slow sinus rate [51]. However it was subsequently observed that the majority of AF patients do not have the typical features described by Coumel et al. and vagal AF was viewed as a rarity [52]. The role of the ANS in AF has since been examined in several studies. It has been observed, that electrical stimulation of autonomic nerves during the atrial refractory period produces rapid ectopic beats from the pulmonary veins, which can initiate AF [53-55]. Studies have also shown that changes in HRV occur at the onset of paroxysmal AF, which suggests an imbalance between the two arms of

the ANS are involved in the pathogenesis of AF [56, 57]. While the mechanisms by which the ANS is involved in the pathogenesis of AF remain incompletely understood, it is widely accepted that the ANS plays a role in both its initiation and maintenance, with consequent potential for therapies that target the ANS such as ganglionated plexus ablation, renal sympathetic denervation and cervical nerve or baroreflex stimulation [50].

1.4 Orthostatic Hypotension

Orthostatic Hypotension (OH) is defined by consensus statement as a sustained reduction in systolic blood pressure (SBP) of at least 20mmHg or diastolic blood pressure (DBP) of at least 10mmHg within 3 minutes of standing [58, 59]. It can be classified as initial OH (an exaggerated drop within 30 seconds of standing), classical OH (between 30 seconds and 3 minutes) or delayed OH (after 3 minutes of standing).

The prevalence of OH increases with age. The prevalence of OH in people over the age of 65 has been reported to be between 5 and 35% [60-63]. The differences in the estimates vary due to a number of factors, including the definition of OH, the population studied (age range, healthy verses select disease groups, institutionalised verses community dwelling), the influence of medications and the level of orthostatic stress [61]. In previous studies, the prevalence of OH in the primary care setting has found to be 15% in older hypertensive patients [64], verses up to 35% in residents of nursing homes [65]. In the population of community-dwelling over 50s studied in the Irish Longitudinal Study on Ageing, the prevalence of impaired BP stabilisation on stand in the first wave of data collection (2009-2011) rose from 14.3% of men and 16.9% of women aged 50-59 to 43.4% of men and 39.9% of women over the age of 80 [66].

Regulation of BP is a complex physiological process, depending on the actions of numerous systems, including neural, renal and endocrine systems to maintain tight control of BP through changes in cardiac output and vascular resistance [67]. The autonomic nervous system plays a key role in mediating these changes. Orthostatic stress is a common physiological challenge for humans, occurring many times each day. On assumption of the upright position, up to 1L of blood pool in the lower limbs and splanchnic area, resulting in a rapid decrease in venous return, ventricular preload and cardiac output. There is a subsequent reduction in the distension of the baroreceptors and a reduction in signalling to the cardiovascular centre in the brain stem. A parasympathetic inhibition and sympathetic activation is then triggered, leading to an increase in heart rate and total peripheral resistance, with subsequent restoration of blood pressure [30]. Orthostatic Hypotension occurs when these regulatory mechanism fail [68]. Figure 1.5 details the normal responses to standing.

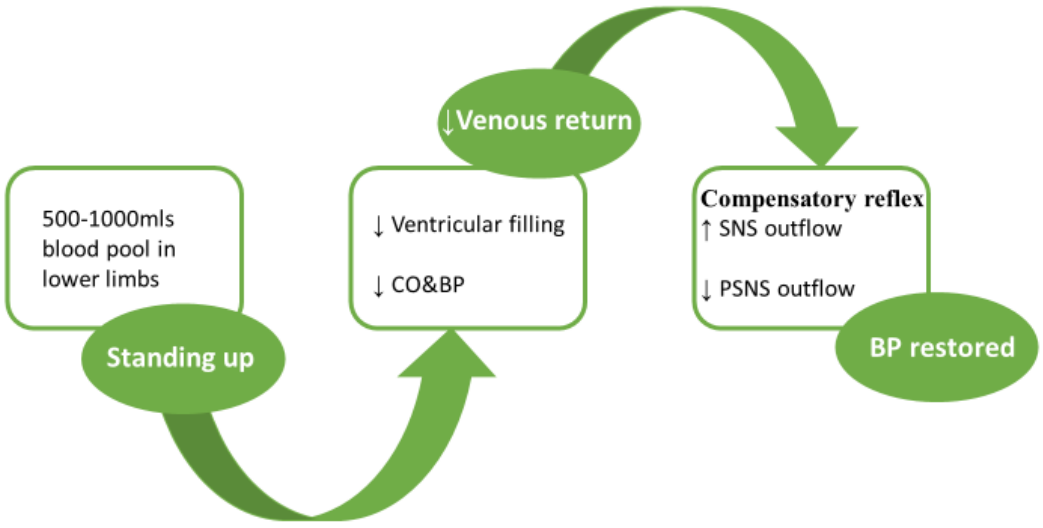

Figure 1.5. Physiology of standing up
CO – Cardiac Output; BP Blood Pressure; SNS – Sympathetic Nervous System; PSNS – Parasympathetic Nervous System

The causes of OH are many, and include impaired baroreflex sensitivity, abnormal neurohumoral regulation, impaired thirst, dehydration and impaired venomotor tone [69]. It is common in conditions that can affect the ANS such as diabetes, and neurological conditions such as Parkinson's disease. Table 1.2 summarises the common primary and secondary causes of OH. OH itself is not a pathological state in but rather a dynamic state. However, it is associated with increased morbidity and mortality. There is increasing evidence linking OH with all-cause mortality [70-72], and it has also been linked to cardiovascular and cerebrovascular disease [72-74]. In addition, OH has been linked with falls [45, 75], depression [76, 77] and cognitive impairment [78, 79].

Primary OH	Secondary OH		
Primary Autonomic Failure	**Secondary Autonomic Failure**	**Drug induced**	**Volume depletion**
Parkinsons disease	Metabolic – e.g. Diabetes, chronic liver failure, chronic renal failure	Cardiac medications: alpha/beta blockers, calcium channel blockers, diuretics, ACE inhibitors, nitrates	Dehydration
Multi-systems atrophy	Autoimmune – e.g. Guillain Bare Syndrome, rheumatoid arthrtitis, Myasthenia Gravis	Neuropsychiatric medications: SSRIs, SNRIs, MAOIs, TCAs, antipsychotics	Diuretic use
Lewy body dementia	Infection	Anti-parkinsonian medications: Levodopa, pramipexole, ropinirole	GI upset – vomiting/diarrhoea
Pure autonomic failure	Paraneoplastic – e.g. small cell lung cancer (anti-Hu antibodies)	Genitourinary medications: anticholinergics, alpha blockers, phosphodiesterase inhibitors	Excessive sweating
	Nutritional – B vitamin deficiencies	Miscellaneous medications: opiates, alcohol	Burns
	Other – e.g. sarcoid, porphyria, amyloid		Sepsis

Table 1.2 Causes of Orthostatic hypotension
SSRI – Serotonin re-uptake inhibitor, SNRI – Serotonin and norepinephrine reuptake inhibitor; MAOI – Monoamine oxidase inhibitors; TCA – Tricyclic anti-depressants

1.4.1 Orthostatic Hypotension and Atrial Fibrillation

The previous sections have highlighted that the ANS plays a role in the pathophysiology of both OH and AF. It is therefore plausible that individuals with AF may be more at risk of developing OH, and equally those with OH may be at higher risk of developing AF. As discussed, there is mounting evidence that OH is a risk factor for cardiovascular disease. A number of recent studies have examined whether OH is a risk factor for AF specifically.

Federowski et al. [80] have found that in a community-dwelling population of adults based in Malmo, Sweden, OH was associated with an increased risk of AF in participants with hypertension after 24 years follow-up. Researchers from the Framingham Heart Study [81] reported the presence of OH at baseline and orthostatic decline in Mean Arterial Pressure (MAP) are both associated with higher risk of incident AF at 10 years follow-up, adjusting for a number of risk factors, including hypertension. OH was also a risk factor for incident AF at an average of 18 years follow-up in another population based study of bi-ethnic men and women aged 45-64 [82].

The link between OH and AF is likely complex. Both conditions are common in ageing, and they share many common risk factors, however the association has been demonstrated independent of common risk factors including age [81, 82].

1.5 Brain health and ageing

Ageing is associated with some decline in cognitive abilities including memory, attention, processing speed, language, and visuospatial and executive function [83]. A number of age-related physiological changes underlie this process, including neuronal decline, neurochemical changes and cerebral atrophy. Mild cognitive impairment (MCI) is a decline in cognition that is worse than normative data for a set age and education level but does not meet the criteria for the diagnosis of dementia [84]. Prevalence data for MCI varies greatly, with the prevalence of MCI having been reported as up to 42% of individuals [85]. MCI can be categorised into amnestic MCI, with memory impairment as a dominating feature, or less commonly, non-amnestic MCI [86].

The main differentiating criteria for dementia is the existence of functional impairment [87]. The rate of conversion from MCI to dementia varies between 8 and 15% yearly [88]. Amnestic subtypes of MCI have a higher conversion rate to Alzheimer's dementia, whereas those with non-amnestic subtype may develop a non-Alzheimer's dementia such as frontotemporal dementia or Lewy Body Dementia.

Dementia is one of the most common neurological disorders. It is estimated that worldwide, 40 million people over the age of 60 have Dementia, with the most prevalent cause being Alzheimer's Dementia (AD), a progressive neurodegenerative disorder that typically presents clinically with memory impairment and executive dysfunction [89]. The hallmarks of AD include the presence of neurofibrillary tangles and hyperphosphorylated β-amyloid plaques (Aβ) [90], which accumulate prior to clinical onset. However, these characteristics are not pathognomonic and may present in normal ageing or other neurodegenerative disease. Autonomic symptoms have been found to be more prevalent in patients with Dementia [91].

Allan et al. demonstrated that autonomic symptoms are more common in Parkinson's Disease Dementia and LBD when compared with controls or with patients with AD [91]. However, those with AD did not complain of significantly more autonomic symptoms than controls [91].

Vascular dementia (VaD) is the second most common subtype of dementia. Both its clinical presentation and neuropathological features are more variable that AD with cognitive changes being dependant on the neural substrates and areas of brain affected. MRI findings suggestive of VaD include cortical infarcts, subcortical lacunes, microbleeds or a substantial burden of white matter lesions (WMLs) [92]. WMLs likely represent areas of incomplete infarction as lack of anastomoses in the vasculature make the areas particularly vulnerable to hypoperfusion [93]. Extensive WMLs are associated with a risk of cognitive decline, and many vascular risk factors such as hypertension, hypercholesterolaemia and diabetes have been identified as modifiable risk factors for WMLs [94, 95]. Dementia may also present as mixed dementia, with one third of AD patients having underlying vascular disease [96]. Many risk factors for AD and VaD overlap, including hypertension, diabetes, and apolipoprotein E (APOE) gene.

Amongst vascular risk factors, chronic arterial hypertension has been proposed as a major contributor to cognitive impairment [97]. However, the role of BP as a risk factor for cognitive impairment is complex. A non-linear, U-shaped relationship between BP and cognitive function has been proposed, with individuals with both high and low BP performing worse on cognitive tests than individuals with BP in the mid-range [98]. However, hypertension has been consistently linked with cognitive impairment and dementia in mid-life [99]. It is postulated that microvascular dysfunction and damage induced by hypertension leads to

white matter disease, microinfarcts, and microhaemorrhages, which are correlated with cognitive dysfunction [100].

Other forms of dementia include dementia with Lewy Bodies (DLB) and frontotemporal dementia (FTD). DLB is a progressive degenerative dementia characterised by the deposition of protein aggregates (Lewy Bodies) in the cerebral cortex. Extrapyramidal features such as bradykinesia and rigidity are common in LBD [101], and autonomic dysfunction is common in LBD [102]. FTD is characterised by degeneration of the frontotemporal lobe, leading to behavioural disturbances such as disinhibition and impulsivity and progressive aphasia. It often presents in younger age groups (45-64), however its exact prevalence is unknown [103].

Summary

The Autonomic Nervous System is involved in the regulation of almost all bodily functions, including the cardiovascular system. It plays a key role in cardiovascular disease, including Atrial Fibrillation and Orthostatic Hypotension. It is also involved in regulation of blood flow to the brain, via Cerebral Autoregulation. Both AF and OH have been proposed as risk factors for cognitive impairment, and cerebral hypoperfusion is implicated in such circumstances. In this thesis, I explore how common manifestations of cardiovascular ageing– AF and OH – impact on cerebral perfusion and cognitive function in a population of community dwelling older adults. Figure 1.6 presents a schematic summary of this PhD thesis.

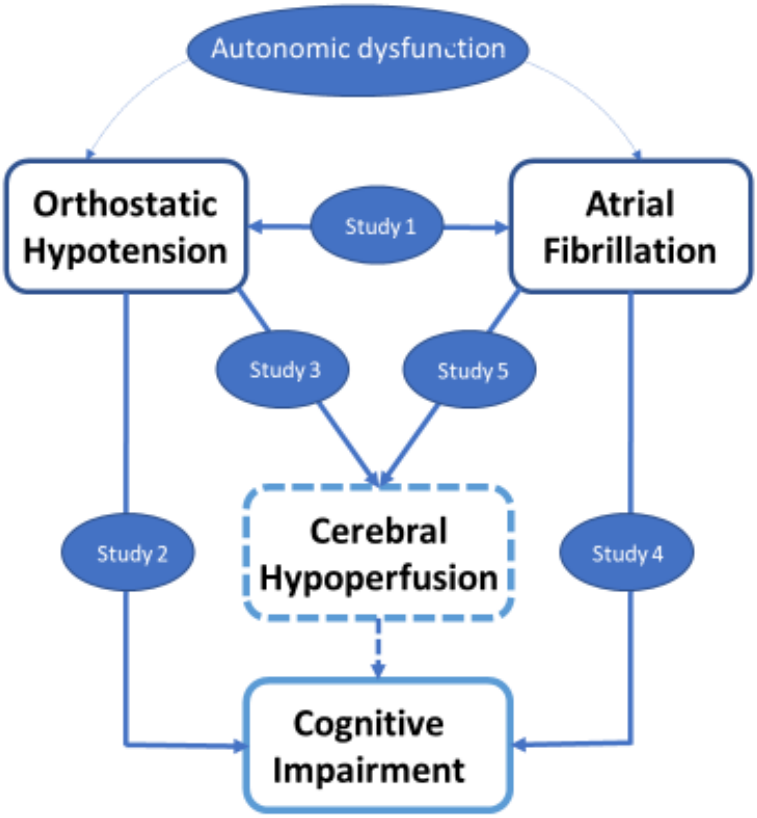

Figure 1.6. Schematic overview of thesis

Chapter 2. Orthostatic Hypotension, Atrial Fibrillation and Cognition – Literature Review

It is well known that vascular risk factors play a role in the pathogenesis of cognitive impairment and dementia. The link between blood pressure behaviour and dementia is complex, with both high and low blood pressure influencing the risk of dementia, often depending on age. In this chapter, the literature examining Orthostatic Hypotension and cognitive outcomes is reviewed. Atrial fibrillation has also been proposed as a risk factor for cognitive decline and dementia, even in the absence of a history of stroke. Existing literature examining the association between AF and dementia is also reviewed.

2.1 Orthostatic Hypotension and cognition

Orthostatic Hypotension has been extensively examined in the literature as a potential risk factor for cognitive impairment, however results of studies to date have been mixed. The prevalence of OH in persons with dementia is higher than in healthy adults (40-60% Vs 4-33%) [104-106]. However, the association between OH and cognitive decline and Dementia remains unclear, with their causal relationship still up for debate. OH and dementia may co-exist in these individuals due to underlying neurodegeneration across multiple domains. However, it has also been postulated that OH can increase the risk of cognitive impairment through alterations in cerebral blood flow caused by hypotensive troughs and hypertensive peaks increasing the risk of brain ischaemia [107].

This question has been addressed extensively in the literature. A majority of cross-sectional studies that have been performed to date have found an association between OH and an increased risk of cognitive impairment (Table 2.1). The most comprehensive cross-sectional studies to date examining this association have been carried out using data from The Irish

Longitudinal Study on Ageing [108, 109]. Using traditional oscillometric measurement of orthostatic BP measurement, participants in TILDA with OH performed worse in all cognitive domains than those without OH [109]. In recent years, more refined methods of measurement of BP behaviour in response to stand, which use beat-to-beat assessments in variation in BP have become available, allowing for more accurate characterisation of cardiovascular responses to orthostasis. Only two previous cross-sectional studies have employed such methods, [108, 110] with conflicting results. Schoon et al.[110] found no association between OH and cognitive impairment, however their sample size was small, with only 184 participants enrolled. Frewen et al. [108] completed a more comprehensive analysis of OH and cognition using beat-to-beat assessment of BP response to stand in 4,690 community dwelling adults over the age of 50. In this study there was an association between OH and cognitive performance which appeared to be dependent on the presence of supine hypertension.

Table 2.1. Cross-sectional studies examining the association between OH and cognitive impairment

Author, Year	Sample	Blood pressure assessment	Cognitive Outcomes	Finding
Suemoto et al. 2019 [111]	N = 12,826 Employees from public institutions in Brazil, aged 35-74.	Oscillometric blood pressure measurement in a seated position, and after postural change.	Consortium to Establish a Registry for Alzheimer's Disease Word List Memory Test, Phonemic Verbal Fluency Test, Trail making test.	Participants with OH had lower phonemic verbal fluency test scores than those without orthostatic changes in blood pressure. There was evidence that those who lack a compensatory heart rate change on postural challenge may have poorer executive function performance.
Bocti et al. 2017[112]	N = 543 Patients attending a memory clinic	Sphygmomanometer measurement of lying and standing BP	Assessment by neurologist or geriatrician; 3 groups: - Subjective cognitive impairment - MCI - Dementia	OH associated with lower cognitive performance in the MCI group – domains of processing speed and executive function.
Torres et al. 2017[113]	N= 961 Community dwelling adults	Automated oscillometric lying and standing BP to assess for OH	Composite scores of 18 individual neuropsychological tests to represent each cognitive domain	Systolic OH was associated with poorer cognitive function.
Punchick et al. 2016[114]	N = 571 Adults aged 65+ undergoing comprehensive geriatric assessment	Oscillometric lying and standing BP at 1 and 3 minutes	MMSE MOCA	No association between cognitive state and OH.

			MCI and dementia diagnosed during geriatric assessment	
Frewen et al. 2014[108]	N = 4690 Community dwelling adults aged 50+ TILDA	Beat-to-beat blood pressure response to stand	MMSE MOCA TMT CRT SART Word recall Picture memory	Association between OH and cognition in adults with supine hypertension. Domains of global and executive function affected.
Frewen et al. 2014[109]	N = 5,936 Community dwelling adults aged 50+ TILDA	Seated and standing BP – single standing BP	MMSE MOCA TMT CRT SART Word recall Picture memory	Participants with OH performed worse in all cognitive domains than those without OH.
Schoon et al. 2013[110]	N = 184 Adults aged 65+ attending a falls and syncope clinic	Beat-to-beat BP and HR response to orthostasis, meal and CSM	MMSE CAMCOG Dementia Diagnosed clinically adherent with guidelines	Cognitive impairment not more likely in patients with hypotensive syndromes.

CzajKowska et al. 2010[115]	N= 74 Asymptomatic adults aged 360-75	Lying standing BP measured by auscultation	COWA TMT Self-rated depression Two item hopelessness test State and trait test for anxiety	Worse BP regulation post stand associated with decreased verbal memory and decreased concentration.
Mehrabian et al. 2010[116]	N = 495 Older adults with complaints of memory loss attending a geriatric clinic	Oscillometric measurements of seated and standing BP	Cognitive efficacy profile Classified as AD, VaD, MCI and Normal	Significant cross-sectional association between OH and cognitive function.
Bendini et al. 2007[117]	N = 36 Aged over 65, admitted to psychogeriatric/ cardiogeriatric services	Oscillometric lying and standing BP at 1- and 3-minutes post stand	MMSE	No strong causal relationship between OH and cognitive impairment.
Matsubayashi et al. 1997[118]	N = 334 Community dwelling adults over 75	Oscillometric lying and standing BP	MMSE, HDSR, VCPS	Those with OH demonstrated poorer neuropsychological scores and more advanced leukocariosis than those without OH.

OH – Orthostatic Hypotension; MCI - Mild Cognitive Impairment; MMSE - Mini-Mental State Exam; MOCA – Montreal Cognitive Assessment; TILDA – The Irish Longitudinal Study on Ageing; TMT - Trail Making Test; CRT – Choice Reaction Time; SART - Sustained Attention to Response Task; CSM – Carotid Sinus Massage; CAMCOG – Cambridge Cognition Examination; COWA - Controlled Oral Word Association Test; BP – Blood pressure; AD – Alzheimer's disease; VaD – Vascular Dementia; HDSR - Hasegawa Dementia Scale Revised; VCPS - Visuospatial Cognitive Performance Score

Several longitudinal studies have also been carried out, which attempt to further understand the causal relationship between OH and cognitive performance (Table 2.2). Again, the results of these studies have been mixed. Two previous longitudinal studies using beat-to-beat BP assessment in response to stand [119, 120] have shown mixed results. Feeney et al. [119] found no association between OH and cognitive decline in the TILDA data, however follow-up period in this study was short (2 years). Earlier studies using traditional BP assessment methods found no association between OH and longitudinal cognitive performance [121-124]. Follow-up periods for these studies were short (1-6 years). However, recently a number of longitudinal studies with more protracted follow-up periods (6-23 years) have found that OH at baseline (using traditional methods to assess lying and standing BP), have found that OH at baseline is associated with cognitive decline or dementia at follow-up [125-129]. It is notable that Wolters et al.[128] found that the association was strongest in those with an impaired HR response to stand. In the absence of medications such as β-blockers, an impaired HR response to stand is suggestive of autonomic dysfunction and OH secondary to autonomic dysfunction could be reflective early signs of neurodegeneration. However, given the long duration of follow-up in this study (median 15 years), reverse causality is unlikely.

In both cross-sectional and longitudinal studies, most did not assess the effect of supine BP status on the association between OH and cognitive performance. Hypertension has been consistently linked with cognitive impairment and dementia, particularly mid-life hypertension [99]. The proposed mechanism for this association is that microvascular dysfunction induced by hypertension leads to white matter disease, microinfarcts, and microhaemorrhages, which are correlated with cognitive dysfunction [100]. In addition, hypertension causes structural alterations in cerebral arteries, with loss of their elasticity and compliance which can affect cerebral autoregulation [69]. Therefore, the presence of supine

hypertension in addition to OH could lead to greater blood pressure variability coupled with diminished ability to protect against periods of hypotension when SBP falls below a critical threshold, further exposing individuals to cerebral damage. In addition, OH has been associated with impaired baroreflex [130], and given that hypertension also leads to diminished baroreflex function [131], the presence of OH coupled with hypertension may lead to a more severe baroreflex dysfunction and exaggerated blood pressure variability. A previous study using data from the TILDA study examined this and found a cross-sectional association between OH and cognition that was dependant on the presence of supine hypertension [108].

Table 2.2. Longitudinal Studies examining the relationship between OH and Cognitive impairment

Author, Year	Sample	Blood pressure assessment	Follow-up period	Cognitive Outcomes	Finding
Zimmerman et al. 2020 [132]	N = 495 Aged between 50 and 80 years	Repeated BP measurements, lying and at 30, 90, 150 and 210 seconds of active standing	6 years	Extended CERAD-plus neuropsychological battery	Participants with OH demonstrate faster deterioration of cognitive function. MRI findings demonstrate higher prevalence of white matter hyperintensities in OH.
Rawlings et al. 2018 [133]	N = 11,709 Adults without a history of coronary heart disease or stroke	Supine and standing BP measured using oscillometric blood pressure measurement	25 years	Cognitive testing and interviews, with expert classification and adjudication of cognitive status. This was carried out at visit 5. For those that did not attend visit 5, additional cases were identified via surveillance of hospitalisations and death certificates, including ICD-9 codes for dementia.	Those with OH at baseline had a higher risk of dementia than those without OH at baseline.
Holm et al. 2017[125]	N = 18,204 Adults living in Malmo	Auscultatory lying and standing BP 2 readings taking after 1-minute standing	23 years	Dementia diagnosis obtained from Swedish National patient register. Validated through review of medical records.	Decrease in diastolic BP on stand is an independent risk factor for dementia.

Cremer et al. 2017[126]	N = 9294 Adults aged 65+ from 3 French cities	Oscillometric lying and standing BP	12 years	Dementia diagnosis made by panel of neurologists and geriatricians with expertise in dementia.	OH at baseline associated with an increased risk of dementia at follow up.
O'Hare et al. 2017[127]	N = 240 Community dwelling adults aged 70-79	Sphygmomanometer measurement of seated and standing BP	15 years	Extensive neuropsychological testing. Adjudicated outcomes taking educational attainment into account: - Normal - MCI - Dementia	Lower standing systolic BP averaged over six years from study entry increased odds of dementia diagnosis at the end of study period.
Wolters et al. 2016[128]	N = 6,204 Community dwelling adults aged 55+	Oscillometric lying and standing BP at 1, 2 and 3 minutes	Median f/u 15 years	Three step protocol: Screened using MMSE and GMS CAMDEX for those with MMSE <26 or GMS > 0 Consensus panel led by consultant neurologist for suspected dementia cases	OH associated with increased risk of incident dementia; Highest risk in those lacking a compensatory HR response.
Curreri et al. 2016[124]	N = 1421 Community dwelling adults aged 65+	Sphygmomanometer measured lying and standing BP at 1 and 3 mins	4 years	MMSE Cognitive impairment – MMSE ≤24 Cognitive decline - decrease ≥3 points on MMSE	Orthostatic hypertension more strongly associated with cognitive decline than Orthostatic Hypotension. OH did not predict cognitive impairment or decline.

Feeney et al. 2016[119]	N = 3417 Community dwelling adults aged 50+	Beat-to-beat BP response to stand	2 years	MMSE Verbal fluency Immediate and delayed recall	No longitudinal association between OH and cognition after considering effects of other confounders.
Hayakawa et al. 2015[120]	N = 150 with MCI N = 75 controls Community dwelling individuals attending a Memory Clinic	Beat-to-beat BP response to stand	3 years	MCI and dementia assessed at consensus meeting with clinical neuropsychologist and consultant psychiatrist.	Individuals with MCI with impaired orthostatic BP response to stand were twice as likely to convert to dementia than those with MCI and no impaired BP response.
Elmstahl et al. 2014[129]	N = 1,480 Cohort study of adults aged 60+ GAS-SNAC study Mean age 68	Lying and standing BP measured at 1, 3, 5- and 10-minutes post stand	6 years	Dementia defined according to DSM-IV – clinical exam and medical records MCI – objective cognitive impairment in absence of dementia.	OH and OI in absence of OH are risk factors for cognitive decline.
Rose et al. 2010[123]	N= 12,702 Prospective cohort study of middle-aged adults African American and Caucasian (ARIC)	Oscillometric lying and standing BP – measured every 30 seconds post stand up to two minutes	6 years	DWRT DSST WFT	Those with OH had worse baseline cognitive function and a larger decrement in function over 6 years, but associations were largely explained by demographic and other risk factors.

Yap et al. 2008[122]	N = 2,321 Community dwelling adults Longitudinal cohort study	Oscillometric lying and standing BP – up to 3 minutes post stand	1-2 years	MMSE Score < 23 classified as cognitively impaired Decline – ≥1 point drop	No clear association between OH and cognitive impairment at baseline. Those with hypotension and OH more likely to have cognitive impairment. No longitudinal decline.
Viramo et al. 1999[121]	N = 1,159 Home dwelling and institutionalised, born before 1920; Mean age 76	Oscillometric lying and standing BP 1 and 3 minutes post stand	2.5 years	MMSE – spelling and calculation tasks removed. Max score 25	No association between OH at baseline and cognitive decline follow-up.
Elmstahl et al. 1997[134]	N= 33	HUTT for 8 minutes BP measured every minute	5 years	MMSE 'Case' – MMSE < 27 at follow-up with clinical signs	Cases had higher orthostatic BP fall at baseline than controls.

CERAD - Consortium to Establish a Registry for Alzheimer's Disease; OH – Orthostatic Hypotension; MRI – Magnetic Resonance Imaging; ICD - International Statistical Classification of Diseases; BP – Blood Pressure; MCI - Mild Cognitive Impairment; MMSE - Mini-Mental State Exam; CAMDEX - Cambridge Examination for Mental Disorders of the Elderly; GMS - Geriatric Mental State Examination; DSM - Diagnostic and Statistical Manual of Mental Disorders; ARIC - Atherosclerosis Risk in Communities Study; DWRT - Delayed Word Recall Test; DSST - Digit Symbol Substitution Test; WFT – Word Fluency Test; HUTT – Head-up Tilt Test

The most frequently proposed and most apparent explanation for the association between OH and cognitive impairment is that recurrent episodes of cerebral hypoperfusion in OH result in cerebral damage. The autonomic nervous system is involved in the maintenance of cerebral flow via cerebral autoregulation and autonomic dysfunction can manifest as OH. Cerebral autoregulation may also be attenuated with ageing, with resulting failure to adapt to changes in BP [135]. This may result in cerebral hypoperfusion and cell damage [136, 137]. Enhanced white matter hyperintensities are evident in such circumstances [118], and an increasing white matter lesion burden is associated with an increased risk of dementia [69]. A number of studies have shown an association between OH and cerebral hypoperfusion [137-142], however to the authors knowledge, no population representative study to date has examined cerebral haemodynamics in response to stand in parallel with cardiovascular responses to stand.

This thesis aims to examine the association between OH and longitudinal change in cognitive performance, as well as the impact of hypertension on this association. In addition, it aims to further understand the mechanisms for this association by examining cerebral perfusion in OH using near infra-red spectroscopy.

2.1 Atrial Fibrillation and Cognition

Atrial Fibrillation and dementia share many risk factors, including age, hypertension and diabetes. Importantly, AF is associated with an increased risk of stroke, which in turn can lead to cognitive impairment and dementia. However, AF has been proposed as a risk factor for cognitive impairment even in the absence of a history of stroke, with mechanisms such as cerebral hypoperfusion, micro-emboli, inflammation and genetic factors potentially playing a role in this association. Many studies have examined the relationship between AF and cognition both in those with and without a history of stroke, with conflicting results. In this section, existing literature examining the association between AF and cognition is reviewed.

Several studies have shown as association between AF and cognitive impairment in populations of patients with a history of stroke [143-146], including a meta-analysis published by Kwok et al. [44] which reports a 2.4-fold increase risk of dementia in stroke in patients with AF. It is postulated that factors such as cerebral hypoperfusion and sub-clinical micro-emboli plays a role in this increased risk. Emerging evidence suggests an association between AF and cognition in the general population. Since the first paper addressing this, published by Ott et al. [147] in 1997 using data from the Rotterdam Study, numerous studies have further investigated this topic.

A large number of cross-sectional studies have consistently reported a link between AF and cognitive impairment in the general population (Table 2.3). However, the many longitudinal studies that have also been carried out (Table 2.4), have reported conflicting results. There is substantial heterogeneity in their design, with variations in the definitions and tools employed to diagnose cognitive impairment and dementia and methods used to evaluate presence of AF. In addition, study design and length of follow-up vary greatly across studies.

Inclusion and exclusion criteria vary greatly, with some but not all studies excluding those with a history of stroke, dementia or both at baseline. AF is associated with a 4-5 fold increased risk of stroke at baseline, and given the powerful association between stroke and cognition [148], presence or absence of stroke in AF is highly relevant to cognitive performance. The meta-analysis by Kwok et al. [44] suggests that the overall increased risk of dementia in AF is primarily driven by the significant and consistent risk in patients with stroke.

Table 2.3. Cross-sectional studies examining association between AF and Cognition

Author, year	Population	Assessment of AF	Cognitive outcomes	Results
Ott et al. 1997[147]	N = 6,583 Adults aged 55+, including those living in institutions	12-lead ECG Analysed by software algorithm	3 phase approach: MMSE/GMS screen CAMDEX Dementia diagnosis confirmed by neurologist	AF is significantly associated with dementia.
Cacciatore et al. 1998[149]	N = 1,075 Adults aged 55+ community dwelling and those living in institutions	Physical examination	MMSE Cognitive impairment defined as MMSE <24	AF is associated with cognitive impairment. Note: CHF was primary predictor of interest in this study.
Kilander et al. 1998[150]	N = 952 Men, mean age 72 (born 1920-1924)	ECG	TMT MMSE	Men with AF had lower cognitive function than those in sinus rhythm, even after exclusion of those with a history of stroke.
Jozwiak et al. 2006[151]	N = 2,314 Adults aged 65+ hospitalised for any reason	12-lead ECG	MMSE – divided into quartiles Impaired cognitive function defined as MMSE ≤23	Significant association between AF and impaired cognitive function.
Elias et al. 2006[152]	N = 1,011 Men without a history of dementia or stroke	ECG or Holter obtained from hospital or outside physician, or at	Battery of neuropsychological tests – composite score	Men with a history of AF performed worse on a range of cognitive performance measures.

	Framingham offspring	Framingham exam. ECG interpretation confirmed by cardiologist		
Bilato et al. 2009[153]	N = 1,576 Adults aged 65+ living in the community	ECG – evaluated by cardiologists	MMSE Cognitive impairment – MMSE < 24	A significantly larger number of participants with AF had cognitive impairment.
Alonso et al. 2017[154]	N = 6,432 Adults aged 45-64	12-lead ECG or past history of AF	Comprehensive neuropsychological testing Participants classed as Normal, MCI or dementia by panel of neurologist and neuropsychologists according to NIAAA.	Higher prevalence of MCI and dementia amongst individuals with AF.

ECG – Electrocardiogram; MMSE – Mini-Mental State Exam; GMS - Geriatric Mental State Examination; CAMDEX - Cambridge Examination for Mental Disorders of the Elderly; AF – Atrial Fibrillation; CHF - Congestive heart failure; TMT – Trail Making Test; MCI – Mild Cognitive Impairment; NIAAA - National Institute on Aging—Alzheimer's Association

Table 2.4. Longitudinal studies examining association between AF and Cognition

Author, year	Population	Assessment of AF	Follow-up period	Cognitive outcomes	Results
Tilvis et al. 2004[155]	N = 650 Adults born in 1904, 1909, and 1914	Not reported	5 and 10 years	MMSE, CDR Impaired cognition – MMSE <24 Presence of dementia determined by a neurologist Decline – decrease in MMSE of 4, or increase in CDR	AF was associated with cognitive decline at 5 years.
Forti et al. 2006[156]	N = 611 Patients seeking medical advice for cognitive complaints Age ≥60	Self-report Review of medical charts where available Confirmed by clinical examination	Mean 3.8 years	MCI – MMSE ≥24 and objective impairment Dementia – deficit in two or more cognitive domains affecting function – diagnosed by geriatrician	AF is an independent risk factor of conversion to dementia from MCI, but not in patients with normal cognition.
Park et al. 2007[157]	N = 423	ECG	12 and 36 months	Battery of neuropsychological tests – change assessed	No significant difference in change in cognitive function between those with and without AF.
Rastas et al. 2007[158]	N = 553 Adults aged 85+ living in the community or in institutions	12-lead ECG or 3-lead Holter monitor or a history of AF in health records	3, 5 or 8 years Mean 3.5 years	Dementia diagnosed by neuropsychological battery of tests and neurologists examination.	AF was not an independent predictor for dementia.

Di Carlo et al. 2007[159]	N = 2,830 Adults aged 65-84 community dwelling or in institutions	Not reported	Mean 4 years	MCI – based on age and education specific cut-offs in neuropsychological testing Dementia diagnosed by structured clinical assessment	No significant association between AF and progression to MCI or dementia.
Peters et al. 2009[160]	N = 3,336 Adults aged 80+ in HYVET trial – hypertensive, randomised to target BP	ECG	2 years	Initial screening with MMSE then further neuropsychological testing if screened positive Cognitive decline – MMSE fell to < 24 or fell by 3 points Dementia – diagnosed by expert committee	No association between AF and dementia.
Bunch et al. 2010[161]	N = 37,025 Adults attending Intermountain healthcare system Mean age 60	Hospital discharge summaries and data from ECG database	5 years	Dementia diagnosed based on ICD – 9 codes. No specific cognitive assessment.	Significant association between AF and dementia.
Dublin et al. 2011[162]	N = 3,045 Community-dwelling, non-demented adults aged 65+	Based on two hospital encounters with ICD codes for AF	Every two years Mean f/u 6.8 years	Dementia diagnosed by multi-disciplinary consensus committee using DSM criteria.	AF was associated with a 40-50% higher risk of both AD and all-cause dementia, independent of history of stroke.

				NINCDS-ADRDA to classify probable and possible AD	
Marengoni et al. 2011[163]	N = 685 Dementia and stroke free adults aged 75+	Based on participants recorded pulse rate and rhythm, medical records, medications and inpatient register database	6 years	MMSE Dementia diagnosed as per DSM-III criteria. Not reported whether physician diagnosis	No association between AF and dementia.
Li et al. 2011[164]	N = 837 Adults aged 55+ with MCI	ECG	5 years	MMSE IADLs Further neuropsychological tests for those with abnormal MMSE MCI diagnosed by Peterson criteria – subjective memory complaint, abnormal cognitive functioning for age and absence of dementia Dementia diagnosis based on DSM-IV criteria	AF not associated with progression from MCI to dementia.
Marzona et al. 2012[165]	N = 31,506 Adults across 40 countries at high risk of cardiovascular disease - aged 55+	Not reported	Mean 4.7 years	MMSE (translations where appropriate) Cognitive decline – decrease of ≥3 points on MMSE	AF was a risk factor for cognitive decline and dementia, independent of previous or incident stroke.

	- established CVD diabetes with end organ damage			Dementia – new diagnosis of dementia or MMSE <23 during follow-up	
Haring et al. 2013[166]	N = 6,455 Cognitively intact post-menopausal women aged 65-79	Self-report	Mean 8.4 years	Modified MMSE to screen and those who screen +ve proceed to neurocognitive and neuropsychiatric assessments. Classed as No dementia, MCI and probably dementia by physician	No statistically significant association between AF and MCI or probably dementia.
Thacker et al. 2013[167]	N = 5, 888 Adults aged 65+ with no history of AF or stroke at baseline	12-lead ECG and hospital discharges based on ICD-9 codes	10 years	Modified MMSE and DSST – cognitive trajectories assessed	Cognitive decline more rapid after incident AF detected.
Rusanen et al. 2014[168]	N = 1,510 Adults aged 65-79	Based on ICD-8 codes	Mean 25.5 years	MMSE screening and referred for clinical evaluations and neuropsychological testing. Dementia diagnosis made by a review board based on DSM-IV criteria Dementia diagnosis also obtained form medical records and register data	AF did not have an effect on the risk of incident dementia.

De Bruijn et al. 2015[169]	N = 6,514 Adults aged 55+	ECG – assessed by software algorithm, and confirmed by physicians. Hospital discharges. Family and specialist physicians.	20 years	MMSE and GMS screening. MMSE < 26 or CMS >0 screen +ve Further neuropsychological testing if screen +ve. Final dementia diagnosis by consensus panel according to DSM-III	Increased risk of incident dementia in participants with AF.
Singh-Manoux et al. 2017[170]	N = 10,214 British civil servants aged 45-69 at the start of follow-up	12-lead ECG and national hospital episodes statistics	15 years	Comprehensive neuropsychological testing – composite global cognitive score created. Dementia diagnosis based on electronic health records.	Greater cognitive decline in those with longer exposure to AF. Decline not explained by stroke, but when stroke and CHD taken into account, no longer significant. Similar finding with incident dementia.
Nishtala et al. 2018[171]	N = 2,682 Dementia free adults aged 40+ Participants with a history of stroke excluded	Self-reported and confirmed from multiple sources including medical records and ECG	3 years or 6 years	Battery of neuropsychological testing.	AF associated with decline in performance on test of executive function.
Chen et al. 2018[172]	N = 12,515	ECGs performed at study visits and	20 years	Neuropsychological testing.	Participants who developed AF had greater cognitive decline and greater risk of incident dementia over 20 years.

	Adults aged 45-64 at baseline. No baseline AF	hospital discharge records.		Dementia diagnosed based on algorithm load on in NIAAA work groups and DSM-VI. Hospital discharges also assessed.	Association attenuated with stroke but remains significant.
Bailey et al. 2021[173]	N = 25,980 Community dwelling black and white adults aged 45 years and older.	ECG, confirmed by a physician.	Mean follow-up 8.06 years	Neuropsychological testing, including: Six-item screener (SIS) Word list learning Word list delayed recall Animal naming test Letter F fluency test NINDS/CSN 5-minute protocol – includes subsets of MOCA.	AF associated with lower baseline cognitive performance. Stepper longitudinal declines in cognitive performance in those with AF, and effect modification by race, sex and incident stroke were also detected.

MMSE- Mini-Mental State Exam; CDR - Clinical Dementia Rating; AF – Atrial Fibrillation; MCI - Mild Cognitive Impairment; ECG – Electrocardiogram; HYVET – Hypertension in the Very Elderly Trial; ICD - International Statistical Classification of Diseases; DSM - Diagnostic and Statistical Manual of Mental Disorders; AD – Alzheimer's Dementia; NINCDS-ADRDA - National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; IADL - Instrumental activities of daily living; CVD – Cardiovascular disease; DSST - Digit Symbol Substitution Test; GMS - Geriatric Mental State Examination; NIAAA - National Institute on Aging—Alzheimer's Association; SIS - Six-item Screener; MOCA – Montreal Cognitive Assessment; NINDS/CSN - National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network

One proposed explanation for the conflicting evidence in studies in the general population is the potential role of age in the association between AF and cognition. In a study by Bunch et al. [161], AF was a risk factor for dementia in adults aged <70 , but not in those aged >80. In the original cross-sectional study by Ott et al. [147] based on participants in the Rotterdam Study, the association between AF and dementia was stronger in those aged <75. In the subsequent longitudinal follow-up of the Rotterdam cohort by de Bruijn et al. [169], it was in participants aged <67 that AF increased the risk of incident dementia. In addition, the studies which enrolled the oldest participants found no longitudinal association between AF and cognitive impairment, including a study by Rastas et al. [158] which enrolled participants aged ≥85 and a study by Peters et al. [160] from the HYVET study which enrolled adults aged ≥80. These findings are similar to results from studies on hypertension, where the link between hypertension and cognition is more consistent in middle-age. It is possible that other risk factors in older populations become more important.

There are many mechanisms proposed for the association between AF and cognition. Figure 2.1 below summarises some of these potential mechanisms.

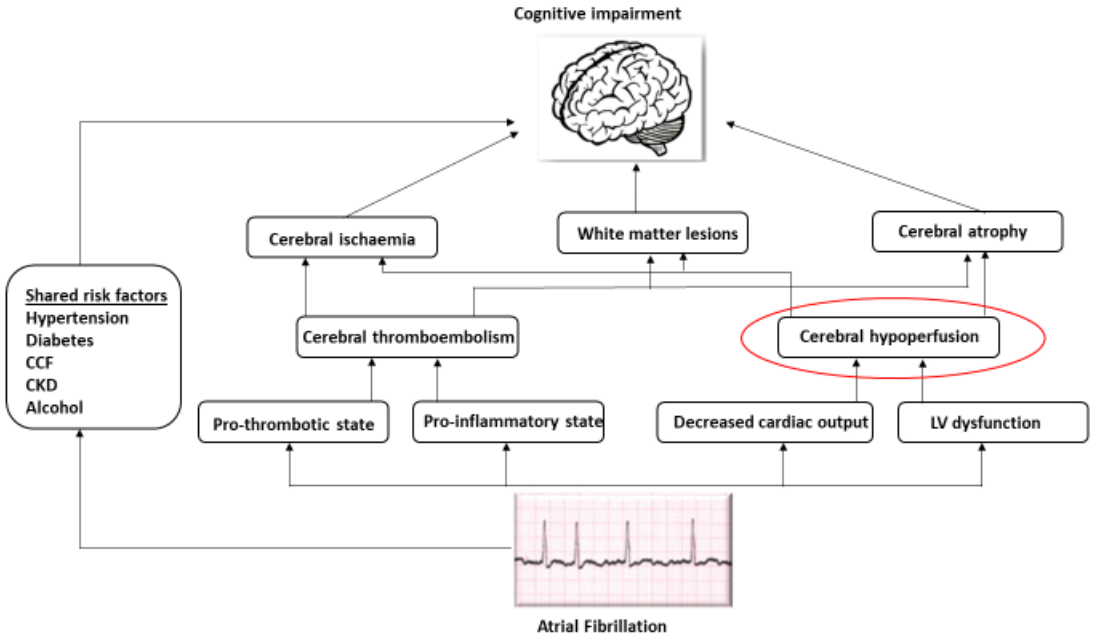

Figure 2.1. Mechanisms linking AF and cognition

One of the most frequently cited mechanisms linking AF and cognitive impairment is cerebral hypoperfusion. Previous studies have found that AF is associated with reduced brain volume, which is independent of cerebral infarcts [174], and it is thought that cerebral hypoperfusion plays a role in the pathogenesis of this [175]. Multiple previous studies have assessed cerebral blood flow in individuals with AF [175-182], however the majority of these studies were not population representative. One previous study carried out using data from the AGES-Reykjavik study found that in a population sample, persistent but not paroxysmal AF was associated with reduced cerebral perfusion using phase contrast MRI [175]. Participants were static during measurement of cerebral flow in this study. In addition, improved cerebral perfusion has been demonstrated on restoration of sinus rhythm after DC cardioversion in patients with AF [183].

In this thesis, cerebral blood flow during dynamic standing is assessed.

2.3 Conclusion

Both OH and AF have been proposed as risk factors for cognitive impairment and have been assessed extensively in the literature. In cross-sectional studies, OH is consistently linked with cognitive impairment, however, results of longitudinal studies are more mixed. Cerebral hypoperfusion is frequently cited as a potential mechanism for cognitive impairment in OH, however the majority of studies investigating cerebral perfusion in OH involve small sample sizes. AF is also consistently linked with cognitive impairment in cross-sectional studies, but results of longitudinal studies are mixed. In the case of stroke, the link between AF and cognitive impairment appears consistent, however in the general population results vary. There are few large studies investigating cerebral perfusion in AF, a frequently proposed mechanism for the link between AF and cognitive decline.

This thesis investigates the relationship between OH and cognitive decline in a population representative sample and examines cerebral perfusion in OH during dynamic standing. The thesis also investigates whether AF is associated with longitudinal cognitive decline in older Irish adults and examines cerebral perfusion in AF.

Chapter 3: Methods

This thesis includes five quantitative studies that use data from The Irish Longitudinal Study on Ageing (TILDA). This chapter introduces TILDA and describes the data used in this thesis

3.1 The Irish Longitudinal Study on Ageing

TILDA is a large study of community-dwelling adults resident in the Republic of Ireland [184]. It is a nationally representative prospective study that is the most comprehensive study of ageing carried out in Ireland to date. TILDA collects information on aspects of health, economic and social circumstances from people aged over 50 in Ireland over a series of data collection "waves" that occur once every two years. It is unique amongst longitudinal studies in the breadth of physical and mental health measures that are collected. In particular, the cardiovascular measures that are collected as part of the TILDA study are unique.

3.1.1 Sampling Methodology

Recruitment for the first wave of the TILDA study began in 2009, with a target population of those aged 50 and over living in the community in the Republic of Ireland, along with their partners (of any age). The sampling methodology chosen for the TILDA study to ensure a population representative cohort study was the RANSAM method [185], designed by the Economic and Social Research Institute of Ireland (ESRI). This method employs a list of all residential postal addresses in the Republic of Ireland, compiled by the Irish postal service (An Post) and Ordnance Survey Ireland. The addresses are grouped into 1433 clusters, each containing 500-1500 addresses, which are stratified according to socio-economic status and geographic location. Of these, 640 cluster were selected with the probability of selection proportional to the number of individuals aged 50+ living within the cluster. Location of the clusters selected is depicted in Figure 3.1. Forty addresses were selected from each cluster

and each selected address was visited by an interviewer who ascertained the eligibility of the address. Invitation letters were sent to each unique address (and hand delivered in the case of non-unique addresses). A home visit was carried out a week later to determine the eligibility of household members, who were invited to take part in the study. The response rate for TILDA was 62%, with over 8000 people taking part in the study.

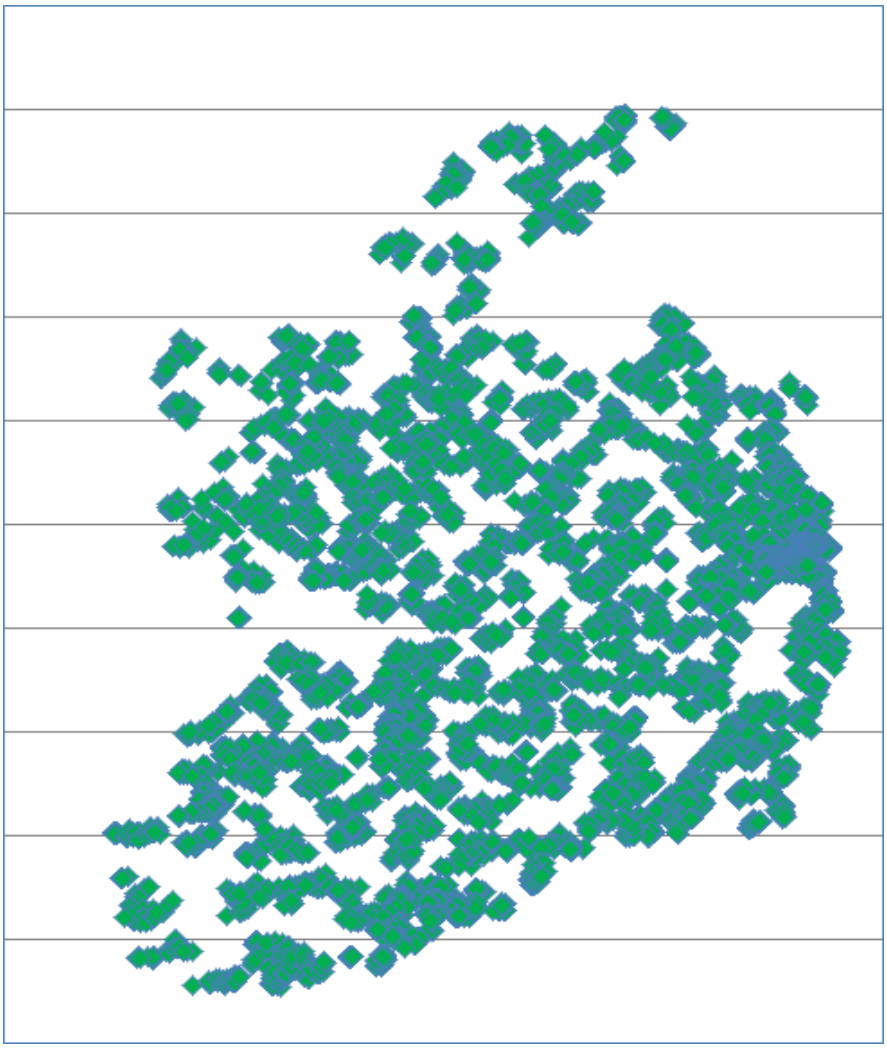

Figure 3.1 Location of cluster selected at random for inclusion in TILDA

3.1.2 Data acquisition

There are three components to the TILDA study by which data on the study participants is acquired. The computer-aided personal interview (CAPI) is administered at each wave of data collection in the participants' own home. The CAPI collects detailed information on

demographics, lifestyle, social, behavioural, mental, and physical health. A self-completion questionnaire (SCQ) was provided for participants which they were invited to complete in their own time and send back to the TILDA centre. Details of data captured in the SCQ and CAPI are summarised in Figure 3.2.

Demographic data
- Education
- Childhood health
- Migration history
- Marital status and marriage history

Social circumstances
- Transfers to (and from) children
- Transfers to (and from) parents
- (Instrumental) activities of daily living
- Helpers
- Social connectedness
- Participation in social/recreation activities
- Relationship quality (SCQ)

Employment and lifelong learning
- Employment situation
- Job history
- Lifelong learning

Retirement and expectations
- Planning for retirement
- Expectations

Income and assets
- Sources of income
- Assets

Transport
- Transportation
- Driving

Medications

Health-care utilization

Physical health
- Self-rated health
- Limiting long-standing illness/disability
- Sensory function
- Cardiovascular disease
- Non-cardiovascular chronic illness
- Falls/fear of falling/steadiness
- Chronic pain
- Incontinence
- Medical screening

Mental health
- Self-reported mental health
- Depression
- Life satisfaction
- Anxiety (SCQ)
- Worry (SCQ)
- Loneliness (SCQ)
- Perceived stress (SCQ)
- Stressful life events (SCQ)
- Quality of life (SCQ)

Cognitive health
- Self-rated memory
- Orientation
- Word-list learning (immediate and delayed recall)
- Verbal fluency
- Prospective memory

Behavioural health
- Smoking
- Physical activity
- Sleep
- Alcohol (SCQ)

Ageing perceptions (SCQ)

Figure 3.2 Summary of data collected in TILDA CAPI and SCQ
(SCQ) – data collected on those who completed SCQ

The third component of the TILDA study involves a comprehensive health assessment, carried out in the TILDA health centre. The health assessment is carried out at alternate waves, with health centre data available for waves 1 and 3 to date. Objective measures of health in participants who attended the health centre was collected. Those who were unable or unwilling to attend the health centre were offered an in-home health assessment where a subset of features was measured. Data collected in the in-centre assessments are

summarised in Table 3.1. Health centre data included in this study will be described in detail later in this chapter.

Neuro-psychological	Cardiovascular	Mobility	Sensory	Anthropometric/Other
MMSE	Pulse wave velocity	TUG	Visual Acuity	Height
MOCA	Seated and standing blood pressure	Repeated Chair stands	Contrast sensitivity	Weight
SART	Phasic blood pressure responses	GAITRite assessment	Macular pigment density	Waist and hip circumference
Picture memory	Heart rate variability		Retinal photographs	Grip strength
NART	Cerebral perfusion		Multisensory integration (SHAMS)	Heel ultrasound
Visual reasoning	ECG			Blood samples
Choice reaction time				Hair samples
Colour trail tests				Accelerometery (subset)
Depressive symptoms				MRI Brain (subset)
Anxiety symptoms				Dental assessment offered

Table 3.1 Health centre assessment data collected

MMSE – Mini-Mental State Examination; MOCA – Montreal Cognitive Assessment; SART – Sustained Attention to Response task; NART – National Adult Reading test; ECG – Electrocardiogram; TUG – Timed up and go; SHAMS – Sound induced flash illusion; MRI – Magnetic Resonance Imaging;

3.1.3 Longitudinal data acquisition

TILDA consists of a series of "waves" of data collection, carried every two years, with health centre data collected at alternate waves. This study employs data from the first to third waves of the TILDA study. The first wave of data collection was carried out from 2009-2011 and included a CAPI, SCQ and comprehensive health centre assessment. The second wave of data was collected in 2012 and included a CAPI and SCQ, and the third wave of data was collected between 2014 – 2015, including a CAPI, SCQ and health assessment. Data collection waves are summarised in Figure 3.3 There was attrition between waves 1 and 3, with 8504 participant interviews at wave 1, and 6566 included at wave 3. Details of sample sizes at waves 1-3 are described in Table 3.2.

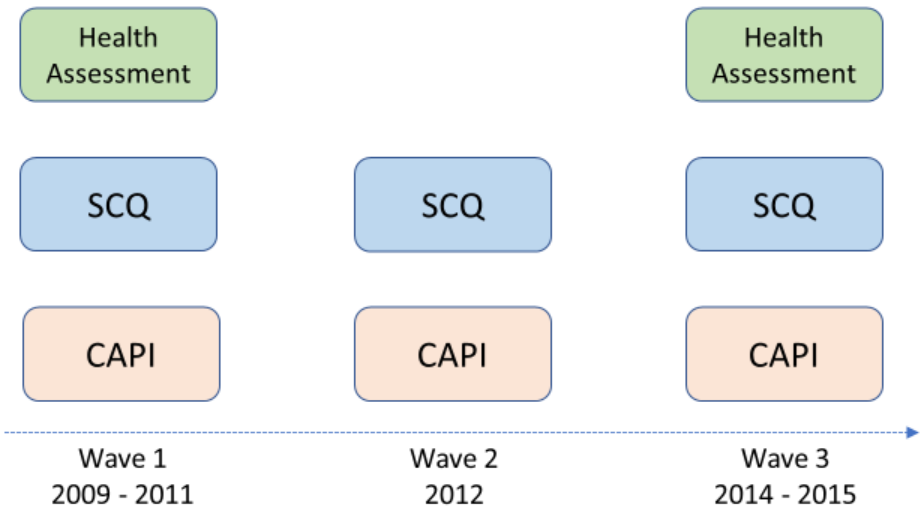

Figure 3.3 Data collection waves 1-3 TILDA
CAPI – Computer-aided personal interview; SCQ – Self completion questionnaire;

	Wave 1	Wave 2	Wave 3
CAPI			
Self	N = 8,504	N = 7,375 (90%)	N = 6,566 (85%)
Proxy	n/a	N = 80 (79%)	N = 121 (62%)
SCQ	N = 7,196 (85%)	N = 6,274 (85%)	N = 5,569 (85%)
Health Assessment	N = 6,150 (72%)	n/a	N = 5,364 (82%)

Table 3.2 Response rates for waves 1-3

CAPI – Computer-aided personal interview; SCQ – Self completion questionnaire; Proxy – proxy interviews were required if a participant was unable to complete and interview themselves.

CAPI self-interview rates based on those eligible to complete CAPI – still participating and cognitively capable to complete

CAPI proxy-interview rates based on those unable to complete a self-interview due to physical or cognitive impairment

SCQ rates based on number of eligible participants (those who completed a self-interview)

Proxy rates based on those requiring proxy interview – i.e. unable to complete interview themselves

Table adapted from O'Donoghue et al[186]

3.1.4 Ethical Approval

Ethical approval for TILDA was provided by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin. All participants provided written informed consent, and all experimental procedures adhered to the Declaration of Helsinki.

3.2 Measures Included in Study

This PhD thesis examined manifestations of cardiovascular autonomic ageing and brain health in an Irish population, and in order to do this, specific measurements within the study were employed which are described in detail in this section.

3.2.1 Orthostatic Blood Pressure Measurements

Participants who attended the health centre for assessment at wave 1 and wave 3 had an active stand test, measuring beat-to-beat blood pressure response to standing up carried out by research nurses. Beat-to-beat blood pressure wave measured non-invasively using a Finometer Midi device (Finapres Medical Systems). A standardised protocol was used in the

assessment of orthostatic BP. Participants lay supine for 10 minutes prior to stand, in a quiet room with ambient temperature 21-23 ^{0}C. Baseline BP was measured as the mean value between 60 and 30 seconds prior to stand. Participants were asked to stand in a timely manner, and the nurse assisted when necessary. Systolic BP, diastolic BP and heart rate were then monitored for a further 120 seconds. After the active stand was complete, participants were asked to report if they had felt any symptoms such as light-headedness, dizziness, or unsteadiness.

At wave 1, BP was calculated at 10 seconds intervals using 5 second moving averages around each point. The 120 second time point for most participants would include edge effects given the use of moving averages, therefore BP was estimated at 10 second intervals up to 110 seconds post stand. At wave 3, BP data was smoothed using 10 seconds moving average around each time point. At wave 1, the point of stand was selected using the data from the graphical user interface on the Finometer. At wave 3, the point of stand was determined using the data from the height correction unit at W3.

Previous analysis of the TILDA data has shown that a majority of participants stabilise their BP within 40 seconds of stand [66]. OH at 40 seconds has been found to be associated with outcomes in the TILDA study, including falls and cognitive decline [79, 187]. In addition, a study by Juraschek et al. using data from the Atherosclerosis Risk in Communities (ARIC) study, found that on repeated measuring of blood pressure post standing, the first two measurements post stand were most associated with outcomes [188]. The first measurement was taken at a mean of 28 seconds (+/- 5.4 seconds standard deviation). The second measurement was taken at a mean of 53 seconds (+/- 7.5 seconds standard deviation. Therefore, in most of the studies contained in this thesis, we use the 40 second time point to

assess for Orthostatic Hypotension, as marker of impaired blood pressure stabilisation. We also assess OH at 110 seconds in Study 2, to represent a more severe subset of participants with OH. These participants have OH at every time point throughout the stand. Figure 3.4 depicts continuous BP monitoring during active stand.

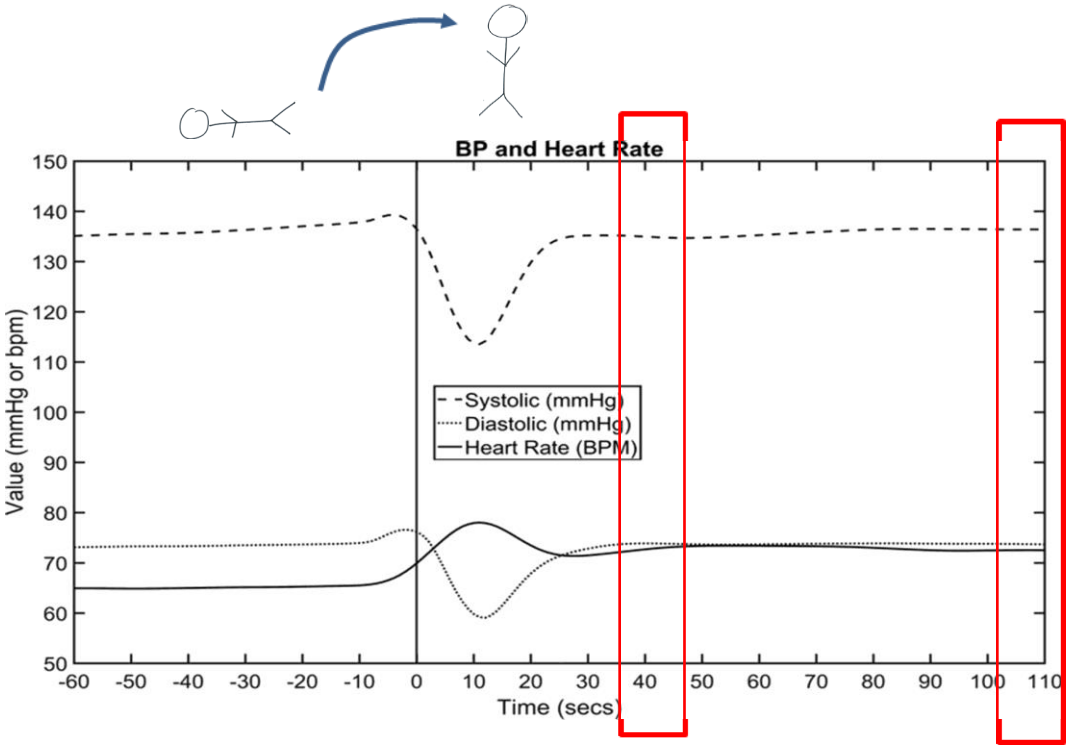

Figure 3.4 Orthostatic blood pressure assessment

3.2.2 Assessment of Atrial Fibrillation

All participants had 10-minute three lead ECG assessment while lying supine. At wave 1, ECGs were screened for AF by two clinicians, according to ESC guidelines [189], and any disagreements were resolved by a cardiologist. At wave 3, all ECGs were screened for AF by a physician according to ESC guidelines, and all cases of AF were confirmed by a second physician.

3.2.3 Assessment of Cerebral Perfusion

During the active stand test, frontal lobe perfusion was measured at baseline and in response to orthostasis at the wave 3 health assessment, using Near infra-red spectroscopy (NIRS). Real time frontal lobe oxygenation was assessed using the Artinis Portalite System, a portable continuous wave NIRS system that uses spatially resolved spectroscopy, designed to measure cerebral perfusion [190]. NIRS is based on the fact that human tissue is relatively transparent to light in the near infra-red spectrum. NIRS measurements have been shown to correlate well with change in functional MRI [191], and transcranial Doppler [192].

Haemoglobin scatters light, and the ratio of infrared light absorbed to light scattered changes depending on the degree of haemoglobin that is binding with oxygen. Absorption of light in the near infra-spectrum is mainly by oxygenated haemoglobin (oxyHb) and deoxygenated haemoglobin (deoxyHb), and both have differing absorption spectra. Therefore, the change in oxyHb and deoxyHb concentration can be calculated by measuring the change in absorption at two or more wavelengths.

Tissue saturation index (TSI, %) is the measure used in this study, and is defined as as (oxyhemoglobin)/ (oxyhemoglobin + deoxyhemoglobin) X 100 and expressed as a percentage [193].

During the active stand procedure, TSI was measured concurrently with beat-to-beat BP measurements.

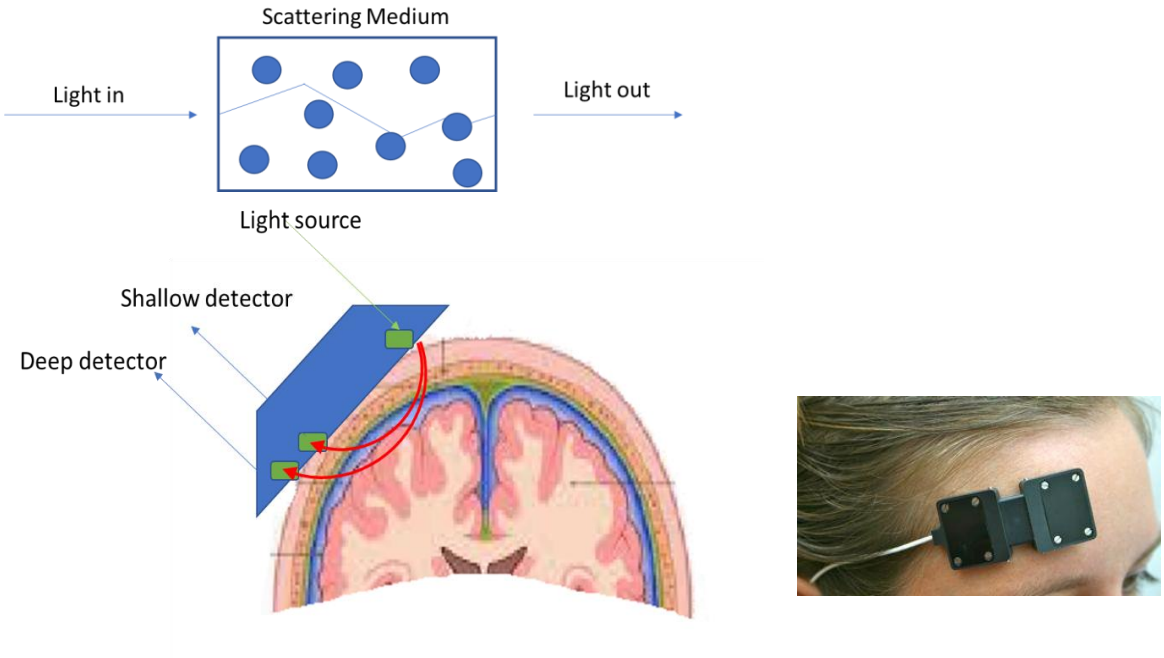

Figure 3.5 Near Infra-red spectroscopy

In the studies included in this these, baseline TSI (average TSI value at 30 and 60 seconds prior to standing) as well as TSI at 10-second intervals post stand are assessed. In addition to this, in Study 3, two additional measures on initial stand were assessed:

(1) *Delta TSI* – this was the size of the drop at the nadir TSI value, i.e. Baseline TSI – Nadir TSI (units - %). The nadir was calculated as the nadir value within the first 25 seconds after standing.

(2) *Nadir width* – this is measured as the width the trough surrounding the nadir i.e. at 50% of the depth of the trough. It is used to measure the time spent in the nadir, i.e. the time it takes from the start to the end of the nadir (units – seconds).

3.2.4 Cognitive assessment

Global cognition was assessed in this study using the Montreal Cognitive Assessment (MOCA). The MOCA includes assessment of the cognitive domains of executive and visuospatial

function, memory, language and attention, yielding a single score ranging from 0 to 30. MOCA was administered at the health centre. The MOCA is used frequently in the clinical setting [194], is sensitive to mild deficits, and is useful in identifying patients with mild cognitive impairment [195]. In addition to this, it demonstrates good test-retest and inter-rater reliability [196]. A copy of the MOCA is supplied in the Appendix 1.

Baseline MOCA was assessed at the wave 1 health centre assessment. Follow-up MOCA was assessed at the wave 3 health assessment – either home health assessment or health centre health assessment.

The MOCA was assessed as a total score (maximum score 30), in order to assess global cognition. The results were then divided into sub domains of MOCA and assessed individually - including recall, visuospatial, executive function, attention and working memory, language, and orientation. Recall was assessed using the delayed recall section of the MOCA (maximum score 5). The visuospatial domain was assessed using cube drawing and clock drawing (maximum score 4). To assess Executive function, the trail test section of MOCA, language fluency and a two-item verbal abstraction task were used (maximum score 4). Attention and working memory were assessed via digits forward and backward, the sustained attention task and the serial subtraction task in MOCA (maximum score 6). Language was assessed using animal naming, repetition and the language fluency task (maximum score 6). Orientation to time and place was assessed using questions regarding date, month, year, day, place and city were used (maximum score 6).

3.3 Objective of thesis

The objective of this doctorate thesis is to use data from the first three waves of data collection in The Irish Longitudinal Study on Ageing to investigate the association between common manifestations of cardiovascular autonomic ageing, that is Orthostatic Hypotension and Atrial Fibrillation, and brain health in a population of adults over the age of 50 in the Republic of Ireland. The following are investigated:

1. The cross-sectional association between Orthostatic Hypotension and Atrial Fibrillation – wave 1
2. The longitudinal association between Orthostatic Hypotension and global cognitive decline – wave 1 to 3
3. The cross-sectional association between Orthostatic Hypotension, symptoms of Orthostatic Intolerance, and cerebral perfusion – wave 3
4. The cross-sectional association between Atrial Fibrillation and cerebral perfusion - wave 3
5. The longitudinal association between Atrial Fibrillation and global cognitive decline – wave 1 to 3

Chapter 4: Is orthostatic hypotension more common in individuals with Atrial Fibrillation? – Findings from the Irish Longitudinal Study on Ageing (TILDA)

4.1 Abstract

Introduction

Atrial Fibrillation (AF) and orthostatic hypotension (OH) share common risk factors such as age, hypertension and cardiovascular disease. The autonomic nervous system (ANS) also plays a role in the pathogenesis of both AF and OH. The aim of this study is to assess whether individuals with AF are more likely to have OH than those without AF.

Methods

Data from wave one of The Irish Longitudinal study on Ageing were used. Beat-to-beat blood pressure was measured during active stand lasting 110 seconds. OH, defined as a drop in systolic SBP ≥20mmHg or a drop in DBP ≥10mmHg at 30, 60, and 90 seconds was assessed. Initial OH was assessed as a drop in systolic BP ≥40mmHg or a drop in diastolic BP≥20mmHg.

Results

4408 participants aged ≥50 had active stand and electrocardiogram data suitable for analysis. AF was identified in 101 of these. Logistic regression found participants with AF were more likely to have OH at 30 (OR 1.95, 95% CI 1.24 – 3.06) and 60 (OR 2.13, 95% CI 1.18 – 3.87) seconds, and IOH (OR 1.81, 95% CI 1.21 - 2.70). The association between IOH and OH at 30 seconds remained significant following adjustment for confounders (age, sex, baseline HR, education, BP, smoking, frailty, BB use, anti-hypertensive use (excluding BBs), and number of cardiovascular conditions.

Conclusion

OH is more common in individuals with AF, this may reflect the role of the ANS in both AF and OH.

4.2 Introduction

Atrial Fibrillation (AF), the most common sustained arrhythmia, is associated with significant morbidity and mortality [197]. Several mechanisms contribute to its pathogenesis, including the autonomic nervous system (ANS), which plays a role in initiation and maintenance of AF [50, 198]. Changes in heart rate variability (HRV), a marker of cardiac autonomic modulation, occur at the onset of paroxysmal AF [56] and reduced HRV has been explored as a risk factor for AF, with conflicting results [199, 200]. The incidence of AF increases with age, and is detected in 3-4% of healthy volunteers over 60, without coronary artery disease [201]. This could be due to changes in the ANS, which changes with age [27], or due to cardiac structural and functional alterations associated with ageing [201].

The ANS also plays a role in the pathogenesis of Orthostatic Hypotension (OH). Orthostasis results in pooling of 0.5L – 1L in the lower limbs and splanchnic vessels, leading to a reduction in venous return, ventricular preload and cardiac output, subsequent reduction in the distension of baroreceptors and reduction in firing of baroreceptors to the cardiovascular centre in the brain stem. This leads to parasympathetic inhibition, sympathetic activation, increased heart rate (HR) and cardiac output (CO), and restoration of blood pressure (BP) and cerebral perfusion [69]. OH is a manifestation of autonomic dysfunction, when adaptive mechanisms fail to compensate for this reduction in venous return that normally occurs on standing.

Prevalence of OH increases with age, and is observed in 5-30% of elderly persons [61]. BP control progressively worsens with ageing, for reasons including impaired baroreflex sensitivity, impaired thirst, dehydration and impaired venomotor tone [68, 69]. Chronic diseases like diabetes and neurodegenerative diseases including Parkinson's disease and MSA

also play a role in its aetiology. Polypharmacy is common in ageing, and medications are often causal in OH [69]. OH is associated with increased morbidity and mortality [202] and it may be a marker for cardiovascular risk [203].

The aim of this study was to assess whether OH is more common in individuals with AF in a community dwelling population over the age of 50. An association between the two could pose clinical challenges given the emerging evidence linking AF to falls [204-206]. There is evidence linking AF with cognitive impairment in the absence of stroke, however the mechanism for this is debated, with proposed mechanisms including periods of cerebral hypoperfusion [207]. Emerging evidence suggests an association between OH and dementia, potentially augmenting risk of cognitive impairment secondary to cerebral hypoperfusion in individuals with AF and co-existent OH [125, 128].

4.3 Methods

Data from wave one of The Irish Longitudinal Study on Ageing (TILDA) were used. TILDA is a large prospective cohort study comprising of community-dwelling people ≥ 50, resident in Ireland. Details are published elsewhere [184]. Briefly, it consists of (1) A computer-assisted personal interview (CAPI), (2) A self-completion questionnaire, and (3) a health assessment (HA). Ethical approval was obtained from the Trinity College Research Ethics committee. Participants provided written informed consent.

4.3.1 Evaluation of AF

Participants were invited to attend one of two health centres for HA. Those that did had a 10 minute surface electrocardiogram (ECG), performed lying supine in a quiet room with ambient temperature 21-23°C. ECGs were screened for AF by two clinicians and inter-rater

disagreement resolved by a cardiologist. Only objective measurements of AF were included in the study.

4.3.2 Measurement of OH

HA included measurement of beat-to-beat BP response to orthostasis with a Finometer© (Finapres Medical Systems BV). The assessment was performed on the same day in the same room as ECGs. Baseline BP and HR were recorded as the mean value between 60 and 30 seconds prior to stand. Beat-to-beat BP was measured for 110 seconds following stand.

Two outcomes were measured in this study – classical OH (COH) and initial OH (IOH). COH is defined as is a sustained reduction in SBP ≥20mmHg or DBP ≥10mmHg within 3 minutes of standing [59]. COH was assessed using OH sustained at 30-, 60- and 90-seconds post stand. IOH is defined as a transient BP decrease, within 15 seconds after standing of ≥40mmHg in SBP or ≥20mmHg in DBP [59]. IOH was measured by BP response at ten seconds post stand. Data was processed using a 5 second moving average filter, therefore the 10 second value is a weighted mean from 5 to 15 seconds.

4.3.3 Statistical Analysis

Statistical analysis was performed using STATA 12 (Stata Corporation). Normally distributed variables (assessed by Q-Q plots) were compared using Student's t-tests, non-normally distributed variables using Mann-Whitney tests and categorical variables using chi-squared tests. Univariate logistic regression was performed to assess whether participants with AF were more likely to have IOH or COH at 30, 60 or 90 seconds. Multivariable logistic regression was performed controlling for age, sex, baseline HR, education, mean SBP, smoking, frailty (assessed using Fried frailty scale [208]), beta-blocker (BB) use, anti-hypertensive medications (not BB), and self-reported cardiovascular co-morbidities.

4.3.4 Covariate Information

Covariate information was obtained during the CAPI and HA. Choice of covariates was based on clinically relevant variables, added to the model in succession. The order of inclusion of the variables was – age, sex, baseline HR, mean SBP, smoking, BMI, level of education, frailty status (assessed using Fried frailty index[208]), BB use, anti-hypertensive use (excluding BBs), polypharmacy, cholesterol, self-reported hypertension, diabetes, angina, heart attack, heart failure, stroke, TIA and murmur. Variables that significantly improved model fit (based on LR chi squared) were kept. The following covariates were included in the final model: age, sex, baseline HR, education, mean SBP, smoking, frailty (not frail or pre-frail/frail), BB use, anti-hypertensive use (excluding BBs), and number of CV conditions (0, 1 or ≥2).

4.4 Results

8,175 participants were recruited to TILDA, of whom 5,035 attended for HA. 4,408 had both active stand data and ECG data adequate for analysis. Of these, 101 participants had AF on ECG (2.29%). Individuals with AF were older, more likely to be male, with higher baseline HR and lower levels of education. They had higher rates of self-reported cardiovascular disease higher levels of anti-hypertensive use (Table 4.1). Of those with AF on ECG, 26 participants (25.7%) had OH sustained at 30 seconds, 13 participants (12.9%) had OH sustained at 60 seconds and 6 participants (5.9%) had OH sustained at 90 seconds. Of those without AF on ECG, 651 participants (15.1%) had OH sustained at 30 seconds, 279 participants (6.5%) had OH sustained at 60 seconds and 192 participants (4.6%) had OH sustained at 90 seconds.

Table 4.1. Population Characteristics – Study 1

Characteristics	AF (n= 101)	No AF (n=4,307)	P-value
Age, mean ± SD	69.68 ± 7.80	61.44 ± 8.20	<0.001
Female, % (n)	20.79 (21)	54.70 (2,356)	<0.001
Baseline heart rate	76.24 ± 16.50	65.01 ± 9.70	<0.001
Education, % (n)			
Primary	42.57 (43)	20.65 (889)	
Secondary	32.67 (33)	42.11 (1,813)	
Third/Higher	24.75 (25)	37.24(1,603)	<0.001
Smoking status, % (n)			
Never	28.71 (29)	46.11 (1,986)	
Past	63.37 (64)	38.87 (1,674)	
Current	7.92 (8)	15.02 (647)	<0.001
Frailty, %(n)			
Not frail	60.20 (59)	72.99 (3,076)	
Pre-frail	35.71 (35)	25.70 (1,083)	
Frail	4.08 (4)	1.31 (55)	0.004
Physical activity (IPAQ), metmins, mean ± SD	3203.47 ± 3887.45	3151.638±3359.35	0.33
Body mass index (kg/m^2), mean ± SD	30.30 ± 5.90	28.50 ± 4.80	0.003
MMSE, mean ± SD	28.40 ± 1.60	28.60 ± 1.80	0.0346
Disease prevalence, % (n)			
Angina	16.83 (17)	4.11 (177)	<0.001
Hypertension	47.50 (48)	32.70(1,409)	0.002
Myocardial infarction	8.91 (9)	3.81 (164)	0.009
Heart failure	5.94 (6)	0.70 (30)	<0.001
Diabetes	14.85 (15)	6.32 (272)	0.001
Stroke/TIA	9.90 (10)	2.51 (108)	<0.001
Heart Murmur	14.85 (15)	4.78 (206)	<0.001
Seated systolic BP, mean ± SD	126.05 ± 22.46	130.47 ± 20.55	0.12
Taking beta blockers	38.61 (39)	11.24 (484)	<0.001
Taking antihypertensive medications (not beta blockers), % (n)	68.32 (69)	29.39 (1,266)	<0.001
Polypharmacy (≥5 meds), % (n)	48 (48)	16.83 (722)	<0.001
Cholesterol, mean ± SD	4.41 ± 1.01	2.18±1.05	<0.001

Results of univariate analysis (Table4.2) found participants with AF were more likely to have COH at 30 seconds (OR 1.95, 95% CI 1.24, 3.06; p= 0.004), 60 seconds (OR 2.13, 95% CI 1.17, 3.87; p = 0.013) and IOH (OR 1.81, 95% CI 1.21, 2.69; p = 0.004). Results of the multivariable model are also displayed in Table 4.2. The association between AF and initial OH (OR 2.48, 95% CI 1.59, 3.87; p < 0.0001) and OH at 30 seconds (OR 1.78, 95% CI 1.07, 2.94; p = 0.025) remained significant following adjustment for confounders. Participants with AF showed a strong trend towards OH at 60 seconds (OR 1.81, 95% CI 0.75, 3.47; p < 0.073) following adjustment for confounders.

Univariate Analysis	**AF on ECG**		
	OR	***CI (95%)***	***P Value***
OH sustained at 90 seconds	1.31	0.57, 3.03	0.527
OH sustained at 60 seconds	2.13	1.18, 3.87	**0.013**
OH sustained at 30 seconds	1.95	1.24, 3.06	**0.004**
Initial OH	1.81	1.21, 2.69	**0.004**
Multivariable Analysis	**AF on ECG**		
	OR	***CI (95%)***	***P Value***
OH sustained at 90 seconds	1.27	0.52, 3.09	0.593
OH sustained at 60 seconds	1.81	0.95, 3.47	0.073
OH sustained at 30 seconds	1.78	1.07, 2.94	0.025
Initial OH	2.48	1.59,3.87	**<0.0001**

Table 4.2. Odds of co-existent OH in participants with AF – univariate and multivariable logistic regression

OH = Orthostatic Hypotension; AF = Atrial Fibrillation; OR = Odds ratio; CI = Confidence interval

Results of the full multivariable model can be found in supplementary dataset, Appendix 2.

4.5 Discussion

Participants with AF are more likely to have COH at 30 and 60 seconds and IOH than participants in sinus rhythm. Both OH and AF share common risk factors such as age, hypertension, and ischaemic heart disease, however the association between COH at 30 seconds and IOH and AF remains significant following adjustment for potential confounders. To our knowledge, this association has not previously been reported. This study demonstrates a correlation between OH and AF, however it is not possible to demonstrate causation based on this cross-sectional study. Two previous studies have found that baseline OH is associated with higher incidence of AF at long term follow-up [80, 82].

Age-related changes in cardiovascular structure and function may underlie the association between AF and OH independent of co-morbidities such as ischaemic heart disease [209]. Another mechanism that could underlie this association is the ANS, which plays a role in the pathogenesis of both AF and OH. Initial restoration of BP on stand is controlled by the ANS via the baroreceptors. A recent study suggests that AF is associated with impairment of the baroreflex, and restoration of sinus rhythm improves baroreflex gain [210]. This may explain the strong association between IOH and AF.

Clinical implications include a potential increased risk of falls and syncope. Emerging literature suggests an association between AF and falls [45, 204-206]. Previous analysis of the TILDA dataset has shown an associated between AF and impaired mobility, syncope and falls [206, 211]. Co-existent OH could further increase this and should be considered in treatment with medications such as BBs, which have shown an association with OH on analysis of TILDA data [212].

Limitations of the current study include that only objective measurements of AF were used. Participants with paroxysmal AF may have been excluded from the AF group. The prevalence of AF was low (2.29%), which may reflect the fact that individuals with paroxysmal AF were not included in this number. Co-morbidities collected in the CAPI relied on self-reported illness.

In conclusion, this study has found an association between OH and AF in a community dwelling population aged over 50. A number of processes could underlie this association, such as the ANS or impairment of the baroreflex. Further analysis of the TILDA data using baseline heart rate variability and baroreflex sensitivity and incident AF and OH at follow-up could help explore this relationship in the future.

Chapter 5: Is baseline orthostatic hypotension associated with a decline in global cognitive performance at four year follow-up? Data from the Irish Longitudinal Study on Ageing (TILDA).

5.1 Abstract

Background

It is postulated that Orthostatic Hypotension (OH), a reduction in blood pressure (BP) (≥20/10mmHg) within 3 minutes of standing, may increase cognitive decline due to cerebral hypoperfusion. This study assesses the impact of OH on global cognition at 4 year follow-up, and the impact of age and hypertension on this association.

Methods and results

Data from waves 1 and 3 of The Irish Longitudinal Study on Ageing were used (4-year follow-up period). Baseline BP response to active stand was assessed using beat-to-beat BP monitoring. Two measures of OH were used –at 40 seconds (OH40) and 110 seconds (OH110). Global cognition was measured using the Montreal Cognitive Assessment (MOCA). Mixed-effects poisson regression assessed whether baseline OH was associated with a decline in global cognition at 4 year follow-up. The analysis was repeated stratifying by age (age 50-64 and age ≥ 65), and including an interaction between OH and hypertension. A total of 3338 participants were included in the study. Baseline OH110 was associated with an increase error rate in MOCA at follow-up (IRR 1.17, p-value = 0.028). On stratification by age, the association persists in ages 50-64 (IRR 1.25, p-value = 0.048), but not ages ≥ 65. Including an interaction with hypertension found those with co-existent OH110 and hypertension (IRR 1.27, p-value = 0.011), or OH40 and hypertension (IRR 1.18, p-value = 0.017), showed an increased error rate, however those with isolated OH110, OH40 or isolated hypertension did not.

Conclusions

OH is associated with a decline in global cognition at 4-year follow-up, and this association is dependent on age and co-existent hypertension.

5.2 Introduction

Orthostatic hypotension (OH) is traditionally defined as a sustained reduction in systolic blood pressure (BP) of at least 20mmHg or diastolic BP of 10mmHg within 3 minutes of standing [59]. It can occur within 15 seconds of stand (initial OH), between 30 seconds and 3 minutes of stand (classical OH) or after 3 minutes of stand (delayed OH) [213]. The prevalence of OH increases with age, and previous analysis of The Irish Longitudinal Study on Ageing (TILDA) data has found a prevalence of impaired blood pressure stabilisation on stand of 15.6% of participants, rising from 14.3% of men and 16.9% of women aged 50-59, to 43.4% of men and 39.9% of women over the age of 80 [66]. Several mechanisms are responsible for impairment in BP control, including impaired baroreflex sensitivity, abnormal neurohumeral regulation, impaired thirst, dehydration and impaired venomotor tone [68, 69].

Recently more refined methods of measurement of BP behaviour during orthostasis using technologies which measure beat-to-beat BP have demonstrated that failure to stabilise BP during early stages of stand are associated with falls and syncope [213], depression [214], and with cognitive impairment [108].

Ageing may be associated with a decline in cognitive abilities such as memory, attention, processing speed, language, visuospatial and executive function [83]. The prevalence of age associated cognitive decline is 15% in persons over 60 years [85]. Mild cognitive impairment (MCI) is a decline in cognition that is worse than normative data for a set age and education level, but does not meet the criteria for the diagnosis of dementia [84]. Prevalence data for MCI varies greatly, with the prevalence of MCI having been reported as up to 42% of individuals [85]. The main differentiating criteria for dementia is the existence of functional impairment [87].

The brain is highly metabolically active and precise regulation of cerebral blood flow (cerebral autoregulation), is required to maintain a constant nutrient and oxygen supply to the brain.[31] There is evidence that cerebral blood flow can be compromised in OH [137, 215], and it has been postulated that OH can increase the risk of cognitive impairment through alterations in cerebral blood flow. Several cross-sectional studies have shown an association between OH and cognitive decline [108, 115, 116, 118], including cross-sectional analysis of the first wave of the TILDA dataset [108]. A number of longitudinal studies have investigated directionality of this association, however in contrast to most cross-sectional studies, a majority did not find an association [119, 121-124]. BP measurement in the majority of these studies was assessed using oscillometric lying and standing BP, a more crude method of BP measurement than beat-to-beat measurement [122-124]. The TILDA dataset provides a unique opportunity to study the effect of more dynamic shifts in orthostatic BP, as measured by beat-to-beat BP, on cognitive function.

The aim of this study is to assess whether baseline OH at 40 seconds and 110 seconds after stand is associated with a decline in cognitive scores at 4 year follow-up in a community dwelling sample over the age of 50.

5.3 Methods

5.3.1 Study Sample

Data from The Irish Longitudinal Study on ageing (TILDA) were used. The anonymised TILDA dataset is available to researchers who meet the criteria for access from the Irish Science Data Archive at University College Dublin and the Interuniversity Consortium for Political and Social Research at the University of Michigan, and TILDA also considers applications for privileged

access to the dataset through an onsite "hot desk" facility (visit www.tilda.ie for further information).

TILDA is a large prospective cohort study comprising community dwelling adults over the age of 50 in the Republic of Ireland, repeatedly assessed at two year intervals. At wave 1, a nationally representative sample was drawn from a listing of all residential addresses in the Republic of Ireland using the RANSAM sampling procedure [216], with a response rate of 62%. Details of the sampling method have been published elsewhere [216].

The TILDA study comprised (1) A computer aided personal interview (CAPI), carried out by trained interviewers in participants' homes, (2) A self-completion questionnaire and (3) a health assessment carried out by trained research nurses. All participants who completed the CAPI were invited to attend one of two health centres for health assessment. As part of a comprehensive health assessment, participants completed a cardiovascular assessment, which included beat-to-beat measurements of blood pressure (BP) during active stand and the Montreal Cognitive Assessment (MOCA).

This study included all participants who completed both the CAPI and health assessment at wave 1 (2009-2011) and had adequate active stand data for analysis of orthostatic BP behaviour, as well as completing both the CAPI and MOCA at wave 3 (4-year follow-up period). Participants who had a self-reported doctor's diagnosis of dementia, a MOCA score < 20, Parkinson's disease or stroke at wave 1 or a subsequent diagnosis of Parkinson's or stroke between waves 1 and 3, were excluded from the analyses.

Ethical approval for TILDA was obtained from the Trinity College Research Ethics committee and participants provided written informed consent.

5.3.2 Blood Pressure Measurement

Continuous blood pressure measurement:

Participants who attended the health centre underwent active stand, which non-invasively measures beat-to-beat BP response to orthostasis using digital photoplethysmography (Fnometer® MIDI device, Finapres Medical Systems). Participants underwent assessment of BP response to stand, following ten minutes of supine rest. Baseline BP was measured as the mean value between 60 and 30 seconds prior to stand, during the supine rest period. BP response to stand was measured up to 110 seconds post stand. BP was estimated at 10 second intervals, using 5 second moving averages around each point.

Two measurements of OH were analysed. OH at 40 seconds (OH40) was defined as a sustained drop of ≥20mmHg SBP or ≥10mmHg DBP at each time point up to 40 seconds post stand. Previous analysis of the TILDA data has demonstrated that while there are a wide range of BP response patterns to active stand, the majority of participants stabilise their blood pressure by 30 second [66], and so we chose the 40 second cut-off to++ represent the participants who fail to stabilise their blood pressure by this time point.

A subset of these participants with OH at 110 seconds (OH110) was also analysed and defined as a sustained drop of ≥20mmHg SBP or ≥10mmHg DBP at each time point up to 110 seconds post stand. As BP was estimated at intervals using 5-second moving averages, the point at 120 seconds (duration of the stand at wave 1) in most individuals would include edge effects and so we chose the 110 second point to assess a subset pf the participants with OH that represent the “worst” group - that is those who do not stabilise their blood pressure throughout.

Standardised protocols were used for the active stand procedure; however, it was not possible to control for factors such as last meal, smoking and time of medication administration. Baseline OH as measured at wave 1 health centre assessment using the finometer, was used.

Oscillometric blood pressure measurement:

Blood pressure was also measured seated, using the traditional oscillometric methods. Two seated SBP and DBP measurements were obtained, separated by 1 minute, using an automatic digital BP monitor (Model M10-IT, OMRON, Kyoto, Japan). Seated hypertension was assessed using oscillometric BP. Hypertension was defined as a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.

5.3.3 Cognitive Assessment

Global cognitive function was assessed using the Montreal Cognitive Assessment (MOCA). The MOCA is a cognitive test including assessment of the cognitive domains of executive and visuospatial function, memory, language and attention; the test yields a single score ranging from 0 to 30. MOCA was administered at the health centre. The MOCA is used frequently in the clinical setting [194], is sensitive to mild deficits, and is useful in identifying patients with mild cognitive impairment [195]. In addition to this, it demonstrates good test-retest and inter-rater reliability [196]. Several validation studies have demonstrated that the MOCA possesses fair sensitivity and specificity [217]. Given the frequency with which MOCA is used both clinically and in the research setting, the MOCA was chosen as it is relatable to both researchers and clinicians. Cognitive performance was compared between groups by comparing the number of errors made in completing the MOCA.

The MOCA was assessed as a total score to assess global cognition (maximum score 30). The results of MOCA were then divided into sub domains and assessed individually, including recall, visuospatial, executive function, attention and working memory, language, and orientation. To assess recall, the delayed recall section of the MOCA was used (maximum score 5). To assess the visuospatial domain, cube drawing and clock drawing were used (maximum score 4). Executive function was assessed using the trail test within the MOCA, language fluency and a two item verbal abstraction task (maximum score 4). Attention and working memory was assessed using digits forward and backward, a sustained attention task and serial subtraction task (maximum score 6). Language was assessed using animal naming, repetition and the language fluency task (maximum score 6). Finally, orientation to time and place was assessed using questions regarding date, month, year, day, place and city were used (maximum score 6).

Baseline results of MOCA from wave 1 and follow-up MOCA scores at wave 3 were used.

5.3.4 Covariates

Results were adjusted for variables that have a known association with OH and cognitive decline. Information on age, sex, education attainment, smoking status, and alcohol use (using the CAGE questionnaire [218]) were collected during the CAPI. The CAPI also collected information on self-reported comorbidities including self-reported hypertension, heart failure, angina, myocardial infarction, diabetes, stroke, TIA, murmur, Atrial Fibrillation or other arrhythmia. Mean of two seated blood pressure measurements were used to assess as objective blood pressure measurements. In wave 1, depressive symptoms were assessed using the Centre for Epidemiological Studies Depression (CES-D) scale [219]. A cut-off score of 16 was used to assess the presence of depression. In wave 3 a short form of the CES-D scale

was used [220], with a cut-off score of 10 used to assess the presence of depression. Height and baseline blood pressure were measured at the health assessment. Frailty was assessed using the Fried frailty index [208], and individuals were grouped in three groups - not frail, pre-frail or frail.

All medications were recorded at the CAPI and classified according to the Anatomical therapeutic classification codes (ATC). Medication categories adjusted for were anti-hypertensive agents ('CO2'), diuretics ('C03'), beta blockers ('C07'), calcium channel blockers ('C08'), ACE inhibitors ('C09'), anti-psychotic ('N05A'), anti-depressants ('N06A'), anxiolytics ('N05B'), hypnotics and sedatives ('N05C'), anti-cholinergic agents ('N04A'), anti-cholinesterase's ('N06DA'), and diabetic medication ('A10').

5.3.5 Statistical Analysis

All statistical analysis were carried out using STATA 14 (Stata Corporation). For description of data, normally distributed continuous variables were compared using t-tests; non-normally distributed continuous variables were compared using Mann Whitney tests and categorical variables were compared using chi-squared tests. Q-Q plots were used to assess normality.

MOCA scores showed a left-skewed distribution at waves 1 and 3. Therefore, we calculated the number of errors on MOCA at each wave (i.e., 30 minus MOCA score), and modelled the change between waves in the number of errors made using mixed effects poisson models. Poisson regression models were used to calculate longitudinal change in incidence rate ratio of errors, as this method allows for calculation of relative risk while also allowing for evaluation of complex interactions with covariates [221]. Interactions with a variable representing wave (wave 1 – baseline assessment; wave 3 – assessment at 4 year follow-up interval) for each predictor variable were included to probe change in number of errors on

the MOCA (presented as incident rate ratio (IRR)). Wave was also included as a fixed effect predictor in the model. For analysis of sub domains in MOCA, the number of errors was calculated by subtracting the score obtained for that domain, from the maximum score possible for the domain. Separate models were fitted to assess the impact of OH40 and OH110 on MOCA. All models treated participant as a random effect, with random intercept (i.e., MOCA errors at wave 1 and wave 3 were nested participant-wise). Three models were fitted for OH40 and for OH110; model A, with fixed effect of OH only; model B, a multivariable model controlling for fixed effects of age, sex and education; and model C, a multivariable model controlling for fixed effects of age, sex, education, self-reported hypertension, self-reported heart failure, number of cardiovascular conditions, diabetes, alcohol use, smoking status, depression, height, frailty, baseline SBP, pulse pressure, HR prior to stand (wave 1) and medication use (grouped as anti-hypertensive use, anti-depressant use, anti-psychotic use, and anti-cholinesterase, anticholinergic or sedative use, anti-diabetic use). Covariates were chosen based on clinical relevance and current literature. Variables were assessed for multicollinearity using variance inflation factors with a cut-off score of 10, with the exception of interactions and the fixed effect for wave. Information on available covariates from both waves were included in the fully adjusted model, and an interaction with the variable representing wave was included.

Models were then repeated testing the interaction between OH and the presence or absence of hypertension; this was assessed by including a three-way interaction term between the variables representing wave, OH and HTN. All models were then repeated including only age group 50-64 and including only age group ≥65, both with and without inclusion of a three way interaction with wave, OH and HTN. This was to assess the impact of the presence of hypertension as well as to assess how the results differ in the younger and older age groups.

5.4 Results

In total, 8175 participants over the age of 50 were recruited to wave 1 of the TILDA study, of whom 5035 attended the health centre for assessment at wave 1. There were 4475 participants' ≥ 50 years of age with adequate active stand data for analysis, of whom 4172 fulfilled inclusion criteria. Of these individuals, 3338 were present at the wave 3 health centre for assessment and did not receive a diagnosis of Parkinson's disease or stroke between waves 1 and 3 and were included in the study. Figure 5.1 details a flow chart of participants included for analysis.

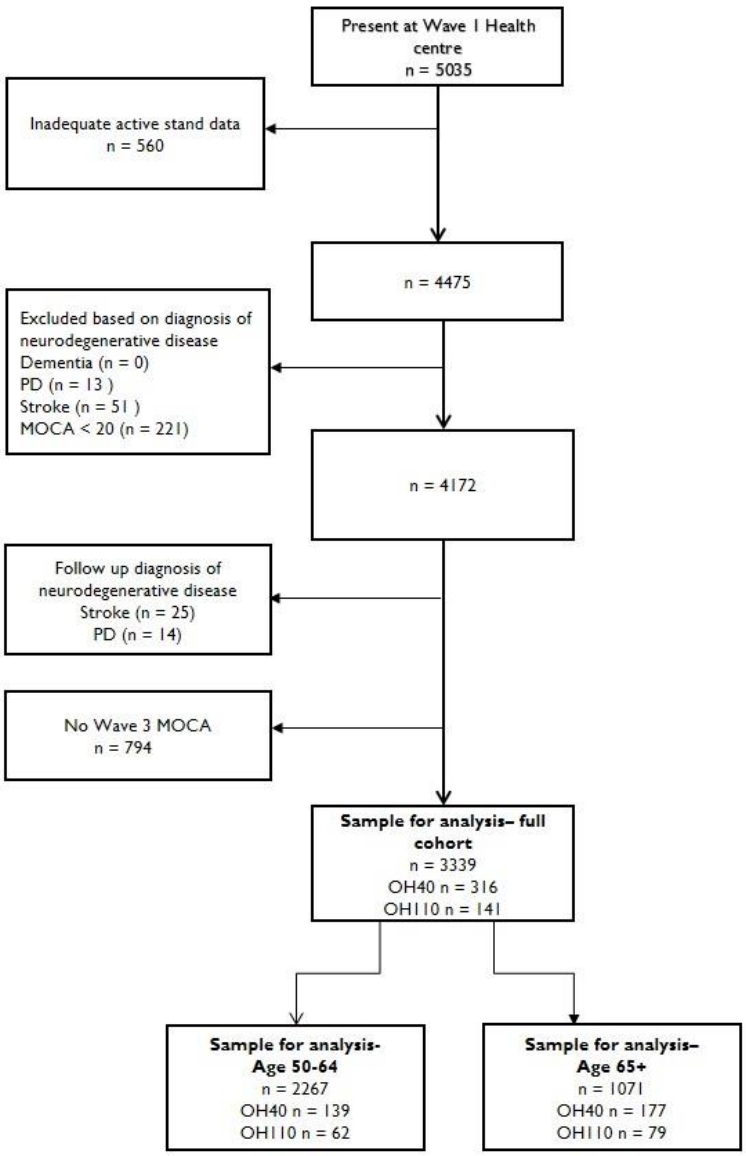

Figure 5.1. Sample for analysis – study 2

CAPI – Computer aided personal interview; PD – Parkinson's disease; MOCA- Montreal Cognitive Assessment; OH40 – Orthostatic hypotension sustained up to 40 seconds post stand; OH110 – Orthostatic hypotension sustained up to 110 seconds post stand

Characteristics of participants who were included in the baseline sample but did not have a follow-up MOCA and therefore were not included in the final sample are provided in, table 5.1. Participants who did not have a follow-up MOCA assessment were older, with lower MOCA scores and higher prevalence of OH.

Table 5.1. Description of attrition

	No Follow-up MOCA N = 794	**Analytic Sample N= 3339**
Age, mean +/- SD	61.9 +/-8.7*	61.1 +/-8.0
MOCA, mean +/- SD	25.0 +/- 2.7***	25.9 +/-2.5
OH40, %(n)	12.5% (99)*	9.5% (316)
OH110, %(n)	4.9 (39)	4.2% (141)
Female, %(n)	54.3 % (431)	54.2% (1808)
Education, %(n)		
Primary	24.1% (191)***	17.4% (581)
Secondary	44.2% (352)***	42.3% (1411)
Higher	31.5% (250)***	40.3% (1347)
Smoking status, %(n)		
Current	20.15% (160)***	13.6% (454)
CVD Disease prevalence, % (n)		
≥ 2 Cardiovascular diseases	12.3% (98)	11.9% (396)
Seated systolic BP, mean ± SD, mean +/- SD	131.6 +/- 21.6*	129.8 +/- 20.3
Seated diastolic BP, mean ± SD, mean +/- SD	68.6 +/-10.8	68.0 +/-10.7
Taking antihypertensive medications, % (n)	12.3% (98)	11.9% (396)
Taking antidepressant medications, % (n)	6.7% (53)	5.2% (174)
Frailty, %(n)		
Pre frail/Frail	30.8% (237)***	24.1% (789)

MOCA – Montreal Cognitive Assessment; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; OH110 – Orthostatic hypotension sustained to 110 seconds post stan d; CVD – Cardiovascular disease; BP – Blood pressure. * p< 0.05; ** p<0.01; *** p<0.001

Population characteristics are described in Table 5.2. OH40 was present in 9.46% of participants, and OH110 was present in 4.22% of participants included for analyses. Individuals with OH40 and OH110 on active stand were older, showed lower levels of education, had higher systolic BP, lower baseline HR, and higher burden of cardiovascular disease. They were more likely to be taking both antihypertensive and antidepressant medications. Those with OH40 also had higher levels of frailty.

Table 5.2 Population Characteristics

Characteristics	OH40 (n= 316)	OH110 (n=141)	No OH (n=3,023)
Age, mean ± SD	66.1 +/- 8.7***	65.3 +/-8.3***	60.7 +/- 7.7
Female, % (n)	60.3% (193)*	66.9% (95)**	53.2% (1623)
Education, % (n)			
Primary	23.8% (76)*	23.9% (34)*	16.9% (517)
Secondary	39.1% (125)*	45.1% (64)*	42.5% (1297)
Third/Higher	37.2% (119)*	30.2% (44)*	40.6% (1239)
Smoking status, % (n)			
Never	45.6% (146)	47.9% (68)	47.3% (1443)
Past	40.0% (128)	34.5% (49)	39.1% (1194)
Current	14.4% (46)	17.6% (25)	13.6% (416)
Alcohol (CAGE)			
0	75.9% (230)	75.7% (100)	75.6% (2048)
1	10.9% (33)	10.6% (14)	12.6% (355)
2	8.3% (25)	4.6% (6)	9.5% (268)
3	1.0% (3)	1.0% (3)	0.7% (19)
Height, mean ± SD	165.1 +/-9.0*	164.1 +/- 9.2***	166.7+/-9.1
MOCA, mean ± SD	25.6+/-2.6*	25.8 +/- 2.6	26.0+/-2.5
Self-reported hypertension, % (n)	38.8% (124)**	40.9% (58)*	30.9% (944)
Self-reported heart failure, % (n)	0.6% (2)	n=0	0.8% (25)
Self-reported diabetes, %(n)	6.9% (22)	7.8% (11)	6.0% (183)
Disease prevalence, % (n)			
≥ 2 Cardiovascular diseases	16.9% (54)***	14.8 (20)*	11.6% (355)
Seated systolic BP, mean ± SD	136.9 +/-23.8***	140.3+/-23.2***	129.1+/-19.8
Seated diastolic BP, mean ± SD	67.8+/-11.1***	70.6+/-11.5**	70.1+/-11.1
Taking antihypertensive medications, % (n)	39.1% (125)***	39.4% (56)**	29.8% (909)
Taking antidepressant medications, % (n)	8.8% (28)*	9.2% (13)*	4.9% (148)
Taking antipsychotic medications, %(n)	1.3% (4)	0.7% (1)	0.9% (28)
Taking antidiabetic medication, %(n)	5.3% (17)	6.3%(9)	4.3% (132)
Frailty, %(n)			
Pre frail/Frail	31.2% (97)**	28.1% (39)	23.5% (706)
CES-D score, mean ± SD	4.8 +/- 5.8	4.3+/-4.8	5.2 +/-6.5
Baseline HR, mean ± SD	62.5%+/-10.1***	61.8+/-934***	65.2/-9.8

OH – Orthostatic Hypotension; OH40 – OH up to 40 seconds; OH110 – OH up to 110 seconds; SD – standard deviation; MMSE – mini mental state exam; MOCA – Montreal cognitive assessment; BP – blood pressure; SD – standard deviation.* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

The change between waves in number of errors on MOCA in individuals with OH40 is described in Table 5.3, with change in rates of errors presented as incident rate ratios (IRR).

Table 5.3. Change in global cognition between waves based on baseline OH

	OH40		OH110	
	IRR (95% CI)	**P-value**	**IRR (95% CI)**	**P-value**
		Full Cohort N = 3338		
Model A	1.12 (1.04, 1.21)	**0.004**	1.17 (1.04, 1.31)	**0.007**
Model B	1.05 (0.97, 1.14)	0.205	1.11 (0.99, 1.25)	**0.065**
Model C	1.09 (0.99, 1.20)	0.067	1.17 (1.02, 1.33)	**0.028**
		Age 50 – 64 N= 2267		
Model A	1.09 (0.96, 1.24)	0.170	1.22 (1.01, 1.47)	**0.038**
Model B	1.09 (0.96, 1.24)	0.197	1.22 (1.02, 1.48)	**0.034**
Model C	1.13 (0.98, 1.31)	0.104	1.25 (1.01, 1.57)	**0.048**
		Age ≥65 N = 1071		
Model A	1.05 (0.95, 1.17)	0.306	1.06 (0.92, 1.22)	0.441
Model B	1.02 (0.92, 1.13)	0.688	1.05 (0.90, 1.21)	0.549
Model C	1.05 (0.92, 1.19)	0.459	1.09 (0.91, 1.30)	0.370

Model A – Univariate; Model B – Controls for age, sex and education; Model C – Controls for all covariates – age, sex, education level, self-reported cardiovascular conditions, diabetes, alcohol use, smoking status, medications, depression, frailty, mean blood pressure, pulse pressure height and baseline heart rate.
OH40 – Orthostatic hypotension sustained to 40 seconds; OH110 – Orthostatic Hypotension sustained to 110 seconds; HTN – Supine HTN; IRR – Incidence rate ration; CI – Confidence interval
Statistically significant p values represented in bold.

Participants with OH40 at baseline had an increase in rates of errors over the 4 years in model A, (IRR 1.12, 95%CI 1.04-1.21, p-value 0.004), however this was no longer significant when controlling for age, sex and level of education (IRR 1.05, 95% CI 0.97-1.15, p-value 0.205), or on controlling for all covariates (IRR 1.09, 95% CI 0.99-1.20, p-value 0.067). Results of the full multivariable analysis are provided in Appendix 3, Table S1. There was no significant increase in rates of errors in MOCA between the two waves including only participants in the age group 50-64, or including only participants in the age group ≥65 (Table 5.3).

The change between waves in rates of errors in MOCA in individuals with OH110 compared to those without OH110 is also described in Table 5.3. Participants with OH110 had an increase in number of errors in MOCA compared to those without OH110 on univariate analysis (IRR 1.17, 95% CI 1.04-1.31, p-value 0.007), this remained significant on controlling for all covariates (1.17, 95% CI 1.02-1.33, p-value 0.028). Results of the full multivariable analysis for the full age cohort are provided in Appendix 3, Table S2.

The analysis was then repeated including only age group 50-64 and including only age group ≥65, and results are also presented in Table 5.3. In the age group 50-64, individuals with OH110 had an increase in rates of errors on the MOCA between waves, compared to those without OH on univariate analysis (IRR 1.22, 95% CI 1.01-1.47, p-value 0.038), which remained significant on controlling for all confounders (IRR 1.25, 95% CI 1.01-1.57, p-value 0.048).

In the age group ≥65 there was no significant increase in rates of errors on MOCA in those with OH110 compared to those without OH110 between waves (Table 5.3). The results of the full multivariable models for age group 50-64 are presented in Appendix 3 Table S3 and Table S4. The results of the full multivariable models for age group ≥65 are presented in Appendix 3 Table S5 and Table S6. The decrease in absolute MOCA scores in those with OH110

compared to those without OH110 is small, however there is a clear divergence between the two groups seen in the results (Figure 5.2). For those with OH110, the mean increase in the number of errors between wave 1 and wave 3 is 0.32 (+/- SD 2.83). Those without OH110 demonstrated an improvement in their MOCA scores between wave 1 and wave 3, with a mean reduction in errors of -0.30 (+/- SD 2.6).

Figure 5.2. Change in MOCA over 4 years by presence of OH110 at baseline

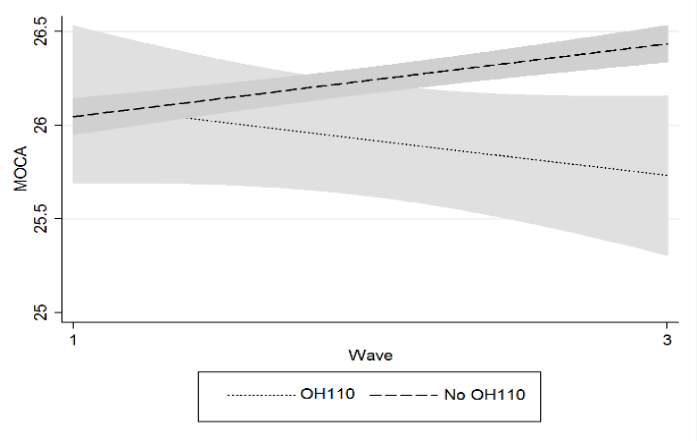

Figure 5.2. MOCA at wave 1 and wave 3 with 95% CI by presence of OH110 at wave 1

MOCA – Montreal cognitive assessment; OH110 – Orthostatic Hypotension sustained to 110 seconds; CI – Confidence Interval.

All analyses were then repeated testing for the interaction with the presence of hypertension (HTN) at baseline in the full age cohort, in the age group 50-64 and in the age group ≥65. These results are presented in Table 5.4.

Table 5.4. Change in rate of errors on MOCA between waves based on baseline OH and stratified by baseline HTN

	OH40		OH110	
	IRR (95% CI)	**P-value**	**IRR (95% CI)**	**P-value**
Full Cohort N= 3338				
Model A (base No OH, no HTN)				
No OH, HTN	1.09 (1.01, 1.12)	**0.013**	1.07 (1.02, 1.13)	**0.006**
OH, No HTN	1.08 (0.94, 1.23)	0.262	1.12(0.92, 1.37)	0.264
OH and HTN	1.19 (1.09, 1.32)	**<0.001**	1.25 (1.09, 1.44)	**0.001**
Model B (base No OH, no HTN)				
No OH, HTN	1.03 (0.97, 1.08)	0.326	1.03 (0.98, 1.08)	0.241
OH, No HTN	1.01 (0.88, 1.15)	0.907	1.08 (0.89, 1.32)	0.438
OH and HTN	1.10 (0.99, 1.22)	0.06	1.16 (1.01, 1.33)	**0.042**
Model C (base No OH, no HTN)				
No OH, HTN	1.03 (0.95, 1.11)	0.478	1.04 (0.96, 1.13)	0.365
OH, No HTN	1.00 (0.86, 1.17)	0.976	1.07 (0.84, 1.35)	0.594
OH and HTN	1.18 (1.03, 1.34)	**0.017**	1.27 (1.06, 1.53)	**0.011**
Age 50 – 64 N= 2267				
Model A (base No OH, no HTN)				
No OH, HTN	1.03 (0.97, 1.10)	0.330	1.04 (0.97, 1.10)	0.265
OH, No HTN	1.00 (0.83, 1.21)	0.982	1.08 (0.83, 1.41)	0.562
OH and HTN	1.20 (1.01, 1.42)	**0.036**	1.42 (1.09, 1.85)	**0.010**
Model B (base No OH, no HTN)				
No OH, HTN	1.03 (0.96, 1.10)	0.394	1.03 (0.97, 1.10)	0.314
OH, No HTN	0.98 (0.82, 1.20)	0.909	1.08 (0.82, 1.41)	0.577
OH and HTN	1.20 (1.01, 1.43)	**0.035**	1.43 (1.10, 1.87)	**0.008**
Model C (base No OH, no HTN)				
No OH, HTN	1.00 (0.91, 1.11)	0.940	1.01 (0.91, 1.13)	0.762
OH, No HTN	1.01 (0.82, 1.24)	0.932	1.07 (0.79, 1.45)	0.670
OH and HTN	1.29 (1.03, 1.62)	**0.025**	1.52 (1.08, 2.15)	**0.017**
Age ≥ 65 N= 1071				
Model A (base No OH, no HTN)				
No OH, HTN	1.05 (0.96, 1.14)	0.302	1.05 (0.96, 1.14)	0.269
OH, No HTN	1.07 (0.89, 1.29)	0.484	1.11 (0.82, 1.50)	0.518
OH and HTN	1.09 (0.96, 1.24)	0.187	1.08 (0.92, 1.28)	0.346
Model B (base No OH, no HTN)				
No OH, HTN	1.03 (0.94, 1.12)	0.573	1.03 (0.95, 1.12)	0.517
OH, No HTN	1.02(0.84, 1.24)	0.837	1.09 (0.81, 1.48)	0.577
OH and HTN	1.04 (0.92, 1.19)	0.511	1.06 (0.89, 1.25)	0.529
Model C (base No OH, no HTN)				
No OH, HTN	1.09 (0.96, 1.25)	0.160	1.09 (0.97, 1.24)	0.148
OH, No HTN	1.05 (0.82, 1.34)	0.690	1.07 (0.73, 1.57)	0.716
OH and HTN	1.15 (0.96, 1.34)	0.126	1.19 (0.95, 1.50)	0.123

Results of comparison to base of No OH and no HTN.
Model A – Univariate; Model B – Controls for age, sex and education; Model C – Controls for all covariates
OH40 – Orthostatic hypotension sustained to 40 seconds; OH110 – Orthostatic Hypotension sustained to 110 seconds; HTN – Hypertension; IRR – Incidence rate ration; CI – Confidence interval
Statistically significant p values represented in bold.

In the full age cohort, individuals with both OH40 and HTN were more likely to show an increased rate of MOCA errors over the 4 year follow-up period, which was significant on controlling for all confounders (IRR 1.18, 95% CI 1.03-1.34, p-value 0.017). Individuals with OH40 alone or HTN alone were no more likely to show a difference in error rate than those without OH40 or HTN on controlling for confounders (Table 5.4). In the age group 50-64, participants with OH40 and HTN at baseline had an increase in the rates of errors on MOCA, which was significant on controlling for all confounders (IRR 1.29, 95% CI 1.03-1.62, p-value 0.025). Again, those with OH40 alone or HTN alone were no more likely to show an increase in rates of errors compared to those with no OH40 and no HTN (Table 5.4). Results of the full multivariable analysis for OH40 in the full cohort are presented in Appendix 3, Table S7.

Participants with OH110 and HTN also showed an increase in rates of errors in MOCA between the time points, compared to those with no OH110 and no HTN, which was significant on controlling for all confounders (IRR 1.27, 95% CI 1.06-1.53, p-value 0.011). Results of the full multivariable analysis are presented in Appedix 3, Table S8. Repeating the analysis including only those in the 50-64 years old age group at baseline, showed similar results, with those with both OH110 and HTN showing an increase in the rates of errors on the MOCA (IRR 1.52, 95% CI 1.08-2.15, p-value 0.017) compared to reference (no OH, no HTN). Again, there was no significant increase in rates of errors in those with OH110 alone or those with HTN alone, nor was there any significant increase in those aged ≥65 (Table 5.4).

When analysing the results of individual sub domains assessed by MOCA, there is an increase in the rate of errors in the domain of executive function in those with OH40 (IRR 1.32; 95% CI 1.11, 1.57; p-value 0.002), which remains significant on controlling for all confounders (IRR

1.27; 95% CI 1.03, 1.56; p-value 0.027). Those with OH110 also showed in increase in the rate of errors made in the domain of executive function (IRR 1.53; 95% CI 1.18, 1.99; p-value 0.002), and again this remained significant on controlling for all confounders (IRR 1.40; 95% CI 1.03, 1.94; p-value 0.032). There was no significant increase in error rates seen in the other sub domains assessed by MOCA.

5.5 Discussion

Adults with OH are more likely to show an increase in rate of MOCA errors at 4 year follow-up, which remains significant following adjustment for confounders. The association is strongest in participants who fail to recover blood pressure throughout the 110 second stand. There is evidence that that cerebral perfusion is impaired in OH [137, 215], and we hypothesize that those individuals who fail to recover their blood pressure throughout the 110 seconds stand at baseline are therefore exposed to the highest "load" of cerebral hypoperfusion. This association may reflect periods of cerebral hypoperfusion. The association appears to be dependent on the presence of coexistent HTN, and on age. Individuals with both OH (OH40, OH110) and HTN showed an increase in rates of errors on MOCA between waves, but this was true only in those aged under 65 years. On analysis of the domains assessed by the MOCA individually, it is the domain of executive dysfunction within the MOCA that appears to drive this increase in errors on MOCA. Hypoperfusion of the prefrontal cortex has been reported in OH compared to controls [222], which may explain these results as executive function is largely controlled by the prefrontal cortex.

The relationship between blood pressure and cognitive function is complex, with both high and low blood pressure being linked with cognitive decline and dementia [99]. A non-linear, U-shaped relationship between BP and cognitive function has been proposed, with individuals with both high and low BP performing worse on cognitive tests than individuals with BP in the mid-range [98]. Hypertension has been consistently linked with cognitive impairment and dementia, particularly mid-life hypertension [99]. It is postulated that microvascular dysfunction and damage induced by hypertension leads to white matter disease, microinfarcts, and microhaemorrhages, which are correlated with cognitive dysfunction

[100]. Several mechanisms are proposed to explain the association between cognitive decline in OH. Cerebral autoregulation may be attenuated with ageing, with subsequent failure to adapt to repeated oscillations in BP[135]. This may result in impaired cerebral perfusion and cell damage [136, 137]. Enhanced white matter hyperintensities are evident in such circumstances [118], and increasing white matter lesion burden is associated with an increased risk of dementia and also predicts an increased risk of cognitive decline in MCI [69].

In the current study, individuals with both OH and HTN exhibited a higher rate of decline in cognitive test scores, whereas individuals with isolated OH or isolated HTN did not show a decline. Both HTN [131] and OH [130] are associated with impaired baroreflex, and co-existent OH and HTN represents a more severe baroreflex dysfunction and exaggerated blood pressure variability. Hypertension causes alterations in the structure and function of cerebral arteries, with loss of elasticity and compliance, resulting in increased myogenic tone, affecting cerebral autoregulation [69]. Thus, hypertension coupled with Orthostatic Hypotension leads to greater blood pressure variability as well as a diminished ability to protect against periods of hypotension when SBP falls below a critical threshold.

These findings are in line with a number of recent longitudinal studies that have found an increase in the rate of incident dementia based on baseline OH, including the Rotterdam Study [128], the Malmo preventative project [125], and the Three-City Study [126][126][126]. The follow-up period for these studies is longer (12-28 years) than in the current study, all assessed incident dementia rather than change in global cognitive test scores such as MOCA. The baseline age ranges were 68.5+/-8.6 in the Rotterdam Study, 45+/-7 and 50+/-5 in the Dementia negative and Dementia positive groups respectively in the Malmo Preventative Project, and 74+/-5 in the Three City Cohort. It is not reported that younger individuals within

these groups showed a stronger association with dementia. In all three studies OH was assessed using traditional oscillometric methods. Phenotypes of OH as defined in the current study (OH40 and OH110), were not assessed, and therefore it is not possible to elicit whether individuals with a higher "load" of cerebral hypoperfusion, i.e. OH110 in the current study, were more likely to develop dementia. However, in the Three City Study, they assessed the traditional thresholds for OH, as well as assessing increasing levels of severity, based on the size of the blood pressure drop, and found that there was a stronger association with the severe OH group [223]. Similarly, in the Rotterdam study, OH was characterised into 3 groups of increasing "severity" of OH, however, in this study they did not observe increasing severity of OH influenced the association with dementia, probably because individuals with more severe OH have higher morbidity and mortality [224]. In the Malmo Preventative Study, postural changes in SBP and DBP were assessed as well as the presence of OH as defined traditionally, and found the association between postural DBP changes and dementia was strongest. These studies did not report that the association between OH and dementia was dependant on co-existent HTN.

The increase rates of errors on MOCA is most robustly observed in the younger age group in our sample (age 50-64). This is consistent with studies on hypertension, where midlife hypertension is consistently linked with cognitive impairment. The picture is more complex in older adults, where the association between late-life measures of BP and cognition are less consistent [225]. Whether OH could represent an early, modifiable risk factor for cognitive impairment and dementia requires further exportation given these observational data. However, the management of supine hypertension coupled with Orthostatic Hypotension is complicated because pharmacological interventions for OH exacerbate supine hypertension

[226]. Management using conservative measures such as fluid hydration, physical counter manoeuvres and compression hosiery may provide a non-pharmacological alternative [227, 228]. Supine hypertension and OH often coexist [227], and hypertension can lead to alteration of cerebral autoregulation capacity, the process of maintaining stable cerebral perfusion despite variation in peripheral blood pressure [31], further exposing individuals with HTN to ischaemia and hypoxia when systemic BP drops [229].

There are some limitations to the current study. The follow-up period is relatively short for assessing decline in global cognition. Cardiovascular confounders that were controlled for relied on self-reported conditions, and exclusion based on a doctor's diagnosis of dementia also relied on self-reporting. The population included in the study was a predominantly Caucasian population. The MOCA was used to assess cognition as it is commonly used in clinical practice, however it is not specifically designed to assess longitudinal changes in cognition. The principle strength of the current study is its use of beat-to-beat measurement of BP response to stand using a finometer, which allows a precise assessment of BP behaviour in response to orthostasis and can detect more subtle fluctuations in BP. TILDA allows inclusion of a large number of confounders, including both self-reported and objective measures. It is noteworthy that individuals without OH110 showed a slight improvement in their MOCA scores, which may reflect in a practice effect [230]. In contrast, cognition declined in those with OH, indicating the potential detrimental effect of blood pressure variability.

In conclusion, we found that OH is associated with a decline in global cognition over a 4-year follow-up period in a community dwelling population over the age of 50. This association appears to be dependent on the presence of coexistent HTN and is strongest in the middle

aged group. Follow-up at future waves of the TILDA dataset will allow assessment of the impact of blood pressure behaviour on the rate of cognitive decline and rate of incident dementia in these individuals.

Chapter 6: Relationship between Symptoms of Orthostatic Intolerance, Orthostatic Hypotension, and Cerebral Haemodynamics in adults – Data from The Irish Longitudinal Study on Ageing (TILDA).

6.1 Abstract

Introduction

Orthostatic hypotension (OH), a reduction in blood pressure (BP) (≥20/10mmHg) within 3 minutes of standing, is postulated to lead to cerebral hypoperfusion, with potential clinical consequences such as cognitive impairment and depression. Orthostatic intolerance (OI) refers to symptoms such as dizziness during standing. This study assesses whether OH and OI are associated with cerebral hypoperfusion.

Methods

Data from wave 3 of The Irish Longitudinal Study on Ageing were used. Frontal lobe haemodynamics were measured during orthostasis using near-infrared spectroscopy (NIRS), reported as tissue saturation index (TSI%). Beat-to-beat BP response to stand was assessed, and a drop of ≥20/10mmHg that did not recover within 40 seconds classified as OH. Participants who answered 'Yes' to whether they felt any symptoms of dizziness, light-headedness or unsteadiness during the active stand were classified as having symptoms of OI. Linear regression assessed whether OH and OI were associated with lower baseline TSI, larger change from baseline TSI, or larger width of the nadir. Mixed effects models compared TSI across specific time points.

Results

There was no difference in baseline TSI in participants with OH or OI. The change from baseline TSI is larger in both symptomatic groups - without OH (β -0.17; 95% CI -0.31, -0.02; p-value 0.022) and with OH (β -0.40; 95% CI -0.70, -0.10; p-value 0.008) but not in participants with asymptomatic OH. The nadir width TSI was longer in participants with symptomatic OH (β 1.04; 95% CI 0.18, 1.91; p-value 0.018). During stabilisation, TSI is lower in those with asymptomatic and symptomatic OH.

Conclusion

Those with symptomatic OH have lower frontal lobe perfusion on initial stand and during stabilisation, and thus have the highest hypotensive load.

6.2 Introduction

Orthostatic Hypotension (OH) is defined by consensus statement as a sustained drop in systolic blood pressure (BP) of at least 20mmHg or diastolic BP of at least 10mmHg, within 3minutes of standing [58, 59]. The prevalence of OH increases with age, and is reported in up to 30% of older people [202]. It is often associated with symptoms of Orthostatic Intolerance (OI), such as dizziness, light-headedness, fatigue and palpitations [231], however similar symptoms can be observed in patients with normal cardiovascular responses to orthostasis, and symptoms are not always present in OH [231, 232].

Assumption of the upright position results in a pooling of 0.5L – 1L in the lower limbs and splanchnic vessels, which leads to a reduction in venous return, ventricular preload and cardiac output. There is a subsequent reduction in the distension of the baroreceptors and reduction in firing of baroreceptor signal to the cardiovascular centre in the brain stem. This leads to parasympathetic inhibition and sympathetic activation, resulting in increased heart rate and cardiac output, and subsequent restoration of blood pressure and cerebral perfusion. OH is a manifestation of autonomic dysfunction, when cardiovascular adaptive mechanisms typically observed on orthostasis fail to compensate for this reduction in venous return that normally occurs on assuming the upright position [30]. It can result from impaired thirst and dehydration, impaired baroreflex sensitivity or impaired venomotor tone [69]. Chronic diseases such as diabetes or neurodegenerative diseases such as Parkinson's disease also play a role. Medications such as antihypertensive medications are often causal [233].

Cerebral autoregulation refers to the ability to regulate and maintain adequate cerebral blood flow during changes in systemic BP. The brain is highly metabolically active and precise regulation of cerebral flow (CBF) is critical for the maintenance of constant nutrient and

oxygen supply to the brain [31]. The partial pressure of arterial carbon dioxide, mean arterial pressure, cerebral metabolism and the autonomic nervous system (ANS) are the principal regulators of CBF [31]. The ANS also plays a key role in restoration of BP following stand, via the baroreceptors [69]. Cerebral hypoperfusion develops when cerebral autoregulation fails in the face of a severe reduction in BP, however cerebral perfusion cannot be predicted perfectly from BP alone. This is because the relationship between BP and cerebral perfusion is nonlinear [137]. Cerebral hypoperfusion may provoke symptoms, such as light-headedness, dizziness, blurred vision and syncope, however many patients with OH are asymptomatic [67].

Near infra-red spectroscopy (NIRS) provides a non-invasive index of frontal lobe cerebral perfusion [192, 234, 235], based on the fact that light in the near infra-red spectrum penetrates the skull and allows measurement of oxy- and deoxy-haemoglobin concentration in the brain [236, 237]. NIRS can measure beat-to-beat variations in the concentrations of oxy- and deoxy-haemoglobin, and these measurements have been shown to correlate well with changes in functional MRI [191], and transcranial Doppler [192].

Orthostatic Hypotension has been associated with falls [75, 188, 238], cognitive impairment [79, 108, 109], dementia [125, 126, 128], and depression [76, 77]. It is thought that cerebral hypoperfusion due to reduction in BP plays a role in such cases. However, most studies do not take into account changes in cerebral haemodynamics during stand. Therefore, the aim of this study is to investigate the relationship between Orthostatic Hypotension at 40 seconds after standing, symptoms of orthostatic intolerance and cerebral oxygenation during standing, as measured by NIRS, in community dwelling adults over 50 years of age.

6.3 Methods

Data from wave 3 of The Irish Longitudinal Study on Ageing (TILDA) were used. NIRS measures of frontal lobe cerebral haemodynamics during orthostasis were conducted at wave 3. TILDA is a large prospective cohort study of community dwelling adults over the age of 50, in which participants were followed at 2-year intervals (waves). Details of the study are described elsewhere [216, 239]. In brief, the study consisted of three main components (1) A Computer Aided Personal Interview (CAPI) carried out in the home by trained interviewers (2) as Self-Completion Questionnaire (3) A health assessment (at alternate waves). This study is a cross-sectional study embedded within the TILDA study.

6.3.1 Ethical Approval

TILDA received ethical approval from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave written informed consent. All experimental procedures adhered to the Declaration of Helsinki.

6.3.2 Participants

This study included all participants who attended the wave 3 health centre for assessment and had adequate active stand data for analysis, including adequate NIRS data, and adequate BP data.

6.3.3 Active stand

At the wave 3 health centre assessment participants underwent an active stand test, which included measurement of frontal lobe perfusion using NIRS in response to orthostasis. NIRS real time frontal lobe cerebral perfusion was measured using the Portalite System (Artinis Medical Systems), a portable continuous wave NIRS system that uses spatially resolved spectroscopy reporting absolute values, developed to measure cerebral perfusion.[190]

Participants lay supine for 10 minutes prior to stand, and were then asked to stand, unaided, in a timely manner. Participants then stood for 3 minutes. Data obtained during the active stand also included beat-to-beat BP assessment measured using digital photoplethysmography (Finometer MIDI device, Finapres Medical Systems). Blood pressure and NIRS measurements were estimated at 10 second intervals, using 5 second moving averages around each time point.

6.3.4 Cerebral perfusion

Tissue saturation index (TSI) was the measure used in this study, and is defined as as (oxyhemoglobin)/ (oxyhemoglobin + deoxyhemoglobin) X 100 and expressed as a percentage [193].

TSI at 0, 10, 30, 40, 60, and 90 seconds post stand are examined. In addition to this, three measures on initial stand were assessed:

(3) *Baseline TSI* –Baseline TSI was measured as the average TSI value at 30 and 60 seconds prior to standing – see Figure 6.1

(4) *Delta TSI* – this was the size of the drop at the nadir TSI value, i.e. Baseline TSI – Nadir TSI (units - %) – see Figure 6.1. The nadir was calculated as the nadir value within the first 25 seconds after standing.

(5) *Nadir width* – this is measured as the width of the trough surrounding the nadir i.e. at 50% of the depth of the trough. It is used to measure the time spent in the nadir, i.e. the time it takes from the start to the end of the nadir (units – seconds) – see Figure 6.1.

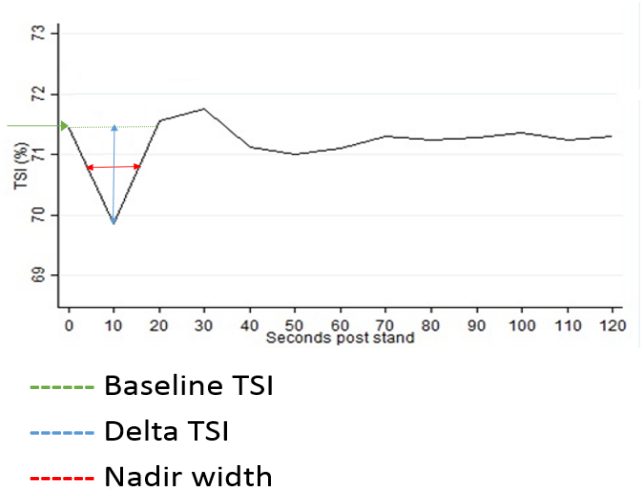

Figure 6.1. NIRS variables assessing response to stand
TSI - tissue saturation index

6.3.5 Orthostatic Hypotension

From previous analysis of the TILDA data, the majority of participants recover BP by 40 seconds post stand [66], and therefore participants were classified as having OH if systolic BP at 40 seconds post stand was ≥20 mmHg below baseline, or their diastolic BP was ≥10 mmHg below baseline.

6.3.6 Orthostatic Intolerance (OI)

Participants were classified first based on whether or not they experienced symptoms of orthostatic intolerance on stand, irrespective of OH status. Those who answered 'Yes' when questioned as to whether they felt any symptoms of dizziness, light-headedness or unsteadiness during the active stand were classified as having symptoms of OI. This question was asked immediately after the active stand.

Participants were then classified into four groups based on their OH and symptom status as follows:

- No OH; No OI – no OH and no symptoms of OI during stand.
- OH; No OI - asymptomatic OH during stand.
- No OH; OI – symptoms of OI, but no OH during stand.
- OH; OI -symptomatic OH during stand.

6.3.7 Covariates

Covariate information was assessed at the CAPI and health assessment. Age, sex, educational attainment, smoking status and cardiovascular conditions were assessed at the CAPI. Anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale – Anxiety (HADS-A) [240]. Depressive symptoms were assessed using the 8-item Centre for Epidemiological Studies Depression Scale (CES-D-8) [241, 242]. Medication information was obtained at the time of the CAPI and cross checked with medication labels. Medications were coded using ATC codes and antihypertensive medications, ATC codes “C02” (anti-hypertensive agents), “C03” (diuretics), “C07” (β-blockers), “C08” (calcium channel blockers), “C09” (angiotensin converting enzyme inhibitors), and anti-depressant medications (ATC codes “N06A”) were controlled for. Objective measurements of height and systolic and diastolic BP were obtained during the health assessment. BP was measured seated, using traditional oscillometric measurements, with an automatic digital BP monitor (OMRON, Kyoto, Japan). Two seated SBP and DBP measurements were obtained, 1 minute apart, and a mean of the measurements used to measure SBP and DBP. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.

6.3.8 Statistical analysis

All statistical analysis were carried out using Stata 14 (Stata Corporation). For descriptive purposes, normally distributed continuous variables were compared using t-tests, non-normally distributed continuous data were compared using Mann Whitney U tests and categorical variables were compared using chi squared tests. Normality was assessed using Q-Q plots and histograms.

Linear regression was used to assess whether baseline TSI (%), Delta TSI (%), or nadir width (seconds) differ in those that complain of symptoms of OI on stand. Univariate models assessed whether there was an association between baseline TSI, delta TSI and nadir width and symptoms of OI on stand, followed by a multivariable model controlling for age, sex, education, number of cardiovascular conditions, SBP, DBP, anti-hypertensive use, anti-depressant use, number of cardiovascular conditions, smoking status, anxiety symptoms, depressive symptoms and height. The analysis was then repeated, categorising participants based on their OH and OI status.

Multilevel mixed effects models were used to compare TSI across specific time points by presence of symptoms, with TSI as the dependant variable nested within participant. This accounts for within participant correlation of the time points. TSI at times 30, 60 and 90 were assessed, as well as TSI at 10 seconds (representing the nadir) and TSI at 40 seconds, as this represents the time point at which OH was assessed for. All models controlled for age, sex, education, number of cardiovascular conditions, SBP, DBP, anti-hypertensive use, anti-depressant use, smoking status, anxiety symptoms, depressive symptoms and height. A three-way interaction between time, OH status and OI status was included to assess how TSI varies across time points by OH and symptoms status.

A p-value of ≤0.05 was considered statistically significant.

6.4 Results

A total of 2884 participants had adequate BP and NIRS data during the active stand and were included in the analysis. Of these, 841 (29.2%) reported symptoms on stand and 366 (12.7%) participants had evidence of OH on active stand. In total, 1,793 (62.3%) had no symptoms and had no evidence of OH. There were 242 (8.4%) participants who had asymptomatic OH, whereas 717 (25.0%) complained of symptoms but did not have OH. A total of 124 (4.3%) had symptomatic OH on active stand.

Population Characteristics are described in table 6.1. Participants who complained of orthostatic symptoms are more likely to be male, with higher levels of OH, lower baseline SBP, lower baseline DBP, more anti-depressant use and higher levels of anxiety symptoms and depressive symptoms.

Table 6.1. Population Characteristics

	No Symptoms of OI on stand (n=2035)	Symptoms of OI on Stand (n=840)	P Value
Age, mean +/-SD	64.3 +/-7.9	64.0 +/-7.9	0.5106
Sex Female, % (n)	55.7% (1133)	51.2% (432)	0.035*
Orthostatic hypotension % (n)	11.9% (242)	14.7% (124)	0.037*
Education Level, %(n) (base primary/none)			
Secondary	40.2% (818)	41.3% (347)	
Third/higher	44.1% (898)	41.2% (347)	0.288
Baseline Mean SBP, mmHg; mean +/- SD	133.3 +/-18.3	130.0 +/- 18.1	<0.001*
Baseline Mean DBP, mmHg; mean +/- SD	81.2 +/- 10.5	79.8 +/- 10.0	0.002*
Anti-hypertensive medications	35.8% (728)	37.1% (312)	0.501
Anti-depressant medications	6.1% (125)	10.2% (86)	<0.001*
Number of CVD conditions, (VS 0)			
1	32.1% (654)	30.2% (254)	
>=2	14.1% (286)	17.1% (144)	0.100
Smoking status, (base never)			
Past	42.1% (856)	42.9% (361)	
Current	9.8% (199)	9.6% (81)	0.914
HADSa	3.3+/-3.2	4.1 +/-3.7	<0.001*
CES-D	2.7 +/-3.3	3.4 +/- 3.9	<0.001*
Height (cm)	165.9 +/-9.2	166.6 +/-8.9	0.097

SBP – Systolic blood pressure; DBP – Diastolic blood pressure; CVD – cardiovascular disorders; HADS-A – Hospital Anxiety and Depression scale (Anxiety subscale); CES-D – Centre for Epidemiological Studies Depression scale.

* P< 0.05

The average time to nadir TSI was 11.4 seconds +/-2.7. There was no evidence that baseline TSI differed in participants who reported OI symptoms (β -0.32; 95% CI -0.72, 0.08; p-value 0.112) on univariate linear regression or controlling for all covariates (β -0.24; 95% CI -0.64, 0.17; p-value 0.254). However, the change from baseline TSI at the nadir value was larger in participants who report OI symptoms during active stand (β -0.25; 95% CI -0.41, -0.14; p-value <0.001) and this remains significant on controlling for all covariates (β -0.19; 95% CI -0.33, -0.06; p-value 0.004). Results of the multivariable linear regression are displayed in Table 6.2. There was no difference in nadir width in participants who reported OI symptoms during active stand on univariate (β 0.06; 95% CI -0.32, -0.44; p-value 0.758) or multivariable (β -0.07; 95% CI -0.45, 0.32; p-value 0.707) linear regression.

Table 6.2. Results of multivariable regression assessing delta TSI at nadir (%) by presence of symptoms of OI on stand

TSI	B Coefficient	95% CI	P Value
OI Symptoms	-0.19*	-0.33, -0.06	0.004
Age, mean +/-SD	-0.02*	-0.03, -0.01	<0.001
Sex Female, % (n)	0.90*	0.70, 1.07	<0.001
Orthostatic hypotension @40 secs, % (n)	-0.10	-0.28, 0.09	0.297
Education Level, %(n) (base primary/none)			
Secondary	-0.12	-0.30, 0.06	0.206
Third/higher	-0.15	-0.33, 0.03	0.110
Mean SBP, mmHg; mean +/- SD	0.01*	0.001, 0.01	0.014
Mean DBP, mmHg	0.001	-0.0005, 0.02	0.063
Anti-hypertensive use	0.12	-0.07, 0.30	0.206
Anti-depressant use	-0.20	-0.43, 0.05	0.124
Number of CVD conditions, (base none)			
1	-0.04	-0.22, 0.13	0.637
>=2	-0.11	-0.34, 0.12	0.358
Smoking status, (base never)			
Past	0.02	-0.11, 0.14	0.786
Current	0.07	-0.15, 0.28	0.543
HADSa	-0.01	-0.03, 0.02	0.627
CES-D	0.004	-0.02, 0.03	0.669
Height (cm)	-0.003	-0.01, 0.01	0.569

OI – Orthostatic Intolerance; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; CVD – cardiovascular disorders; HADS-A – Hospital Anxiety and Depression scale (Anxiety subscale); CES-D – Centre for Epidemiological Studies Depression scale.
* P< 0.05

Participants were then categorised based on OH and OI status. Again, there is no evidence after covariate adjustment that baseline TSI differs in participants with asymptomatic OH (β 0.02; 95% CI -0.66, 0.70; p-value 0.953), symptoms without OH (β -0.20; 95% CI -0.63, 0.25; p-value 0.394), or symptomatic OH (β -0.51; 95% CI -1.43, 0.42; p-value 0.282) compared to participants with neither OH nor symptoms. Delta TSI is significantly larger in both symptomatic groups i.e without OH (β -0.17; 95% CI -0.31, -0.02; p-value 0.022) and with OH (β -0.40; 95% CI -0.70, -0.10; p-value 0.008) but not in participants with asymptomatic OH (β -0.03; 95% CI -0.25, 0.20; p-value 0.816). Results of the full multivariable linear regression are displayed in Table 6.3. Categorising based on OH and symptom status, nadir width was longer in participants with symptomatic OH on active stand (β 1.04; 95% CI 0.18, 1.91; p-value 0.018) controlling for all covariates, however it was not significantly longer in those without symptoms of OI, either without OH (β -0.28; 95% CI -0.70, 0.13; p-value 0.177), or those with OH (β -0.22; 95% CI -0.87, 0.42; p-value 0.502).

Table 6.3. Results of multivariable regression assessing delta TSI at nadir (%) by OH/OI category

	β	95% CI	P Value
OH/Symptoms status, (base No OH, No SOI)			
OH, No OI	-0.03	-0.25, 0.20	0.816
No OH, OI	-0.17*	-0.31, -0.02	0.022
OH, OI	-0.40*	-0.70, -0.11	0.008
Age, mean +/-SD	-0.02*	-0.03, -0.01	<0.001
Sex Female, % (n)	0.90*	0.71, 1.08	<0.001
Education Level, %(n) (base primary/none)			
Secondary	-0.12	-0.29, 0.06	0.203
Third/higher	-0.14	-0.32, 0.03	0.114
Mean SBP, mmHg; mean +/- SD	0.01*	0.001, 0.01	0.014
Mean DBP, mmHg	0.009	-0.0005, 0.02	0.065
Anti-hypertensive use	0.12	-0.06, 0.30	0.198
Anti-depressant use	-0.18	-0.42, 0.06	0.132
Number of CVD conditions, (base none)			
1	-0.05	-0.22, 0.13	0.610
>=2	-0.11	-0.35, 0.12	0.357
Smoking status, (base never)			
Past	0.02	-0.11, 0.14	0.781
Current	0.07	-0.14, 0.28	0.533
HADSa	-0.006	-0.03, 0.02	0.628
CES-D	0.004	-0.02, 0.03	0.686
Height (cm)	-0.003	-0.01, 0.01	0.586

OH – Orthostatic hypotension at 40 seconds post stand; OI – Orthostatic Intolerance; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; CVD – cardiovascular disorders; HADS-A – Hospital

Anxiety and Depression scale (Anxiety subscale); CES-D – Centre for Epidemiological Studies Depression scale.
* P< 0.05

Mixed effects models were used to compare TSI at different time points. Table 6.4 displays the results of the three-way interaction between time, OH and OI. At 10 seconds, OI symptoms are associated with lower TSI. Compared to base (no OH, no OI), both those with symptoms without OH (β -0.18; 95% CI -0.30, -0.06; p-value 0.004) and those with symptomatic OH (β -0.44; 95% CI -0.69, 0.18; p-value 0.001) demonstrated lower TSI at 10 seconds (corresponding with the nadir). From 40 seconds onwards however, lower TSI appears to be driven by the presence of OH, rather than symptoms of orthostatic intolerance, with those with asymptomatic OH demonstrating lower TSI (β -0.47; 95% CI -0.65, -0.28; p-value <0.001) and similarly those with symptomatic OH demonstrating lower TSI (β -0.41; 95% CI -0.67, -0.15; p-value 0.002). These results are displayed graphically in Figure 6.2. Participants with symptomatic OH have the lowest TSI levels at all time points, as can be seen in Figure 6.2.

Table 6.4. Results from mixed effects linear regression - change in TSI during stand, based on OH and Symptoms status

TSI (%)	β Coefficient	95% CI	P-value
Time # OH # Symptoms: (base -no OH, no Symptoms)			
- 10 seconds			
No OH, OI	-0.18	-0.30, -0.06	0.004*
OH, No OI	-0.05	-0.23, 0.14	0.614
OH and OI	-0.44	-0.69, -0.18	0.001*
- 30 seconds			
No OH, OI	0.12	0.002, 0.24	0.047*
OH, No OI	-0.26	-0.44, 0.07	0.007*
OH and OI	-0.11	-0.37, 0.14	0.379
- 40 seconds			
No OH, OI	0.04	-0.07, 0.16	0.477
OH, No OI	-0.47	-0.65, -0.28	<0.001*
OH and OI	-0.41	-0.67, -0.15	0.002*
- 60 seconds			
No OH, OI	0.002	-0.11, 0.12	0.973
OH, No OI	-0.29	-0.48, -0.10	0.002*
OH and OI	-0.42	-0.68, -0.17	0.001*
- 90 seconds			
No OH, OI	0.02	-0.10, 0.14	0.785
OH, No OI	-0.33	-0.52, -0.15	<0.001*
OH and OI	-0.25	-0.50, -0.01	0.06

OH40 – Orthostatic hypotension at 40 seconds post stand; OI – Orthostatic intolerance - report dizziness at time of active stand

* P< 0.05

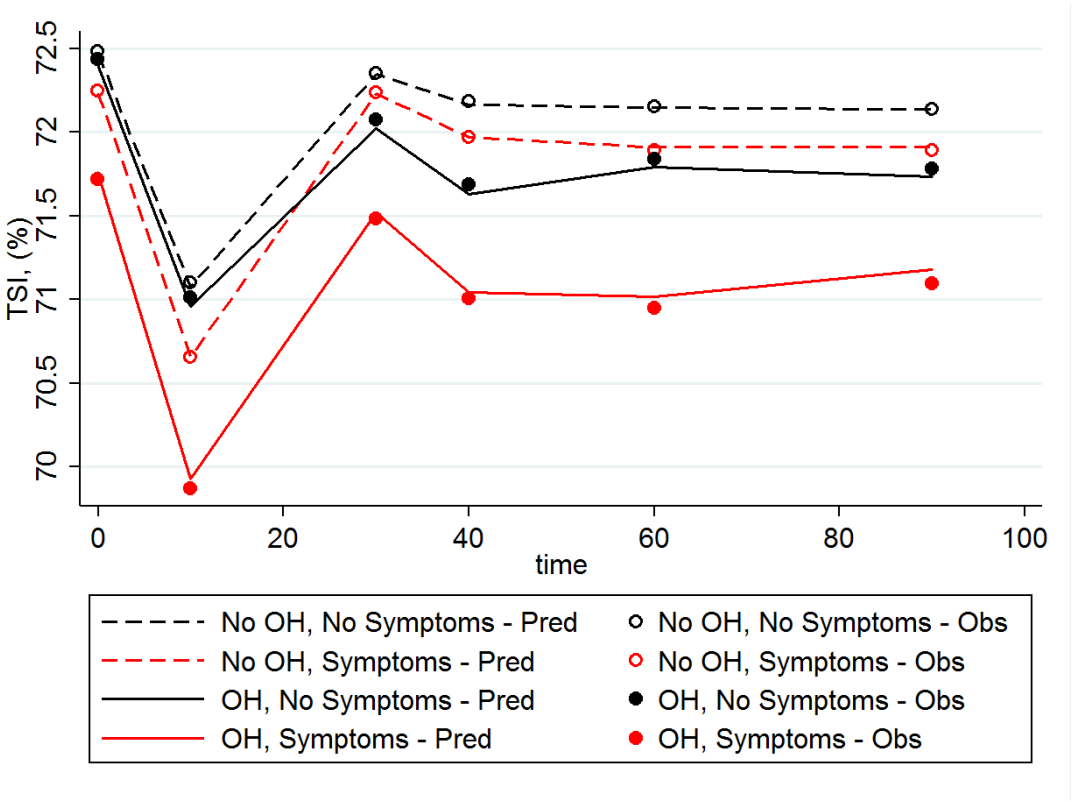

Figure 6.2. Change in TSI during stand based on OH40/Symptoms status

Results from mixed effects model, adjusting for all covariates
OH – Orthostatic hypotension at 40 seconds post stand; Pred – predicted results; Obs – observed results; Symptoms – Symptoms of Orthostatic Intolerance - report dizziness at time of active stand.

6.5 Discussion

Results presented here suggest that symptoms during orthostatic change are associated with larger drops in TSI during the initial stand period, however OH is associated with lower TSI than symptoms during the stabilisation period after the initial drop. OH has been linked with many negative outcomes which are thought to be secondary to cerebral hypoperfusion, and typical symptoms of OH are thought to reflect cerebral hypoperfusion, yet cerebral haemodynamics and the effect of OH on cerebral perfusion are often overlooked [243]. Orthostatic dizziness is common, however many population studies have shown a dissociation between symptoms such as dizziness and OH [244-247]. These studies however, do not measure cerebral haemodynamics at the time of stand. In this study we have shown that dynamic shifts in cerebral perfusion during initial stand (the change from baseline at the nadir and absolute TSI at 10 seconds) are associated with orthostatic symptoms, whereas OH is associated with lower TSI during the stabilisation period (40 seconds to 90 seconds), and therefore those with OH may be exposed to longer periods of hypoperfusion in this study. Those with symptomatic OH have lower absolute TSI values than those with asymptomatic OH. While this study has demonstrated a cross-sectional correlation between OH, OI and cerebral flow, this does not imply causation.

Cerebral autoregulation can be divided into static autoregulation, referring to long-term "steady-state" control, whereas dynamic autoregulation refers to adaptation of perfusion to beat-to-beat variations in intracranial pressure and BP [248, 249]. Chronic periods of hypotension due to OH may impair static autoregulation, reflected by the impaired stabilisation of TSI following initial stand in this study, whereas orthostatic symptoms may be

more reflective of dynamic autoregulation, and are therefore reflected by the period immediately after stand.

The findings in relation to OH and frontal lobe perfusion, are consistent with a number of previous studies which have demonstrated that cerebral perfusion is impaired in Orthostatic Hypotension [137-142]. However, some studies have demonstrated minimal reductions in cerebral flow despite significant reductions in BP [250], which may reflect preservation of cerebral autoregulation in some people. Novak et al [137] assessed cerebral blood flow velocity in patients with autonomic failure and OH using transcranial Doppler (TCD). They found that with normal autoregulation, there was no correlation between BP and blood flow velocity, whereas with expanded autoregulation, BP and blood flow velocity were correlated, but blood flow velocity declined only mildly in an upright position.

Previous studies have also shown that symptoms such as dizziness on stand, may reflect cerebral haemodynamics, even in the absence of systemic BP changes [232, 251]. Harms et al. [141] assessed cerebral perfusion using TCD and cerebral flow using NIRS in patients with OH and normal controls, demonstrating that the reduction in cerebral blood flow velocity and oxygenation in patients with autonomic dysfunction was larger than normal controls. In addition, they found that those who developed symptoms had a more pronounced drop. Novak [251] describes a novel syndrome of orthostatic cerebral hypoperfusion in individuals with normal BP and HR response to stand, but reduced orthostatic cerebral blood flow, using TCD.

This study suggests that cerebral perfusion may decline at different times during orthostasis, with those with OH having a more sustained drop during stand. OH has been associated with syncope and falls [75, 188, 238], cognitive impairment [79, 108, 109], dementia [125, 126,

128], and depression [76, 77], and cerebral hypoperfusion has been implicated. However, these studies do not include measurement of cerebral haemodynamics, and measurement of cerebral haemodynamics in patients with OH is not common in clinical practice. Bachus et al. [142] have proposed the use of NIRS as a tool for the assessment of cerebral haemodynamics in the case of syncope and found that loss of consciousness occurs at a cut-off of TSI of 60%. In addition, previous analysis of the TILDA data has shown an association between frontal lobe perfusion and depression [252]. Further studies are required to assess the usefulness of measurement of cerebral haemodynamics in clinical practice in syndromes of orthostatic intolerance and autonomic dysfunction such as OH. To our knowledge, the current study is the first large population representative study assessing cerebral haemodynamics in response to orthostasis, and how this relates to OH and symptoms of OI on orthostasis.

There are a number of limitations to this study. Assessment of symptoms was performed at the time of active stand, however there is no information on the timing, duration, or severity of symptoms. Therefore, symptoms did not necessarily correlate with the timing of nadir TSI. Participants were questioned as to whether they felt dizzy, lightheaded, or unsteady at the time of stand, however OH can present with more non-specific symptoms such as fatigue, shoulder and neck pain, leg buckling or headache. Use of a scale such as the Orthostatic Hypotension Questionnaire would allow assessment of severity of symptoms and functional impairment [253].Different NIRS devices use different algorithms and validation approaches, and therefore the absolute TSI values reported in this study may not be comparable when using a different device. NIRS provides a measure of frontal lobe perfusion rather than whole-brain perfusion patterns, however the frontal lobe plays a role in a myriad of functions, including playing a large role in voluntary movement, emotional expression, and executive function. Therefore the frontal lobe plays a role in many important functions which have been

linked to OH including mood [76] and cognition [79]. The principal strength of this study is its use of real-time cerebral measurements, and its use of beat-to-beat BP analysis to assess for OH. The TILDA dataset includes information on a large number of covariates, therefore allowing us to control for many potential confounders in this study.

In conclusion, this study demonstrates that both orthostatic symptoms and Orthostatic Hypotension are associated with cerebral hypoperfusion, with symptoms reflecting shifts on initial stand, and Orthostatic Hypotension reflecting lower cerebral perfusion during the stabilisation period. Those with symptomatic Orthostatic Hypotension have the highest burden of cerebral hypoperfusion. Further studies are required to assess whether these patterns are associated with clinical consequences such as falls and cognitive impairment.

Chapter 7: Global cognitive performance at 4 year follow-up in individuals with Atrial Fibrillation – findings from The Irish Longitudinal Study on Ageing.

7.1 Abstract

Introduction

Atrial Fibrillation (AF) has been proposed as a risk factor for cognitive impairment, even in the absence of a history of stroke. This study investigates whether AF is associated with increased risk of cognitive decline in a community-dwelling population of adults over the age of 50.

Methods

Data from the first and third waves of The Irish Longitudinal Study on Ageing (TILDA) were used (4-year follow-up period). TILDA is a large prospective cohort study of community-dwelling adults over the age of 50 in Ireland. AF was assessed via ECG. Global cognitive function was assessed at baseline and follow-up using MOCA. Analysis of global cognition was repeated stratifying by age. Mixed-effects poisson regression was used to assess for change in rate of errors on MOCA and MOCA subdomains.

Results

A total of 3417 participants were included in the study. Results found that participants with AF on ECG had a greater increase in rate of errors on MOCA over four-year follow-up compared to those without AF on ECG (IRR 1.18; 95% CI 1.02, 1.36; P-value 0.024). However, this was no longer significant on controlling for age, sex and level of education (IRR 1.08; 95% CI 0.93, 1.25; p-value 0.332). There was no difference when stratifying by age group, or when separating MOCA into subdomains.

Conclusion

Individuals with AF were more likely to show an increase in rate of errors between waves 1 and 3 (4 year follow-up period) in the TILDA population, however results were not significant when controlling for age, sex and level of education.

7.2 Introduction

Atrial Fibrillation (AF) is the most common sustained arrhythmia, and has been associated with significant mortality, functional decline and reduced quality of life [254]. AF is associated with increased morbidity and mortality, including a five-fold increased risk of stroke [40, 41]. The prevalence of AF increases with age, and AF has been detected in approximately 3-4% of healthy volunteers over the age of 60 years [201] , rising to 16% in those aged 85-89 years [255]. Ageing is also associated with a decline in cognitive abilities [256]. It is well established that AF is associated with an increased risk of dementia and cognitive impairment in individuals with a history of previous stroke [44, 257], with emerging evidence suggesting that AF may also be a risk factor for cognitive decline and dementia in the general population, independent of a history of prior stroke [207, 258].

Multiple risk factors for dementia have been identified, including cardiovascular risk factors such as hypertension, diabetes, smoking and stroke [259]. Vascular risk factors have been shown to play a role in not only vascular subtypes of dementia, but also in Alzheimer's disease [260]. AF shares many risk factors with cognitive impairment and dementia. Ott et al.[147] first reported a significant cross-sectional association between AF and dementia in a population-based study, independent of any prior history of stroke. Since this time, multiple studies examining this subject have been completed. Most cross-sectional studies show an association between AF and cognitive impairment [147, 150-154], but results of longitudinal studies vary [155-159, 161, 162, 170, 172]. Multiple potential mechanisms are proposed for such an association, including cerebral hypoperfusion, vascular inflammation, cerebral small vessel disease, cerebral atrophy and shared risk factors.

The aim of this study was to assess whether community dwelling individuals, aged ≥50, with AF at baseline were more likely to show a decline in global cognitive function at 4 year follow-up compared to those without AF.

7.3 Methods

7.3.1 Study Sample

Data from wave 1 and wave 3 of the Irish Longitudinal Study on Ageing (TILDA) were used (4-year follow-up period). TILDA is a large prospective cohort study comprising of community dwelling adults over the age of 50 in the Republic of Ireland, repeatedly assessed at 2-year intervals (waves). At wave 1 (2009-2011), the study comprised (1) A computer aided personal interview (CAPI), carried out by trained interviewers in participants' homes, (2) A self-completion questionnaire and (3) a health assessment carried out by trained research nurses. As part of a comprehensive health assessment, participants underwent an electrocardiogram (ECG) to screen for AF and the Montreal Cognitive Assessment (MOCA) to assess global cognition. All participants who completed both the CAPI and the health assessment at wave 1 (2009-2011) and completed the health assessment at wave 3 (4 year follow-up), were included for analysis in this study. Participants with a self-reported doctor's diagnosis of dementia, stroke or Parkinson's disease at baseline were excluded, as well as those who reported a diagnosis of Parkinson's at follow-up.

Ethical approval for TILDA was obtained from the Trinity College Research Ethics committee and participants provided written informed consent for participation.

7.3.2 Evaluation for AF

Participants who underwent the health assessment at wave 1 had a 10-minute surface ECG recording. ECGs were performed lying supine in a quiet room with ambient temperature 21-

23°C. ECG records were screened for AF by two clinicians, and inter-rater disagreement was resolved by a cardiologist. Only objective measurements of AF recorded at the health centre were included.

7.3.3 Cognitive Assessment

Global cognition was assessed using the MOCA, which includes assessment of the cognitive domains of executive and visuospatial function, memory, language, and attention. It yields a score ranging from 0 to 30 and was administered at the health centre. The MOCA test is used frequently in clinical setting [194]. It is sensitive to mild deficits and is useful in identifying patients with mild cognitive impairment [195]. Baseline results of MOCA from wave 1 and follow-up MOCA scores at wave 3 were used.

The MOCA was assessed as a total score (maximum score 30), in order to assess global cognition. The results were then divided into sub domains of MOCA and assessed individually - including recall, visuospatial, executive function, attention and working memory, language, and orientation. Recall was assessed using the delayed recall section of the MOCA (maximum score 5). The visuospatial domain was assessed using cube drawing and clock drawing (maximum score 4). To assess Executive function, the trail test section of MOCA, language fluency and a two-item verbal abstraction task were used (maximum score 4). Attention and working memory were assessed via digits forward and backward, the sustained attention task and the serial subtraction task in MOCA (maximum score 6). Language was assessed using animal naming, repetition and the language fluency task (maximum score 6). Orientation to time and place was assessed using questions regarding date, month, year, day, place and city were used (maximum score 6).

7.3.4 Covariates

Results were adjusted for covariates based on known clinical association with AF and cognitive decline. Information on age, sex, educational attainment, smoking status, and alcohol use (using the CAGE questionnaire [218]) were collected during the CAPI. The CAPI also collected information on self-reported comorbidities including self-reported hypertension, heart failure, angina, myocardial infarction, diabetes, stroke, TIA, murmur, or arrhythmia. In wave 1, depressive symptoms were assessed using the Centre for Epidemiological Studies Depression (CES-D) scale [219]. A cut-off score of 16 was used to assess the presence of depression. In wave 3 a short form of the CES-D scale was used [241], with a cut-off score of 9 used to assess the presence of depression. Objective measurements of baseline heart rate and blood pressure were assessed at the health centre. Frailty was assessed using the Fried Frailty scale [208], and individuals were grouped in three groups - not frail, pre-frail or frail. Previous analysis of the TILDA data has shown that Orthostatic Hypotension is associated with decline in cognition at 4 year follow-up [79] and was therefore included as a covariate. Orthostatic Hypotension was assessed using beat-to-beat blood pressure response to orthostasis, using digital photoplethysmography (Finometer MIDI device; Finapres Medical Systems). Orthostatic Hypotension was defined as those who had a sustained drop of ≥20 mm Hg systolic BP (SBP) or ≥10 mm Hg diastolic BP (DBP) at each time point up to 110 seconds post stand [79].

All medications were recorded at the CAPI and classified according to the Anatomical therapeutic classification codes (ATC). Medication categories adjusted for were anti-hypertensive agents (ATC codes ‘CO2’, ‘C03’, C07’, C08’ ‘C09’), anti-psychotic agents (‘N05A’), anti-depressants agents (‘N06A’), anxiolytics, hypnotics and sedatives, anti-cholinergic agents and anti-cholinesterase’s (ATC codes ‘N05B’, ‘N05C’, ‘N04A’, and ‘N06DA’). Previous analysis

of the TILDA data has shown good agreement between self-reported medication use and pharmacy dispensing records [261].

7.3.5 Statistical Analysis

All statistical analysis was carried out using Stata 14 (Stata Corporation). For descriptive data, normally distributed variables were compared using t-tests; non-normally distributed continuous variables were compared using Mann Whitney U tests and categorical variables were compared using chi-squared tests. Q-Q plots and histograms were used to assess normality.

MOCA scores had a left-skewed distribution, therefore the number of errors on MOCA at each wave were calculated (30 minus MOCA score) and the change in participants' MOCA error rates between wave 1 and wave 3 were modelled using mixed effects poisson regression models. Interactions with a variable representing wave (wave 1 – baseline; wave 3 – assessment at 4-year follow-up) for each predictor were included to assess change in error rate on the MOCA (presented as incident rate ratio (IRR)), based on presence of AF at baseline. A univariate model was fitted, followed by a model that controlled for age sex and education level, and a model that controlled for all covariates (age, sex, education, seated hypertension, number of cardiovascular conditions, alcohol use, smoking status, depression, frailty status, Orthostatic Hypotension, and medication use – grouped as anti-hypertensive use, anti-depressant use, anti-psychotic use, and anti-cholinesterase, anticholinergic, or sedative use). The analysis was then repeated stratifying by age groups, age 50-64 and age ≥65.

The sub domains of MOCA were then assessed using similar mixed effects models. The number of errors in each sub domain were calculated by subtracting the total score obtained from the maximum possible score.

The level of significance was set at 5% (p-value < 0.05).

7.4 Results

In total, 8175 participants over the age of 50 were recruited to wave 1 of the TILDA study, of whom 5035 attended the health centre for assessment at wave 1. There were 4651 individuals who had both MOCA, and an ECG performed at wave 1 and who fulfilled the inclusion criteria. Of these participants, 4313 did not report a doctor's diagnosis of dementia, stroke, or Parkinson's. A total of 3417 had a follow-up MOCA available at wave 3, and this was the baseline sample used. Figure 7.1 details a flow chart of individuals included for analysis.

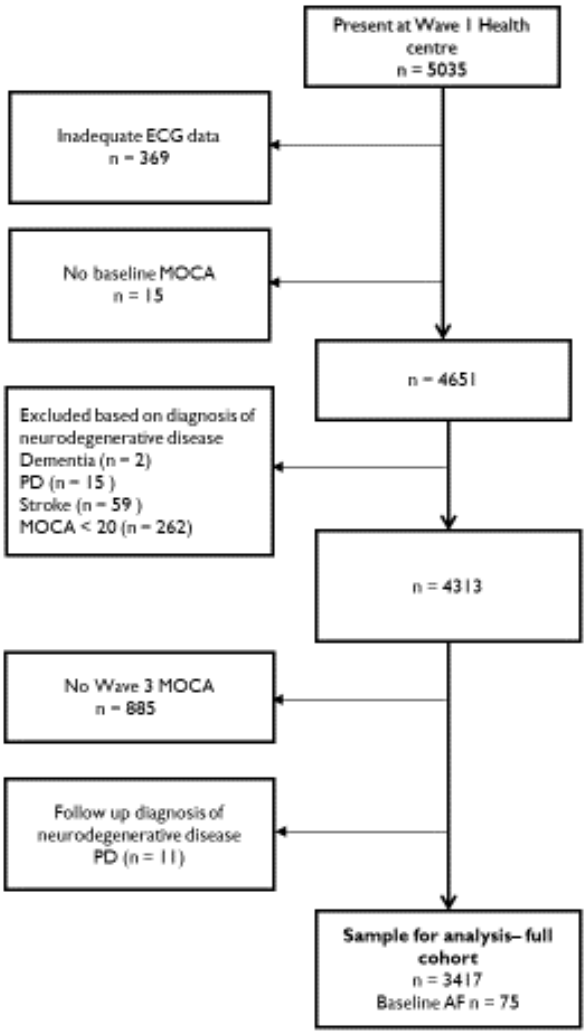

Figure 7.1. Sample for analysis

ECG – Electrocardiogram; MOCA – Montreal Cognitive Assessment; PD – Parkinson's Disease; AF – Atrial Fibrillation

Population characteristics are described in Table 7.1.

Table 7.1. Population characteristics

Characteristics	AF N=74 (2.1%)	No AF N= 3541 (97.88%)	P-value
Age, mean +/- SD	69.9 +/- 8.1	61.2 +/-7.9	<0.001*
Male, % (n)	75.7% (64)	45.0% (1592)	<0.001*
Education, %(n)			
Primary	31.1% (23)	17.8% (622)	
Secondary	37.8% (28)	42.0% (1,487)	
Third/Higher	31.1% (23)	40.4% (1,432)	0.010*
Smoking Status, %(n)			
Never	31.1% (23)	47.3%(1,675)	
Past	63.5% (47)	38.9% (1,378)	
Current	5.4% (4)	13.8% (488)	<0.001*
CAGE score >=2, %(n)	16.2% (12)	13.2% (469)	0.714
MOCA, mean +/- SD	25.3, +/- 2.6	25.9 +/- 2.5	0.036*
Seated HTN, mean +/- SD	48.7% (36)	32.2 (1,140)	0.003
Disease prevalence, %(n)			
≥2 Cardiovascular diseases	51.4% (38)	11.4% (405)	<0.001
Taking anti-hypertensive medications, %(n)	71.6% (53)	30.5% (1,079)	<0.001
Taking anti-depressant medications, %(n)	6.7% (5)	5.2% (183)	0.542
Taking anti-psychotic medications, %(n)	1.3% (1)	1.0% (33)	0.783
Taking anticholinesterase, anticholinergic or sedative mediation, %(n)	2.6% (2)	2.9% (96)	0.890
Taking anti-coagulation, %(n)	36.4% (28)	0.9% (31)	<0.001*
CES-D score, mean +/- SD	4.4 +/- 5.1	5.2+/-6.5	0.745

AF – Atrial Fibrillation; MOCA – Montreal Cognitive Assessment; CAGE[218] – Cut, annoyed, guilty, eye questionnaire; HTN – Hypertension; CES-D[219] – Centre for Epidemiological Studies Depression Scale.

Atrial Fibrillation was present in 75 (2.1%) of the baseline sample. Individuals with AF were older, more likely to be male, with lower levels of education and more likely to have smoked in the past. Those with AF had higher burden of cardiovascular disease, higher seated systolic BP and higher levels of anti-hypertensive use.

The change between wave in number of errors in MOCA (presented as IRR), is presented in Table 7.2.

Table 7.2. Change in rate of errors in MOCA between baseline and 4 year follow-up

Model A - Univariate Analysis			
	IRR	95% CI	P-value
Wave#AF	1.18	1.02, 1.36	0.024
Model B – Controlling for age, sex and education			
	IRR	95% CI	P-value
Wave#AF	1.07	0.93, 1.24	0.348
Model C – Controlling for all covariates			
	IRR	95% CI	P-value
Wave#AF	1.07	0.91, 1.26	0.410

AF – Atrial Fibrillation; IRR – Incident Rate Ratio; CI – Confidence Interval

Results of univariate mixed effects poisson regression found that individuals with AF at baseline had an increase in rate of errors in MOCA over four-year follow-up (IRR 1.18; 95% CI 1.02, 1.36; P-value 0.024). However, this was no longer significant on controlling for age, sex and level of education (IRR 1.08; 95% CI 0.93, 1.25; p-value 0.332), or on controlling for age, sex, education, seated hypertension, number of cardiovascular conditions, alcohol use, smoking status, depression, frailty status, Orthostatic Hypotension, and medication use (IRR

1.07; 95% CI 0.91, 1.27; P-value 0.382). Results of the full multivariable analysis are displayed in the supplementary data, Appendix 4.

Change from baseline MOCA is displayed in Figure 7.2

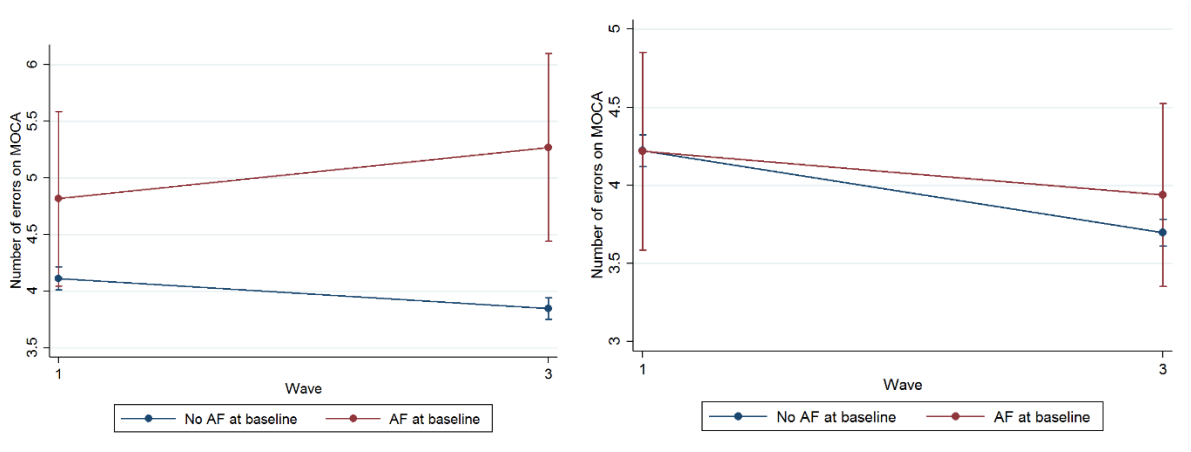

Figure 2a. Univariate analysis **Figure 2b. Controlling for age, sex and education**

Figure 7.2. Change in rate of error in MOCA between baseline and 4-year follow-up

AF – Atrial Fibrillation; MOCA – Montreal Cognitive Assessment;

On stratifying by age group, there was no significant increase in rate of errors on MOCA in the age group 50-64 at baseline (IRR 0.91; 95% CI 0.67, 1.24; P-value 0.550), or in those aged ≥65 (IRR 1.16; 95% CI 0.98, 1.37; P-value 0.075).

The difference in absolute number of errors in MOCA between the groups with and without AF is small. For those with AF, the mean increase in the absolute number of errors between wave 1 and wave 3 is 0.53 (+/- SD 2.43). Those without AF demonstrated an improvement in their MOCA scores between wave 1 and wave 3, with a mean reduction in errors of -0.24 (+/- SD 2.50).

The MOCA was divided into subdomains which were assessed individually. On univariate analysis, there was no increase in the rate of errors in recall (IRR 1.17; 95% CI 0.94, 1.45; p-

value 0.151), visuo-spatial (IRR 1.12; 95% CI 0.79, 1.58; p-value 0.525), executive function (IRR 1.36; 95% CI 0.98, 1.99; p-value 0.067), attention and memory (IRR 1.40; 95% CI 0.85, 2.31; p-value 0.192), language (IRR 1.04; 95% CI 0.78, 1.39; p-value 0.790), or orientation (IRR 0.85; 95% CI 0.34, 2.12; p-value 0.726). As there were no univariate associations for any of the domains, the subdomain analyses were not repeated controlling for covariates.

7.5 Discussion

Individuals with Atrial Fibrillation were more likely to show an increase in rate of errors over a four-year follow-up period in the TILDA population, however results were no longer significant when controlling for age, sex and level of education. The mean age of participants in this study was relatively young (61.4 +/-8.1), and the prevalence of AF was low in this population (2%), which may have limited the power of the study. Numerous studies have investigated this association, and while there is much evidence supporting an association between AF and cognitive impairment in individuals with a history of stroke, there remains uncertainty in respect to non-stroke patients.

Ott et al. [147] first reported a cross-sectional relationship between AF and cognitive impairment in the Rotterdam study in 1997. Since this time there has been numerous studies, both cross-sectional and prospective, examining this question. The relationship between AF and cognitive decline and dementia in patients with a history of stroke is well established [143-146], with a meta-analysis by Kwok at all reported a 2.4-fold increased risk of dementia in stroke patients with AF [44]. However results studying the general population have bene more mixed [155-159, 161, 162, 170, 172]. The meta-analysis published by Kwok et al in 2011 [44] concluded that the overall increased risk of dementia in AF is primarily driven by the significant and consistent risk in patients with stroke. This study excludes those with a

baseline diagnosis of stroke but did not exclude those with incident stroke throughout the 4 year follow-up period. The participants General Practitioners were informed if they had evidence of AF on ECG at wave 1 of the TILDA study, therefore they may have been more likely to receive treatments such as anti-coagulation as a result of participating in the study. However, it is not clear whether anti-coagulation in AF has benefits for cognition, with studies to date demonstrating conflicting results [262-265].

Multiple mechanisms are proposed for a potential association between AF and cognitive impairment. Because AF is a potent risk factor for stroke, post stroke vascular dementia is proposed as a causative mechanism, and evidence suggests a more robust link between AF and dementia in patients with a history of stroke [44]. Other potential mechanisms such subclinical micro-emboli [266], white matter lesions [267], and cerebral hypoperfusion [268] due to reductions in cardiac output in AF.

The principal strength of this study is that it involves a large, population representative sample. The breadth of data collected in TILDA allowed us to control for a wide range of confounders. There are a number of limitations to the current study. While the sample size was large, the number of participants with AF on ECG was small. In addition, while we excluded those with a self-reported history of stroke, no brain imaging was available to exclude participants who may have a history of silent infarcts in the past. Only those with objective measurements of AF on ECG were included in the study, which may mean a number of participants with paroxysmal AF were not included in the AF group. While MOCA is used frequently in the clinical setting, it is not specifically designed to assess longitudinal cognitive changes.

In conclusion, while there was an increase in rate of errors on MOCA at 4 year follow-up in participants with AF, the association was no longer significant on controlling for age, sex and level of education. Follow-up at future waves in TILDA is required to assess for decline over longer follow-up periods.

Chapter 8: Cerebral haemodynamics during orthostatic challenge in people with Atrial Fibrillation in the TILDA population study

8.1 Abstract

Background

It is postulated that cerebral hypoperfusion in Atrial Fibrillation (AF) contributes to falls risk, cognitive impairment, and worse outcome in stroke.

Objectives

This study assesses frontal lobe haemodynamics in response to orthostasis in participants with AF compared to those without AF. Modifying effects of Orthostatic Hypotension (OH) on frontal lobe haemodynamics in participants with AF are also assessed.

Methods

This study is a cross-sectional study using data from The Irish Longitudinal Study on Ageing (TILDA), comparing cerebral haemodynamics in study participants with AF to those without AF. TILDA is a nationally representative study of community-dwelling adults aged over 50 in the Republic of Ireland. Frontal lobe haemodynamics during orthostasis was measured using near infra-red spectroscopy (NIRS), reported as tissue saturation index (TSI%). OH was assessed simultaneously using beat-to-beat blood pressure. Linear regression assessed association between AF and baseline TSI. Mixed effects linear regression assessed TSI at specific time-points - initial stand (10, 20, 30, 40 seconds (s)), and stabilisation (60, 90, 120s). An interaction with OH assessed the impact of OH on this.

Results

A total of 2794 participants had adequate ECG and NIRS data for analysis and were included in the study. Of those included, 70 (2.5%) had AF identified on ECG. Baseline TSI did not differ in participants with AF. Lower TSI in AF was demonstrated at 10s (β -0.52; 95% CI -0.88, -0.16; p-value 0.004), 40s (β -0.40; 95% CI -0.76, -0.04; p-value 0.031) and 60s (β -0.40; 95% CI --0.76, -0.04; p-value 0.028). In AF without OH, TSI was lower at 10s (β -0.62; 95% CI -1.04, -0.19; p-value 0.005). In AF with OH, TSI was lower at at 40s (β -0.89; 95% CI -1.55, -0.24; p-value 0.007), 60s (β -0.89; 95% CI -1.54, -0.23; p-value 0.008) and 90s (β -0.68; 95% CI -1.33, -0.03; p-value 0.041).

Conclusion

There is evidence that frontal lobe haemodynamics differ during orthostasis in individuals with AF, and that OH modifies this association.

8.2 Introduction

Atrial Fibrillation (AF) is the most common sustained arrhythmia, and its prevalence increases with age [269]. AF is associated with increased morbidity and mortality, including a 4-5 fold increased risk of stroke, and a threefold risk of heart failure [40, 41]. AF is also associated with cognitive impairment, even in the absence of a history of stroke [207]. Multiple mechanisms have been proposed for these associations, including subclinical micro-emboli, vascular inflammation, genetic factors and cerebral hypoperfusion [207, 270].

Cerebral hypoperfusion has been shown to lead to white matter hyperintensities [34] and cerebral atrophy [35, 36]. AF is also associated with reduced brain volume, independent of cerebral infarcts [174], and it is thought that cerebral hypoperfusion plays a role in the pathogenesis of this process [175]. Multiple previous studies have assessed cerebral blood flow in individuals with AF [175-182]. One previous study carried out using data from the AGES-Reykjavik study found that in a population sample, persistent AF was associated with reduced cerebral perfusion using phase contrast MRI [175]. Participants were supine during measurement of cerebral flow in this study.

Technologies such as near Intra-red spectroscopy (NIRS), which provides a non-invasive measurement of frontal lobe perfusion, allow for measurement of cerebral haemodynamics during dynamic movements. NIRS provides a measurement of perfusion based on the fact that light in the near infra-red spectrum penetrates the skull and allows measurement of oxy- and deoxy-haemoglobin concentration in the brain [236, 237], and these measurements have been shown to correlate well with changes in functional MRI [191], and transcranial Doppler [192].

Previous analysis of the TILDA data has found that participants with AF were more likely to have Orthostatic Hypotension (OH) [233]. OH is defined by consensus statement as a sustained drop in systolic blood pressure (BP) of at least 20mmHg or diastolic BP of at least 10mmHg, within 3minutes of standing [59, 271] , and OH has been linked with cerebral hypoperfusion [137-139]. Therefore, the aim of this study is to assess the relationship between AF and frontal lobe haemodynamics during orthostasis, as measured by NIRS, in community dwelling adults in Ireland, and to examine how the presence of OH modifies this relationship.

8.3 Methods

This study is a cross-sectional study, embedded within the TILDA study, comparing cerebral haemodynamics in TILDA participants with evidence of AF on ECG to those without AF on ECG. Data from the third wave of the Irish Longitudinal Study on Ageing (TILDA) were used. TILDA is a large prospective cohort study of community dwelling adults over the age of 50, in which participants were followed at two-year intervals (waves). Comprehensive health assessments were carried out at alternate waves, and the health assessment at wave 3 included measurement of cerebral haemodynamics during orthostasis using NIRS. The study is described in detail elsewhere [184, 239]. In Brief, the TILDA study consisted of three main components (1) A Computer Aided Personal Interview (CAPI) carried out in the home by trained interviewers (2) as Self-Completion Questionnaire and (3) A health assessment (at alternate waves).

8.3.1 Ethical Approval

Ethical approval for TILDA was obtained from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin and all participants gave written informed consent. All experimental procedures adhered to the Declaration of Helsinki.

8.3.2 Analytic sample

This study included all participants who had adequate ECG data available for analysis, as well as adequate beat-to-beat blood pressure measurements and NIRS data in response to orthostasis.

8.3.3 Measurement of Atrial Fibrillation

AF was assessed using surface electrocardiogram (ECG). ECGs were screened for AF by a physician, and all cases of AF were confirmed by a second physician.

8.3.4 Measurement of frontal lobe haemodynamics

At the wave 3 health centre assessment, all participants underwent an active stand, during which cerebral haemodynamics in response to orthostasis were assessed using the Artinis Portalite System, a continuous-wave NIRS system using spatially resolved spectroscopy developed to measure cerebral perfusion. Participants lay supine in a quiet room for 10 minutes prior to stand and were then asked to stand in a timely manner.

Tissue saturation index (TSI) was the measure of frontal lobe perfusion used in this study. TSI is defined as (oxyhemoglobin)/ (oxyhemoglobin + deoxyhemoglobin) X 100 and expressed as a percentage. Baseline TSI was measured as the average TSI value at 30 to 60 seconds prior to stand. After standing, TSI was measured for a further 180 seconds. TSI was estimated at 10 second intervals using a 5-second moving averages around each time point. For this study, the time points 10, 20, 30, 40, 60, 90 and 120 seconds were assessed, to examine the changes during initial standing period (10, 20, 30, 40 seconds), and the stabilisation period (60, 90, 120 seconds).

8.3.5 Measurement of Orthostatic Hypotension

During the active stand test, beat-to-beat blood pressure assessment in response to orthostasis was carried out in parallel with cerebral haemodynamics, using a Finometer Midi device (Finapres Medical Systems, Netherlands). Previous analysis of the TILDA data has found that the majority of participants stabilise their blood pressure within 40 seconds of stand [66], therefore the 40 second time point was used to assess for OH. Participants were classified as having OH if systolic BP at 40 seconds post stand was ≥20 mmHg below baseline, or their diastolic BP was ≥10 mmHg below baseline.

8.3.6 Covariate Information

Covariate information was assessed during the CAPI and at the health assessment. Age, sex, educational attainment, smoking status and cardiovascular conditions were assessed at the CAPI. Information on self-reported cardiovascular co-morbidities was collected at the CAPI - self-reported hypertension, heart failure, angina, myocardial infarction, diabetes mellitus, stroke, transient ischemic attack, and heart murmur. A categorical variable representing number of cardiovascular co-morbidities was created, grouping participants into those with no cardiovascular co-morbidities, those with one cardiovascular co-morbidity and those with two or more cardiovascular co-morbidities. Depressive symptoms were assessed using the 8-item Centre for Epidemiological Studies Depression Scale (CES-D-8) [241]. Medication information was obtained at the time of the CAPI and cross checked with medication labels. Medications were coded using ATC codes and antihypertensive medications with the exception of β-blockers - ATC codes “C02” (anti-hypertensive agents), “C03” (diuretics), “C08” (calcium channel blockers), “C09” (angiotensin converting enzyme inhibitors) - were controlled for. A separate variable representing β-blockers (ATC code “C07”) was created, given the frequency with which β-blockers are prescribed in AF. Anti-depressant medications were also controlled for (ATC codes “N06A”). Objective measurements of height and systolic BP (SBP) and diastolic BP (DBP) were obtained during the health assessment. BP was measured seated, using traditional oscillometric measurements, with an automatic digital BP monitor (OMRON, Kyoto, Japan). Two seated SBP and DBP measurements were obtained, 1 minute apart, and a mean of the measurements used to measure SBP and DBP. Problematic alcohol use was assessed using the CAGE questionnaire [218]. A CAGE score of ≥ 2 was defined as problematic alcohol use. Frailty was assessed using the Fried Frailty index [208].

8.3.7 Statistics

All data were analysed using STATA 14 (Stata Corporation). For descriptive purposes, normally distributed continuous variables were compared using t-tests, non-normally distributed continuous variables were compared using Mann Whitney U tests, and categorical variables were compared using Chi squared tests. Normality was assessed using Q-Q plots and histograms.

Linear regression was used to assess whether baseline TSI (%) differed in individuals with and without AF. Univariate analysis was performed, followed by multivariable linear regression controlling for age, sex, level of education obtained, mean SBP, mean DBP, OH, anti-hypertensive (not β-blockers) use, β-blockers use, anti-depressant use, no. of cardiovascular comorbidities, smoking status, depressive symptoms, height, frailty status and problematic alcohol use.

To compare TSI across specific time points in participants with and without AF, multilevel mixed effects models with TSI as the dependant variable nested within participant were used. The time points assessed in this study were 10, 20, 30, 40, 60,, 90 and 120 seconds. A two-way interaction between time and AF status was included in the model to assess the effect of AF at specific time points on TSI. The use of mixed effects models accounts for within individual variation as well as between individual variations. Models were adjusted for age, sex, level of education obtained, mean SBP, mean DBP, OH, anti-hypertensive (not β-blockers) use, β-blockers use, anti-depressant use, no. of cardiovascular comorbidities, smoking status, depressive symptoms, height, frailty status and problematic alcohol use. Covariates were chosen a priori based on their potential role in modifying the relationship between AF and TSI, hypothesised based on current literature and clinical experience.

A further analysis was carried out including a three-way interaction between time, AF and OH, in order to assess whether the presence of OH modifies the relationship between AF and TSI. This model controls for age, sex, level of education obtained, mean SBP, mean DBP, OH, anti-hypertensive (not β-blockers) use, β-blockers use, anti-depressant use, no. of cardiovascular comorbidities, smoking status, depressive symptoms, height, frailty status and problematic alcohol use.

8.4 Results

A total of 6687 participants completed the wave 3 CAPI, of whom 4309 attended the wave 3 health assessment. After removing participants with inadequate ECG data (n=269), inadequate NIRS data (n=1206), or who were identified as having another arrhythmia (n=40), a sample size of 2794 was obtained. Of those included 70 (2.5%) had AF identified on ECG. Population characteristics are described in Table 8.1. Participants with AF on ECG were older, more likely to be male, with lower levels of education, more OH, more anti-hypertensive use, more β-blocker use, more CV co-morbidities, higher levels of past smoking and taller.

Table 8.1. Population Characteristics

	No AF (n= 2724)	AF (n =70)	P Value
Age, mean ± SD	63.91 +/- 7.7	72.56 +/-7.4	<0.001
Female, % (n)	55.65% (1,516)	15.71 % (11)	<0.001
Education, % (n)			
Primary	15.82 (431)	28.57 (20)	
Secondary	40.71(1109)	40.00 (28)	
Third/Higher	43.47 (1184)	31.43 (22)	0.010
Mean SBP, mmHg	132.20 +/- 18.1	129.28 +/- 16.3	0.188
Mean DBP, mmHg	80.89 +/- 10.2	79.56 +/- 12.4	0.310
OH @ 40 Seconds	12.03 (326)	30.43 (21)	<0.001
Anti-hypertensive medications (not β-blockers)	30.43 (829)	62.86 (44)	<0.001
β-blockers use	10.83 (295)	55.71 (39)	<0.001
Anti-depressant medications	7.38 (201)	8.57 (6)	0.707
No. of CV conditions			
0	55.07 (1500)	7.14 (5)	
1	31.20 (850)	34.29 (24)	
≥2	13.73 (374)	58.57 (41)	<0.001
Smoking status			
Never	48.49 (1321)	35.71 (25)	
Past	41.70 (1136)	62.43 (43)	
Current	9.80 (267)	2.86 (2)	0.002
Depressive Symptoms	2.91 +/- 3.5	3.08 +/- 3.1	0.344
Problematic alcohol use (CAGE ≥2)	12.15 (331)	8.57 (6)	0.448
Frailty status			
Pre-frail/Frail	34.29 (934)	48.57 (34)	0.013
Height	165.97 +/- 9.1	170.17 +/- 9.0	<0.001

SBP – Systolic blood pressure; DBP – Diastolic blood pressure; OH – Orthostatic Hypotension; CAGE – "Cut eye guilty eye-opener";

Results of linear regression to assess for an association between baseline TSI and AF status found no significant difference in baseline TSI between the two groups on univariate analysis (β -0.68; 95% CI -1.9, 0.48; p-value 0.253), or on controlling for age, sex, level of education obtained, mean SBP, mean DBP, OH, anti-hypertensive (not β-blockers) use, β-blockers use, anti-depressant use, no. of cardiovascular comorbidities, smoking status, depressive symptoms, height, frailty status and problematic alcohol use (β -0.57; 95% CI -1.83, 0.69; p-value 0.378).

Multilevel models were used to compare TSI across specific time points in participants with and without AF. Results of the AF X Time interaction are provided in Table 8.2, and absolute TSI values across all time points displayed in Figure 8.1. These results are adjusted for age, sex, level of education obtained, mean SBP, mean DBP, OH, anti-hypertensive (not β-blockers) use, β-blockers use, anti-depressant use, no. of cardiovascular comorbidities, smoking status, depressive symptoms, height, frailty status and problematic alcohol use. Participants with AF had a larger drop at the 10 second time point than participants without AF (β -0.52; 95% CI -0.88, -0.16; p-value 0.004). In addition to a larger initial drop, there is evidence of impaired stabilisation of frontal lobe perfusion compared to those without AF, with a larger drop in TSI in those with AF at the 40 second (β -0.40; 95% CI -0.76, -0.04; p-value 0.031) and 60 second (β -0.40; 95% CI --0.76, -0.04; p-value 0.028) time points.

The analysis was repeated including a Time X AF X OH interaction, to assess for modifying effects of OH on this relationship. The results of this analysis are displayed in Table 8.3. Participants with isolated OH have a lower TSI compared to baseline than those without AF or OH at all time points (Table 8.3). Those with isolated AF how a lower initial drop in TSI at 10 seconds (β -0.62; 95% CI -1.04, -0.19; p-value 0.005). However, during the stabilisation

period, those with both AF and OH have a lower TSI at 40 seconds (β -0.89; 95% CI -1.55, -0.24; p-value 0.007), 60 seconds (β -0.89; 95% CI -1.54, -0.23; p-value 0.008) and 90 seconds (β -0.68; 95% CI -1.33, -0.03; p-value 0.041). Those with isolated AF (that is without co-existent OH), do not have lower TSI during the stabilisation period.

Table 8.2. Multi-level mixed effects model with TSI (%) as dependant variable - Time X AF interaction

	β	95% CI	P Value
Time X AF			
10 seconds	-0.52	-0.88, -0.16	0.004
20 seconds	-0.24	-0.61, 0.11	0.183
30 seconds	0.01	-0.34, 0.37	0.963
40 seconds	-0.40	-0.76, -0.04	0.031
60 seconds	-0.40	-0.76, -0.04	0.028
90 seconds	-0.23	-0.59, 0.13	0.213
120 seconds	-0.15	-0.51, 0.21	0.418

Adjusted for age, sex, level of education obtained, mean SBP, mean DBP, OH, anti-hypertensive (not β-blockers) use, β-blockers use, anti-depressant use, no. of cardiovascular comorbidities, smoking status, depressive symptoms, height, Frailty status and problematic alcohol use

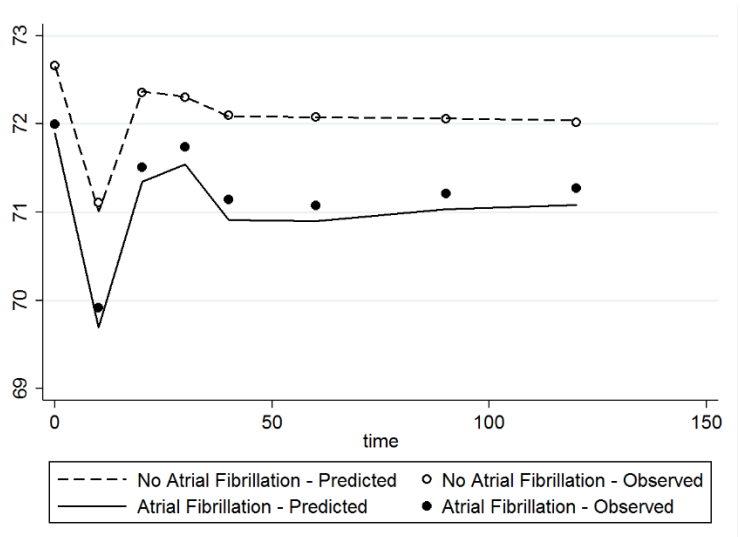

Figure 8.1. Multi-level models of absolute TSI (%) by presence of Atrial Fibrillation (Observed and predicted)

Adjusted for age, sex, level of education obtained, mean SBP, mean DBP, OH, anti-hypertensive (not β-blockers) use, β-blockers use, anti-depressant use, no. of cardiovascular comorbidities, smoking status, depressive symptoms, height, Frailty status and problematic alcohol use

Table 8.3. Multi-level mixed effects model with TSI (%) as dependant variable - Time X AF x OH interaction to assess for modifying effects of OH

	β	95% CI	P Value
Time X AF X OH			
10 seconds			
No AF, OH	-0.17	-0.34, 0.001	0.052
AF, no OH	-0.62	-1.04, -0.19	0.005
AF, OH	-0.38	-1.03, 0.28	0.257
20 seconds			
No AF, OH	-0.47	-0.65, -0.30	<0.001
AF, no OH	-0.25	-0.68, 0.18	0.256
AF, OH	-0.43	-1.08, 0.23	0.200
30 seconds			
No AF, OH	-0.25	-0.42, -0.07	0.005
AF, no OH	0.18	-0.24, 0.61	0.400
AF, OH	-0.48	-1.14, 0.17	0.147
40 seconds			
No AF, OH	-0.48	-0.65, -0.30	<0.001
AF, no OH	-0.27	-0.70, 0.16	0.222
AF, OH	-0.89	-1.55, -0.24	0.007
60 seconds			
No AF, OH	-0.344	-0.52, -0.17	<0.001
AF, no OH	-0.26	-0.68, 0.17	0.241
AF, OH	-0.89	-1.54, -0.23	0.008
90 seconds			
No AF, OH	-0.33	-0.50, -0.15	<0.001
AF, no OH	-0.09	-0.52, 0.34	0.672
AF, OH	-0.68	-1.33, -0.03	0.041
120 seconds			
No AF, OH	-0.31	-0.48, -0.13	0.001
AF, no OH	-0.04	-0.47, 0.39	0.852
AF, OH	-0.53	-1.17, 0.13	0.115

Adjusted for age, sex, level of education obtained, mean SBP, mean DBP, OH, anti-hypertensive (not β-blockers) use, β-blockers use, anti-depressant use, no. of cardiovascular comorbidities, smoking status, depressive symptoms, height, Frailty status and problematic alcohol use

8.5 Discussion

This study demonstrates that in a cohort of community dwelling older adults, participants with AF at the time of assessment have a larger drop in TSI on initial stand, and those with AF and co-existent OH have larger drop in TSI during the stabilisation period. These findings are independent of a range of potential confounders. To our knowledge this is the first population representative study assessing cerebral haemodynamics during dynamic standing in individuals with AF, and the impact of co-existent OH on this association. It has been shown previously in the TILDA population that participants with AF are more likely to have OH, and one possible explanation for this is autonomic dysfunction [233]. It is during the initial stand that those with AF have the largest drop in TSI, and this may represent autonomic dysfunction as the autonomic nervous system plays a crucial role in adaptive mechanisms that normally occur in response to orthostasis [30]. Participants with isolated AF recover their TSI after the initial stand period (within 20 seconds), however those with co-existent OH appear not to be able to recover during the stabilisation period and experience persistent hypoperfusion from 40-90 seconds post stand. The ANS plays a role in OH [59], AF [233] and in cerebral autoregulation [31], and this may represent the group with the most severe autonomic dysfunction. As this is a cross-sectional study, it is not possible to demonstrate causation based on the findings of this study.

The risk of stroke in AF is well established, however more recently AF has been linked with cognitive impairment [207] and falls [204]. In addition, in patients with stroke, AF is associated with a worse outcome, with greater disability and mortality [179]. Cerebral hypoperfusion has been linked with an increased risk of dementia [272], and this may play in a role in the mechanism of these associations. However, the majority of studies that have

examined cerebral perfusion in AF have involved small sample sizes [176-180, 182]. One large study that assessed cerebral perfusion in participants with AF, found that those in AF at the time of assessment had lower cerebral perfusion compared to those in sinus rhythm [175]. The patients in this study were static at the time of MRI. One small study previously examined cerebral perfusion during dynamic movements in individuals with AF, measuring middle cerebral artery blood flow (with Transcranial Doppler) during exercise in 9 patients with AF and 5 age-matched controls. This study found that middle cerebral artery blood velocity is impaired in AF during moderate to high intensity exercise [181].

Perfusion deficits in AF have been attributed to beat-to-beat variation in stroke volume and blood flow, leading to subsequent endothelial dysfunction, and therefore could be independent of arterial blood pressure [178]. However, in this study we see that participants with both AF and impaired blood pressure stabilisation experience a drop in TSI sustained for a longer period of time, whereas those with isolated AF have a drop in TSI at 10 seconds post stand, but not during the stabilisation period. One explanation for this is that participants with both AF and OH represent the group with more severe autonomic dysfunction, which could impact cerebral autoregulation given the key role of the autonomic nervous system in cerebral autoregulation. Both AF and OH have been linked with cognitive impairment [79, 172], falls [45, 206] and depression [76, 273] and OH may contribute to the risk of such clinical consequences in individuals with AF. It has been suggested that worse outcome in stroke in patients with AF is secondary to cerebral hypoperfusion [179], and this study supports this. It is also important to recognise impaired blood pressure stabilisation in these patients, as this may be the group most at risk of poor clinical outcomes secondary to hypoperfusion.

The principal strength of this study is its use of real-time cerebral measurements during dynamic standing in parallel with beat-to-beat blood pressure measurement in a large population sample. The TILDA data includes information on a large number of comorbidities, demographic details, and health behaviours, allowing us to control for many potential confounders. There are limitations to the current study. NIRS provides a measurement of frontal lobe haemodynamics and therefore we can only make inferences in relation to frontal lobe perfusion based on the results of this study. In addition to this, algorithms and validation approaches differ between NIRS devices, and therefore the absolute values obtained in this study may not be comparable when using a different NIRS device. Information on past medical history was obtained via self-report, and this may lead to some bias. Participants with stroke, which can impact TSI, were included in the study. Stroke was not included in the model as a control variable alone, but as part of a composite variable representing the number of cardiovascular comorbidities. The population examined in this study are predominantly Caucasian

8.6 Conclusion

In conclusion, this study demonstrates that AF is associated with lower frontal lobe perfusion compared to sinus rhythm during orthostasis, and this association is modified by the presence of co-existent OH. Further follow-up studies are required at future waves to assess implications for clinical consequences such as falls and cognitive function.

Chapter 9: Discussion

The overall aim of this thesis was to investigate the relationship between two common clinical manifestations of cardiovascular autonomic dysfunction in ageing (OH and AF), and brain health in older adults. Specifically, we set out to examine association between the two indices, OH and AF, and clinical outcomes, cognitive function. We also aimed to examine indices of cerebral perfusion in OH and AF, an often-implicated mechanism in the association between cardiovascular disease and cognitive impairment. In addition, we assessed whether individuals with AF are more likely to have OH, given the role the ANS plays in the pathogenesis of the two clinical entities.

In this chapter, the key findings of the thesis are summarised and discussed. Potential limitations are addressed, and possible clinical implications of the findings are discussed. Finally, topics for future research are identified.

9.1 Key Findings

9.1.2 Participants with AF are more likely to have OH

The ANS plays a role in the pathogenesis of both OH and AF and in addition they share many common risk factors, such as age and hypertension. We hypothesised that individuals with AF would be more likely to have impaired blood pressure stabilisation on stand, and that this association would be independent of shared common risk factors, given the role the ANS plays in the pathogenesis of both. We found that participants with AF were more likely to have OH in the first 30 seconds post stand, and this was independent of shared common risk factors. OH was assessed by measuring beat-to-beat blood pressure response to active standing, using a finometer, which allows for accurate characterisation of blood pressure, particularly advantageous during the initial stand period.

The ANS plays a key role in the initial response to shifts in blood pressure which occur when we stand up and OH occurs when these adaptive mechanisms fail. Given that it is in the first 30 seconds post standing that we see impaired blood pressure stabilisation that is independent of shared common risk factors and independent of HR rise on stand, this may reflect autonomic dysfunction.

Other potential mechanisms for this association include age-related increase in vessel stiffness. Increased pulse wave velocity (PWV), an index of arterial stiffening, increases with age in populations with little or no atherosclerosis, suggesting that vascular stiffening can occur with age, independent of atherosclerosis [209]. Age-related changes in cardiovascular structure and function may underlie the association between AF and OH independent of co-morbidities such as ischaemic heart disease.

The finding in this thesis that individuals with AF are more likely to have OH is consistent with previous studies which have found that OH is a risk factor for the development of incident AF at long term follow-up [80, 82]. OH has also been associated with co-morbid AF in hospitalised patients [274] and syncope secondary to OH has been reported in patients with AF [275]. However, to our knowledge, this is the first population based study to demonstrate a cross-sectional association between the two.

9.3.2 Orthostatic Hypotension and brain health

Study 2 in this thesis found that OH, measured by assessing beat-to-beat blood pressure response to stand, is associated with a decline in global cognitive performance over a four-year follow-up period. OH is defined by consensus statement as a sustained reduction in SBP ≥20mmHg of or DBP ≥10mmHg of within the first 3 minutes after standing. In this study, OH was assessed in two ways. First, we measured OH sustained up to 40 seconds post stand, and

then we measured OH sustained up to 110 seconds post stand. We hypothesised that those who failed to recover their blood pressure throughout the 110 seconds post stand would be exposed to the highest "load" of cerebral hypoperfusion. On stratifying by the presence of seated hypertension, we found that it was those participants with both OH and hypertension that showed a decline in global cognitive performance over four year follow-up. Hypertension leads to alteration in cerebral autoregulation capacity, thus leaving individuals with hypertension more exposed to reductions in cerebral blood flow when systemic blood pressure drops.

Many previous studies have investigated the relationship between blood pressure and cognitive function. The relationship between the two is complex, with both high and low blood pressure linked with cognitive decline and dementia [99]. Mid-life hypertension is consistently linked with cognitive impairment [99], and it is thought that the mechanism behind this is that microvascular dysfunction induced by hypertension leads to white matter disease, microinfarcts, and microhaemorraghes [100]. Numerous mechanisms are proposed for the association between OH and cognitive impairment, with cerebral hypoperfusion often implicated. Supine HTN and OH often coexist [227]. HTN can lead to alteration of cerebral autoregulation capacity [31], further exposing those with HTN to ischaemia and hypoxia during drops in BP on standing in Orthostasis [229]. To our knowledge, Study 2 in this thesis was the first study to investigate the impact of supine HTN on the longitudinal association between OH and cognitive decline.

Cerebral hypoperfusion is often cited as a potential mechanism for cognitive decline in OH. However, most studies to date have been carried out on small populations. In study 3, we

therefore assessed cerebral perfusion in TILDA participants with and without OH during active stand and assessed the role symptoms play in impaired cerebral flow.

Cerebral perfusion was assessed using NIRS and measured as TSI (%). We found that individuals who complained of symptoms on standing had a larger drop in TSI on initial stand; however, those with OH had larger drops in TSI during the stabilisation period. Those with symptomatic OH had the lowest absolute values of TSI both on initial stand and during the stabilisation period, supporting the hypothesis that cerebral hypoperfusion in OH is a potential causative mechanism for cognitive decline.

Many population studies report a dissociation between orthostatic dizziness and OH [244-247], however cerebral haemodynamics were not measured at the time of assessment. We have demonstrated that dynamic shifts in cerebral perfusion during initial stand are associated with orthostatic symptoms, whereas OH is associated with lower TSI during the stabilisation period. Therefore, those with OH are exposed to a higher load of cerebral hypoperfusion. This may play a role in the findings in relation to cognitive function demonstrated in Study 2.

The findings in study 3 are consistent with previous studies that have demonstrated cerebral hypoperfusion in OH [137-142]. However, to our knowledge, Study 3 is the first large population representative study to assess cerebral haemodynamics in response to orthostasis, and how this relates to OH and symptoms of OI on orthostasis.

9.3.3 AF and brain health

AF is often cited as a risk factor for cognitive decline. Results of cross-sectional studies consistently report a relationship between AF and cognitive impairment; however, results are less consistent amongst longitudinal studies. AF is associated with a 4-5 fold increased risk of

stroke, and results of studies assessing cognitive decline in patients with a history of stroke consistently find an association, however results of studies carried out on general populations are more mixed. We sought to examine whether there is a longitudinal decline in global cognitive performance in the TILDA population over four year follow-up.

We found that participants with AF did have a decline in global cognition as compared with those in sinus rhythm, however this association was no longer significant on controlling for basic demographic factors – age, sex and level of education. AF is the most common sustained arrhythmia, with a marked increase in prevalence with increasing age. Cognitive impairment is also considerably more common as we age, therefore age is a potential confounder between AF and cognitive function.

The prevalence of AF in this population was low (2%), which may have limited the power of the study. In addition to this, the period of follow-up in this study was considerably shorter than in previous studies that have investigated this association, and therefore may not have provided sufficient time to demonstrate an association between AF and cognitive impairment.

As the literature frequently cites cerebral hypoperfusion as a potential causative mechanism for cognitive decline in AF, we sought to examine cerebral perfusion in participants with AF. In study 5 we measured TSI at baseline and in response to active stand, using NIRS. We compared baseline TSI in participants with and without AF, however we found no difference between the two groups.

We then compared TSI in response to standing up between the two groups and found that those with AF had a larger drop on standing initially, and in addition had impaired stabilisation of TSI following standing. As Study 1 demonstrated that those with AF were more likely to

have OH, which has been linked with cerebral hypoperfusion, we then stratified by the presence of OH. We found that those with AF had a larger initial drop in TSI on stand, however it was those with both AF and OH who had the higher burden of cerebral hypoperfusion, with impaired stabilisation of TSI up to 90 seconds after standing.

Findings in Study 5 are consistent with previous studies that have assessed cerebral blood flow in individuals with AF [175-182]. These include one previous population study carried out using data from the AGES-Reykjavik study, which reported that persistent AF was associated with reduced cerebral perfusion using phase contrast MRI [175]. However, participants were supine during measurement of cerebral flow in this study, whereas to our knowledge, Study 5 in this thesis is the first large study to examine cerebral flow in response to a dynamic manoeuvre (orthostasis).

9.4 Clinical Implications

Both OH and AF represent potentially modifiable risk factors for brain health in ageing. OH is often modifiable with simple conservative measures such as increasing fluid intake, compression hosiery, withdrawal of culprit medications and physical counter manoeuvres [276], however while many report observed benefit in their clinical practice, there is a need for more research into the efficacy of non-pharmacological methods [276, 277]. There are also a number of pharmacological treatments for OH, however they should only be implemented when conservative measurements fail [278]. There is currently no effective treatment for cognitive decline and dementia, and therefore recognition of risk factors and prevention of the development of dementia is key, in particular modifiable vascular risk factors [279].

AF is a well-recognised risk factor for stroke, and it is also known that individuals with AF who develop stroke have worse clinical outcomes than those in sinus rhythm, attributed to cerebral hypoperfusion [179]. OH is also associated with cerebral hypoperfusion, and the finding that those with AF are more likely to have OH suggests that recognition of OH in this group is important to limit hypoperfusion in AF. Although this thesis has not demonstrated an association between AF and cognitive function, many previous studies with longer follow-up periods have demonstrated such an association. Because OH can be asymptomatic, awareness of this association and recognition and treatment of OH in patients with AF may help to limit clinical implications of AF on brain health, such as cognitive impairment and falls.

9.5 Strengths and Limitations

9.5.1 Limitations

Potential limitations of each of the individual studies have been addressed in the relevant chapters. There are some limitations common to all of the papers published.

Firstly, many of the covariates that were used to control for potential confounding, such as relevant medical history, relied on participant self-report. Patient information in the Irish health care system is not collected electronically and there is no data linkage between hospitals or between hospitals and primary care, and therefore self-report of data was the most efficient means to collect this information. We therefore relied on self-reporting via computer-aided personal interviews. However, these interviews were consistent between participants and carried out by trained interviewers. Individuals with cognitive impairment may be more likely to misreport medical conditions. However, for the purposes of this thesis, self-reported variables were only used in adjusting for confounding factors and were not the primary outcome of interest in these studies. Furthermore, all TILDA participants were

screened for dementia prior to invitation to participate, and those with significant cognitive impairment were excluded from the study.

Data obtained during the active stand in the health assessment was used in all studies included in this thesis. It was not practically feasible to standardise lifestyle factors such as time from last meal, caffeine or alcohol intake, smoking, medication administration or the time of day the active stand was carried out given the large number of health assessments that were performed on participants living in locations throughout the country. However, the active stand protocol itself was standardised between participants and was carried out by trained research nurses according to standardised protocols.

OH is a heterogenous condition with a variety of underlying causes, both neurogenic and non-neurogenic, which may impact on outcomes. The underlying cause of OH in participants included in the studies in this thesis are not known.

9.5.2 Strengths

The main strength of the thesis is its use of the TILDA dataset. TILDA provides a well described cohort of older people in Ireland that is based on a nationally representative sample, representing 1 in 156 people aged over 50 in Ireland. Interviews were carried out by trained interviewers, and health assessments were carried out by trained research nurses using standardised protocols. In all studies in this thesis, OH was assessed by measuring beat-to-beat blood pressure response to active standing, using a finometer, which allows for accurate characterisation of blood pressure response to stand. Comprehensive assessment of covariates in the TILDA dataset allows a large number of confounders to be considered in the study.

9.6 Future Research

We demonstrated a cross-sectional relationship between OH and AF. Longitudinal follow-up to assess for a causal link between the two could be carried out using the data collected in waves 1 and 3 of TILDA, and in subsequent waves securing a longer follow-up period. A number of processes could underlie the association between OH and AF. The TILDA study also examined measures including Baroreflex Sensitivity (BRS), Pulse Wave Velocity (PWV) and Heart Rate Variability (HRV). Therefore studies assessing the association between baseline measures such as BRS, PWV and HRV and incident OH and AF, may add to the understanding of the mechanisms behind this association.

We have demonstrated an association between OH and declining cognition over a 4 year follow-up period, and the impact of supine HTN on this. Follow-up at future ways of TILDA will allow assessment of the impact of blood pressure behaviour on the rate of cognitive decline. In addition, longer follow-up periods would allow assessment of the impact of blood pressure behaviour on rates of incident dementia. We have also assessed cerebral perfusion and how it relates to OH and symptoms of OI in this thesis. We hypothesise that impaired cerebral flow increases the risk of cognitive decline and dementia in patients with impaired blood pressure stability on stand. Follow-up at future waves will allow objective assessment of the impact of cerebral hypoperfusion on cognitive function on longitudinal follow-up.

While we did not find an association between AF and cognitive decline over 4 years, this may be a result of the low prevalence of AF, and the relatively short follow-up period compared to previous studies. Follow-up at future waves will allow assessment of whether AF is associated with cognitive decline over longer follow-up periods. Cerebral hypoperfusion in AF is often cited as a potential mechanism for the association between AF and cognitive decline.

This thesis demonstrated lower frontal lobe perfusion in individuals with AF, and follow-up at future waves will allow assessment of the clinical consequences of this, such as cognitive decline, falls and depression.

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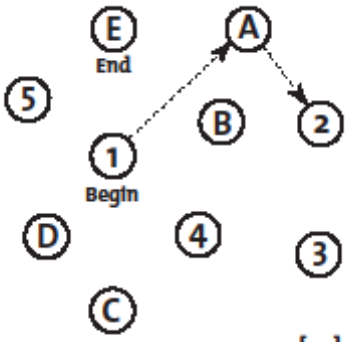
Appendix 1 - MOCA

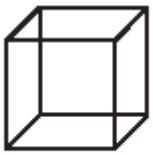
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



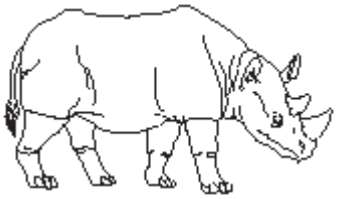
[ ] [ ]

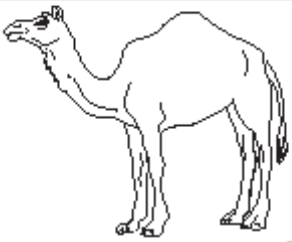
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING





[ ] [ ] [ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Appendix 2 – Study 1 Supplementary Data

Study 1. Supplemental data - Results of Multivariable Logistic Regression

Initial OH		**OR**	**95% CI**	**P value**
	AF	2.48	1.59, 3.87	<0.0001
	Age	1.02	1.00, 1.02	<0.0001
	Sex (male)	1.03	0.90, 1.16	0.689
	Baseline HR	0.96	0.96, 0.97	<0.0001
	Education (base none)			
	Seconday	0.97	0.82, 1.14	0.737
	Third level/higher	1.10	0.93, 1.32	0.25
	Smoker (base never)			
	Past	0.91	0.79, 1.04	0.171
	Current	0.85	0.70, 1.02	0.086
	Mean SBP mmHg	1.00	1.00, 1.00	0.414
	On beta blocker	0.98	0.77, 1.24	0.864
	On anti-hypertensive (Not BB)	1.07	0.86, 1.32	0.544
	Frail/Pre-frail	1.03	0.90,1.19	0.648
	Self-reported Cardiovascular Co-Morbitides (base none)			
	1 co-morbidity	0.83	0.70, 1.00	0.035
	≥2 comorbidities	0.84	0.65, 1.09	0.193
OH sustained at 30 seconds		**OR**	**95% CI**	**P value**
	AF	1.78	1.07, 2.95	0.025
	Age	1.07	1.06, 1.08	<0.0001
	Sex (male)	1.67	1.39, 2.00	<0.0001
	Baseline HR	0.97	0.96, 0.98	<0.0001
	Education (base primary)			
	Seconday	0.83	0.67, 1.04	0.102
	Third level/higher	0.83	0.66, 1.04	0.11
	Smoker (base never)			
	Past	1.24	1.02,1.50	0.028
	Current	1.47	1.13, 1.91	0.004
	Mean SBP mmHg	1.00	1.00,1.00	0.79
	On beta-blocker	1.10	0.81, 1.48	0.55
	On anti-hypertensive (Not BB)	0.82	0.62, 1.09	0.545
	Frail/Pre-frail	1.17	0.97, 1.41	0.11
	Self-reported Cardiovascular Co-Morbitides (base none)			
	1 co-morbidity	1.15	0.90, 1.46	0.26
	≥2 comorbidities	1.42	1.02, 1.96	<0.0001
OH sustained at 60 seconds		**OR**	**95% CI**	**P value**
	AF	1.81	0.95, 3.47	0.073
	Age	0.07	1.06, 1.09	<0.0001
	Sex (male)	1.6	1.24, 2.09	<0.0001
	Baseline HR	0.98	0.97, 1.00	0.001
	Education (base none)			
	Seconday	0.82	0.60, 1.12	0.211
	Third level/higher	0.75	0.54, 1.04	0.087
	Smoker (base never)			
	Past	0.94	0.711, 1.24	0.647
	Current	1.29	0.89, 1.87	0.18
	Mean SBP mmHg	1.00	1.00, 1.00	0.551
	On beta blocker	1.54	1.02, 2.31	0.038
	On anti-hypertensive (Not BB)	0.76	0.51, 1.14	0.189
	Frail/Pre-frail	1.09	0.83, 1.43	0.531
	Self-reported Cardiovascular Co-Morbitides (base none)			
	1 co-morbidity	1.32	0.95, 1.84	0.094
	≥2 comorbidities	1.14	0.72, 1.81	0.578

Appendix 3 – Study 2 Supplemental Data

Table S1.

Total Errors	IRR	95% CI	P- value
Wave	0.4887	[0.3316]--[0.7203]	0.0003
OH40, (base 0)	0.9883	[0.9091]--[1.0743]	0.7817
Age	1.0098	[1.0064]--[1.0133]	<0.0001
Sex	0.9182	[0.8565]--[0.9843]	0.0162
Education, (base "Primary/none")			
Secondary	0.8584	[0.8036]--[0.9168]	<0.0001
Third level/higher	0.6678	[0.6234]--[0.7153]	<0.0001
No. Cardiovascular conditions, (base "0")			
1	1.0507	[0.9781]--[1.1288]	0.1756
2	0.9697	[0.8695]--[1.0816]	0.581
Hypertension, (Base "No")	0.9897	[0.9217]--[1.0627]	0.7747
Heart failure, (base "No")	1.1446	[0.8911]--[1.4703]	0.2903
Diabetes, (base "No")	1.116	[0.9411]--[1.3233]	0.2071
Alcohol CAGE score, (base 0)			
1	0.9347	[0.8698]--[1.0045]	0.066
2	0.8887	[0.8164]--[0.9674]	0.0064
3	0.928	[0.8301]--[1.0375]	0.1891
4	1.1398	[0.8788]--[1.4785]	0.324
Smoking status, (base "Never smoked")			
Past smoker	0.9823	[0.9314]--[1.0360]	0.5106
Current smoker	1.1047	[1.0250]--[1.1905]	0.0091
Anticholinesterase or Anticholinergic	1.1857	[1.0362]--[1.3567]	0.0132
Antihypertensive medications	1.0168	[0.9444]--[1.0947]	0.6591
Antipsychotic medications	0.98	[0.7806]--[1.2304]	0.8618
Antidepressant medications	1.0261	[0.9225]--[1.1412]	0.6357
Diabetic medications	1.0122	[0.8344]--[1.2279]	0.902
Depression	1.0353	[0.9503]--[1.1280]	0.4271
Pulse pressure, mmHg	1.0003	[0.9972]--[1.0034]	0.8444
Systolic BP, mmHg	1	[0.9976]--[1.0024]	0.9805
Wave#OH40	1.0927	[0.9919]--[1.2037]	0.0726
Wave# age	1.0105	[1.0063]--[1.0147]	<0.0001
Wave# Sex	0.9768	[0.9192]--[1.0381]	0.4496
Wave# Education, base primary/none			
Secondary	0.9631	[0.8922]--[1.0397]	0.3359
Third/higher	0.9809	[0.9059]--[1.0620]	0.634
Wave# No. CVD conditions, (base 0)			
1	0.985	[0.8914]--[1.0884]	0.7666
≥2	1.0264	[0.8927]--[1.1801]	0.7146
Wave# Hypertension	1.0415	[0.9608]--[1.1289]	0.3228
Wave# heart failure	0.6684	[0.4514]--[0.9896]	0.0442
Wave# Diabetes	0.9542	[0.7516]--[1.2114]	0.7003

Wave# CAGE score, base 0			
1	0.9475	[0.8600]--[1.0440]	0.2761
2	0.993	[0.8873]--[1.1114]	0.9027
3	0.9571	[0.8212]--[1.1155]	0.575
4	0.7217	[0.4323]--[1.2050]	0.2124
Wave# Smoking status, base never			
Past	1.0226	[0.9619]--[1.0872]	0.474
Current	0.9905	[0.8957]--[1.0955]	0.8531
Wave# Anticholinesterase/Anticholinergic medication	0.9641	[0.8168]--[1.1380]	0.6659
Wave# Antihypertensive medication	0.979	[0.8821]--[1.0866]	0.6903
Wave# Anti-psychotic medication	1.2177	[0.9191]--[1.6134]	0.17
Wave# Anti-depressant	1.1454	[1.0072]--[1.3025]	0.0385
Wave# Diabetic medication	1.0481	[0.8050]--[1.3647]	0.7271
Wave# Depression	1.009	[0.8909]--[1.1428]	0.8879
Wave# Pulse Pressure	0.9975	[0.9930]--[1.0021]	0.2921
Wave# Mean SBP	1.0002	[0.9969]--[1.0035]	0.8949
Frailty, base not frail			
Pre-frail	1.0765	[1.0240]--[1.1317]	0.0038
Frail	1.111	[0.8524]--[1.4481]	0.4361
Height, sm	0.9956	[0.9921]--[0.9991]	0.0133
Baseline HR, bpm	1.0003	[0.9981]--[1.0025]	0.8148

Table 1. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH40 for full cohort

IRR – Incidence rate ratio; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S2.

Total Errors	IRR	95% CI	P- value
Wave	0.4841	[0.3290]--[0.7124]	0.0002
OH110, (base 0)	0.9453	[0.8380]--[1.0665]	0.3609
Age	1.0099	[1.0064]--[1.0133]	<0.0001
Sex	0.9201	[0.8582]--[0.9864]	0.019
Education, (base "Primary/none")			
Secondary	0.8583	[0.8036]--[0.9168]	<0.0001
Third level/higher	0.6671	[0.6227]--[0.7147]	<0.0001
No. Cardiovascular conditions, (base "0")			
1	1.0508	[0.9782]--[1.1289]	0.1747
2	0.9704	[0.8701]--[1.0824]	0.59
Hypertension, (Base "No")	0.9887	[0.9208]--[1.0617]	0.7547
Heart failure, (base "No")	1.1406	[0.8879]--[1.4652]	0.3031
Diabetes, (base "No")	1.1163	[0.9414]--[1.3238]	0.2057
Alcohol CAGE score, (base 0)			
1	0.9353	[0.8703]--[1.0051]	0.0686
2	0.8885	[0.8162]--[0.9672]	0.0063
3	0.9294	[0.8313]--[1.0391]	0.1982
4	1.1462	[0.8837]--[1.4868]	0.3038
Smoking status, (base "Never smoked")			
Past smoker	0.9818	[0.9309]--[1.0355]	0.4994
Current smoker	1.105	[1.0254]--[1.1908]	0.0089
Anticholinesterase or Anticholinergic	1.1882	[1.0384]--[1.3595]	0.0121
Antihypertensive medications	1.018	[0.9456]--[1.0960]	0.6354
Antipsychotic medications	0.9746	[0.7762]--[1.2238]	0.8248
Antidepressant medications	1.0264	[0.9229]--[1.1415]	0.6313
Diabetic medications	1.0136	[0.8355]--[1.2296]	0.8912
Depression	1.0324	[0.9475]--[1.1249]	0.4663
Pulse pressure, mmHg	1.0003	[0.9972]--[1.0034]	0.8313
Systolic BP, mmHg	1	[0.9976]--[1.0024]	0.9979
Wave#OH110	1.1683	[1.0164]--[1.3430]	0.0286
Wave# age	1.0107	[1.0065]--[1.0149]	<0.0001
Wave# Sex	0.9752	[0.9176]--[1.0364]	0.4183
Wave# Education, base primary/none			
Secondary	0.9635	[0.8925]--[1.0400]	0.3402
Third/higher	0.9831	[0.9080]--[1.0645]	0.6753
Wave# No. CVD conditions, (base 0)			
1	0.9869	[0.8932]--[1.0906]	0.7964
≥2	1.0286	[0.8947]--[1.1825]	0.6919
Wave# Hypertension	1.0434	[0.9626]--[1.1310]	0.3013
Wave# heart failure	0.6742	[0.4554]--[0.9983]	0.049
Wave# Diabetes	0.9528	[0.7505]--[1.2096]	0.6914
Wave# CAGE score, base 0			
1	0.9466	[0.8591]--[1.0430]	0.2676

2	0.9929	[0.8871]--[1.1112]	0.9007
3	0.96	[0.8236]--[1.1188]	0.601
4	0.7168	[0.4294]--[1.1967]	0.203
Wave# Smoking status, base never			
Past	1.0242	[0.9634]--[1.0888]	0.4434
Current	0.989	[0.8943]--[1.0938]	0.8297
Wave# Anticholinesterase/Anticholinergic medication	0.9642	[0.8169]--[1.1380]	0.6662
Wave# Antihypertensive medication	0.9755	[0.8789]--[1.0826]	0.6402
Wave# Anti-psychotic medication	1.2216	[0.9219]--[1.6188]	0.1635
Wave# Anti-depressant	1.1494	[1.0110]--[1.3068]	0.0335
Wave# Diabetic medication	1.0484	[0.8051]--[1.3651]	0.7258
Wave# Depression	1.0112	[0.8927]--[1.1454]	0.8611
Wave# Pulse Pressure	0.9977	[0.9931]--[1.0022]	0.3161
Wave# Mean SBP	1.0001	[0.9968]--[1.0034]	0.9334
Frailty, base not frail			
Pre-frail	1.0769	[1.0244]--[1.1321]	0.0037
Frail	1.1056	[0.8482]--[1.4410]	0.4579
Height, sm	0.9957	[0.9922]--[0.9991]	0.0144
Baseline HR, bpm	1.0002	[0.9980]--[1.0024]	0.8502

Table 2. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH110 for full cohort

IRR – Incidence rate ratio; OH110 – Orthostatic hypotension sustained to 110 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S3.

Total Errors	IRR	95% CI	P- value
Wave	0.7484	[0.3947]--[1.4194]	0.3749
OH40, (base 0)	0.9539	[0.8340]--[1.0910]	0.4909
Age	1.0082	[1.0004]--[1.0160]	0.0397
Sex	0.9379	[0.8557]--[1.0281]	0.1713
Education, (base “Primary/none”)			
Secondary	0.8326	[0.7581]--[0.9145]	0.0001
Third level/higher	0.6226	[0.5644]--[0.6867]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.062	[0.9660]--[1.1675]	0.2132
2	0.8917	[0.7625]--[1.0429]	0.1515
Hypertension, (Base “No”)	0.9941	[0.9030]--[1.0945]	0.9044
Heart failure, (base “No”)	1.264	[0.8949]--[1.7852]	0.1837
Diabetes, (base “No”)	1.1788	[0.9216]--[1.5078]	0.1902
Alcohol CAGE score, (base 0)			
1	0.96	[0.8803]--[1.0469]	0.3558
2	0.8995	[0.8142]--[0.9938]	0.0373
3	0.9138	[0.7999]--[1.0439]	0.1842
4	1.3093	[0.8760]--[1.9569]	0.1888
Smoking status, (base “Never smoked”)			
Past smoker	0.9807	[0.9143]--[1.0521]	0.5873
Current smoker	1.0848	[0.9907]--[1.1879]	0.0787
Anticholinesterase or Anticholinergic	1.1647	[0.9201]--[1.4744]	0.2049
Antihypertensive medications	1.0322	[0.9324]--[1.1427]	0.5414
Antipsychotic medications	1.0612	[0.8226]--[1.3690]	0.6477
Antidepressant medications	0.9891	[0.8633]--[1.1333]	0.8746
Diabetic medications	1.0445	[0.7910]--[1.3791]	0.759
Depression	1.0343	[0.9298]--[1.1506]	0.5346
Pulse pressure, mmHg	1.0005	[0.9963]--[1.0047]	0.8184
Systolic BP, mmHg	0.9998	[0.9967]--[1.0029]	0.9143
Wave#OH40	1.1318	[0.9750]--[1.3137]	0.1036
Wave# age	1.0028	[0.9939]--[1.0116]	0.5412
Wave# Sex	0.9407	[0.8710]--[1.0160]	0.1197
Wave# Education, base primary/none			
Secondary	0.94	[0.8449]--[1.0457]	0.2551
Third/higher	0.9927	[0.8883]--[1.1093]	0.8966
Wave# No. CVD conditions, (base 0)			
1	1.0065	[0.8879]--[1.1409]	0.9193
≥2	1.1145	[0.9193]--[1.3510]	0.2698
Wave# Hypertension	1.0201	[0.9165]--[1.1353]	0.716
Wave# heart failure	0.5107	[0.3071]--[0.8493]	0.0096
Wave# Diabetes	0.9037	[0.6435]--[1.2689]	0.5586
Wave# CAGE score, base 0			
1	0.9645	[0.8582]--[1.0840]	0.5444

2	1.0134	[0.8904]--[1.1534]	0.8401
3	0.9727	[0.8118]--[1.1654]	0.7639
4	0.5464	[0.2912]--[1.0256]	0.0599
Wave# Smoking status, base never			
Past	1.026	[0.9485]--[1.1098]	0.5219
Current	1.0141	[0.9019]--[1.1403]	0.8148
Wave# Anticholinesterase/Anticholinergic medication	0.9725	[0.7400]--[1.2781]	0.8417
Wave# Antihypertensive medication	0.9434	[0.8232]--[1.0812]	0.4024
Wave# Anti-psychotic medication	1.1553	[0.8386]--[1.5915]	0.3772
Wave# Anti-depressant	1.2183	[1.0407]--[1.4261]	0.014
Wave# Diabetic medication	1.1246	[0.7701]--[1.6421]	0.5434
Wave# Depression	0.9944	[0.8549]--[1.1567]	0.9424
Wave# Pulse Pressure	0.9955	[0.9895]--[1.0016]	0.1492
Wave# Mean SBP	1.0015	[0.9972]--[1.0057]	0.4966
Frailty, base not frail			
Pre-frail	1.0509	[0.9821]--[1.1246]	0.1506
Frail	1.4248	[0.9445]--[2.1492]	0.0914
Height, sm	0.9949	[0.9904]--[0.9995]	0.0309
Baseline HR, bpm	0.9999	[0.9969]--[1.0028]	0.922

Table 3. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH40 for Age group ≥50 and <65

IRR – Incidence rate ratio; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate. (N=2148)

Table S4.

Total Errors	IRR	95% CI	P- value
Wave	0.7537	[0.3974]--[1.4296]	0.3867
OH110, (base 0)	0.9157	[0.7473]--[1.1220]	0.3953
Age	1.0081	[1.0003]--[1.0159]	0.0419
Sex	0.9393	[0.8569]--[1.0296]	0.181
Education, (base “Primary/none”)			
Secondary	0.8342	[0.7595]--[0.9161]	0.0002
Third level/higher	0.6233	[0.5651]--[0.6875]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0604	[0.9645]--[1.1658]	0.225
2	0.8916	[0.7624]--[1.0427]	0.1509
Hypertension, (Base “No”)	0.9929	[0.9019]--[1.0932]	0.8848
Heart failure, (base “No”)	1.2675	[0.8974]--[1.7904]	0.1785
Diabetes, (base “No”)	1.1849	[0.9263]--[1.5157]	0.1769
Alcohol CAGE score, (base 0)			
1	0.9602	[0.8805]--[1.0471]	0.358
2	0.8996	[0.8143]--[0.9939]	0.0375
3	0.9139	[0.8001]--[1.0440]	0.1851
4	1.3139	[0.8791]--[1.9636]	0.183
Smoking status, (base “Never smoked”)			
Past smoker	0.9799	[0.9135]--[1.0512]	0.5714
Current smoker	1.0857	[0.9914]--[1.1889]	0.076
Anticholinesterase or Anticholinergic	1.1697	[0.9239]--[1.4809]	0.1929
Antihypertensive medications	1.033	[0.9332]--[1.1436]	0.5309
Antipsychotic medications	1.0533	[0.8164]--[1.3590]	0.6896
Antidepressant medications	0.9876	[0.8621]--[1.1314]	0.8572
Diabetic medications	1.0375	[0.7855]--[1.3704]	0.7952
Depression	1.0319	[0.9276]--[1.1480]	0.5633
Pulse pressure, mmHg	1.0005	[0.9964]--[1.0047]	0.8025
Systolic BP, mmHg	0.9998	[0.9967]--[1.0029]	0.9134
Wave#OH110	1.2541	[1.0012]--[1.5709]	0.0488
Wave# age	1.0029	[0.9941]--[1.0117]	0.5263
Wave# Sex	0.9379	[0.8683]--[1.0131]	0.1034
Wave# Education, base primary/none			
Secondary	0.9365	[0.8417]--[1.0419]	0.2279
Third/higher	0.991	[0.8868]--[1.1075]	0.8738
Wave# No. CVD conditions, (base 0)			
1	1.0097	[0.8908]--[1.1445]	0.8798
≥2	1.1135	[0.9186]--[1.3499]	0.2735
Wave# Hypertension	1.0228	[0.9189]--[1.1384]	0.6801
Wave# heart failure	0.5102	[0.3068]--[0.8485]	0.0095
Wave# Diabetes	0.9014	[0.6419]--[1.2658]	0.5489
Wave# CAGE score, base 0			
1	0.9623	[0.8562]--[1.0816]	0.5195

2	1.0134	[0.8904]--[1.1533]	0.8405
3	0.9773	[0.8157]--[1.1710]	0.8033
4	0.5434	[0.2896]--[1.0199]	0.0576
Wave# Smoking status, base never			
Past	1.0273	[0.9497]--[1.1112]	0.502
Current	1.0138	[0.9016]--[1.1399]	0.8194
Wave# Anticholinesterase/Anticholinergic medication	0.9655	[0.7345]--[1.2691]	0.8011
Wave# Antihypertensive medication	0.9406	[0.8208]--[1.0780]	0.3786
Wave# Anti-psychotic medication	1.1656	[0.8458]--[1.6062]	0.3491
Wave# Anti-depressant	1.2207	[1.0429]--[1.4287]	0.013
Wave# Diabetic medication	1.1339	[0.7764]--[1.6561]	0.5155
Wave# Depression	0.9958	[0.8561]--[1.1584]	0.9566
Wave# Pulse Pressure	0.9957	[0.9897]--[1.0018]	0.1678
Wave# Mean SBP	1.0013	[0.9971]--[1.0056]	0.5384
Frailty, base not frail			
Pre-frail	1.0513	[0.9825]--[1.1250]	0.1473
Frail	1.4186	[0.9404]--[2.1400]	0.0956
Height, sm	0.995	[0.9904]--[0.9996]	0.032
Baseline HR, bpm	0.9999	[0.9970]--[1.0028]	0.9303

Table 4. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH110 for Age group ≥50 and <65

IRR – Incidence rate ratio; OH110 – Orthostatic hypotension sustained to 110 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S5.

Total Errors	IRR	95% CI	P- value
Wave	0.72	[0.3088]--[1.6788]	0.4469
OH40, (base 0)	1.012	[0.9146]--[1.1198]	0.8178
Age	1.0092	[1.0014]--[1.0171]	0.021
Sex	0.8872	[0.7983]--[0.9860]	0.0263
Education, (base “Primary/none”)			
Secondary	0.8808	[0.8039]--[0.9651]	0.0065
Third level/higher	0.7326	[0.6665]--[0.8052]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0263	[0.9205]--[1.1442]	0.6405
2	1.0307	[0.8857]--[1.1994]	0.6961
Hypertension, (Base “No”)	0.9829	[0.8854]--[1.0912]	0.7465
Heart failure, (base “No”)	0.9763	[0.6710]--[1.4206]	0.9002
Diabetes, (base “No”)	1.0359	[0.8238]--[1.3027]	0.7626
Alcohol CAGE score, (base 0)			
1	0.8781	[0.7689]--[1.0028]	0.0549
2	0.9131	[0.7701]--[1.0828]	0.2961
3	0.9969	[0.8069]--[1.2315]	0.9767
4	1.0424	[0.7436]--[1.4613]	0.8097
Smoking status, (base “Never smoked”)			
Past smoker	0.9727	[0.8970]--[1.0548]	0.5031
Current smoker	1.1163	[0.9717]--[1.2824]	0.1202
Anticholinesterase or Anticholinergic	1.1725	[0.9997]--[1.3752]	0.0505
Antihypertensive medications	1.0025	[0.9018]--[1.1145]	0.9625
Antipsychotic medications	0.6929	[0.3782]--[1.2692]	0.2348
Antidepressant medications	1.0681	[0.8982]--[1.2701]	0.4563
Diabetic medications	0.9671	[0.7434]--[1.2583]	0.8035
Depression	1.0526	[0.9089]--[1.2190]	0.4937
Pulse pressure, mmHg	1.0002	[0.9955]--[1.0049]	0.9389
Systolic BP, mmHg	1.0001	[0.9962]--[1.0039]	0.9663
Wave#OH40	1.0497	[0.9232]--[1.1935]	0.4593
Wave# age	1.0075	[0.9976]--[1.0174]	0.1373
Wave# Sex	1.0359	[0.9359]--[1.1466]	0.496
Wave# Education, base primary/none			
Secondary	0.9927	[0.8847]--[1.1139]	0.9008
Third/higher	0.952	[0.8457]--[1.0715]	0.4147
Wave# No. CVD conditions, (base 0)			
1	0.928	[0.7821]--[1.1011]	0.392
≥2	0.9181	[0.7397]--[1.1394]	0.4379
Wave# Hypertension	1.0967	[0.9683]--[1.2422]	0.1464
Wave# heart failure	1.0682	[0.5719]--[1.9952]	0.836
Wave# Diabetes	1.0403	[0.7469]--[1.4489]	0.8152
Wave# CAGE score, base 0			
1	0.9363	[0.7836]--[1.1187]	0.4688

2	0.8692	[0.6866]--[1.1004]	0.2441
3	0.9162	[0.6799]--[1.2346]	0.5652
4	1.3827	[0.4941]--[3.8695]	0.5372
Wave# Smoking status, base never			
Past	1.0226	[0.9249]--[1.1305]	0.6628
Current	0.9643	[0.7845]--[1.1852]	0.7296
Wave# Anticholinesterase/Anticholinergic medication	0.9752	[0.7905]--[1.2030]	0.8144
Wave# Antihypertensive medication	1.0276	[0.8700]--[1.2139]	0.7483
Wave# Anti-psychotic medication	1.5783	[0.7966]--[3.1272]	0.1908
Wave# Anti-depressant	1.0672	[0.8501]--[1.3399]	0.5751
Wave# Diabetic medication	0.9847	[0.6828]--[1.4202]	0.9343
Wave# Depression	0.9976	[0.7957]--[1.2507]	0.9831
Wave# Pulse Pressure	1.0015	[0.9945]--[1.0086]	0.6758
Wave# Mean SBP	0.9973	[0.9921]--[1.0026]	0.325
Frailty, base not frail			
Pre-frail	1.1242	[1.0467]--[1.2075]	0.0013
Frail	0.9269	[0.6678]--[1.2866]	0.6501
Height, sm	0.9969	[0.9917]--[1.0020]	0.2321
Baseline HR, bpm	1.0004	[0.9972]--[1.0037]	0.8069

Table 5. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH40 for Age group ≥65

IRR – Incidence rate ratio; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S6.

Total Errors	IRR	95% CI	P- value
Wave	0.6911	[0.3001]--[1.5919]	0.3855
OH110, (base 0)	0.9747	[0.8468]--[1.1220]	0.7214
Age	1.0094	[1.0017]--[1.0172]	0.0167
Sex	0.8897	[0.8005]--[0.9888]	0.0301
Education, (base “Primary/none”)			
Secondary	0.8806	[0.8037]--[0.9650]	0.0064
Third level/higher	0.7314	[0.6653]--[0.8041]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0276	[0.9216]--[1.1457]	0.6241
2	1.0328	[0.8875]--[1.2018]	0.6768
Hypertension, (Base “No”)	0.983	[0.8855]--[1.0914]	0.7485
Heart failure, (base “No”)	0.9714	[0.6674]--[1.4140]	0.8796
Diabetes, (base “No”)	1.0311	[0.8202]--[1.2961]	0.7931
Alcohol CAGE score, (base 0)			
1	0.8784	[0.7691]--[1.0031]	0.0556
2	0.9112	[0.7685]--[1.0804]	0.2846
3	0.9989	[0.8084]--[1.2342]	0.9916
4	1.0474	[0.7471]--[1.4684]	0.7884
Smoking status, (base “Never smoked”)			
Past smoker	0.9729	[0.8972]--[1.0550]	0.5064
Current smoker	1.1208	[0.9767]--[1.2860]	0.1042
Anticholinesterase or Anticholinergic	1.1749	[1.0020]--[1.3777]	0.0472
Antihypertensive medications	1.0036	[0.9027]--[1.1157]	0.9477
Antipsychotic medications	0.6917	[0.3775]--[1.2673]	0.2328
Antidepressant medications	1.0699	[0.8997]--[1.2723]	0.4447
Diabetic medications	0.9743	[0.7487]--[1.2678]	0.8464
Depression	1.0495	[0.9059]--[1.2159]	0.52
Pulse pressure, mmHg	1.0001	[0.9954]--[1.0049]	0.9613
Systolic BP, mmHg	1.0002	[0.9964]--[1.0040]	0.9267
Wave#OH110	1.085	[0.9075]--[1.2971]	0.3707
Wave# age	1.008	[0.9983]--[1.0178]	0.1047
Wave# Sex	1.0353	[0.9352]--[1.1460]	0.5039
Wave# Education, base primary/none			
Secondary	0.9932	[0.8852]--[1.1144]	0.9077
Third/higher	0.9543	[0.8477]--[1.0743]	0.4388
Wave# No. CVD conditions, (base 0)			
1	0.9291	[0.7830]--[1.1023]	0.3989
≥2	0.9207	[0.7421]--[1.1424]	0.4529
Wave# Hypertension	1.0989	[0.9703]--[1.2445]	0.1376
Wave# heart failure	1.087	[0.5820]--[2.0305]	0.7935
Wave# Diabetes	1.0419	[0.7482]--[1.4508]	0.8081
Wave# CAGE score, base 0			
1	0.937	[0.7842]--[1.1196]	0.4737

2	0.8677	[0.6856]--[1.0983]	0.238
3	0.9179	[0.6811]--[1.2370]	0.5735
4	1.3721	[0.4903]--[3.8399]	0.5468
Wave# Smoking status, base never			
Past	1.0244	[0.9267]--[1.1325]	0.6373
Current	0.9608	[0.7818]--[1.1808]	0.704
Wave# Anticholinesterase/Anticholinergic medication	0.9766	[0.7917]--[1.2045]	0.8246
Wave# Antihypertensive medication	1.0236	[0.8666]--[1.2089]	0.7839
Wave# Anti-psychotic medication	1.5747	[0.7946]--[3.1207]	0.1932
Wave# Anti-depressant	1.0733	[0.8551]--[1.3471]	0.5418
Wave# Diabetic medication	0.9796	[0.6792]--[1.4129]	0.9121
Wave# Depression	0.9988	[0.7964]--[1.2526]	0.9917
Wave# Pulse Pressure	1.0016	[0.9946]--[1.0087]	0.6518
Wave# Mean SBP	0.9973	[0.9920]--[1.0026]	0.3104
Frailty, base not frail			
Pre-frail	1.1248	[1.0472]--[1.2081]	0.0013
Frail	0.9213	[0.6635]--[1.2793]	0.6247
Height, sm	0.997	[0.9918]--[1.0021]	0.2465
Baseline HR, bpm	1.0003	[0.9971]--[1.0036]	0.8449

Table 6. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH110 for Age group ≥65

IRR – Incidence rate ratio; OH110 – Orthostatic hypotension sustained to 110 seconds post stand; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S7.

Total Errors	IRR	95% CI	P- value
Wave	0.4888	[0.3317]--[0.7205]	0.0003
OH40#HTN, (base No HTN, No OH40)			
No OH40, HTN	0.9896	[0.9204]--[1.0640]	0.7772
OH40, No HTN	0.9941	[0.8690]--[1.1372]	0.9315
OH40 and HTN	0.9751	[0.8647]--[1.0995]	0.6802
Age	1.0098	[1.0063]--[1.0133]	<0.0001
Sex	0.9179	[0.8562]--[0.9840]	0.0158
Education, (base “Primary/none”)			
Secondary	0.8583	[0.8036]--[0.9168]	<0.0001
Third level/higher	0.6675	[0.6231]--[0.7151]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0517	[0.9790]--[1.1298]	0.1681
2	0.9705	[0.8701]--[1.0824]	0.5903
Heart failure, (base “No”)	1.1415	[0.8886]--[1.4663]	0.3004
Diabetes, (base “No”)	1.1167	[0.9418]--[1.3242]	0.2041
Alcohol CAGE score, (base 0)			
1	0.9351	[0.8701]--[1.0049]	0.0676
2	0.8887	[0.8164]--[0.9674]	0.0064
3	0.9273	[0.8294]--[1.0367]	0.1846
4	1.1428	[0.8810]--[1.4824]	0.3146
Smoking status, (base “Never smoked”)			
Past smoker	0.9819	[0.9310]--[1.0356]	0.5016
Current smoker	1.1049	[1.0252]--[1.1907]	0.009
Anticholinesterase or Anticholinergic	1.1845	[1.0351]--[1.3554]	0.0138
Antihypertensive medications	1.0163	[0.9440]--[1.0942]	0.6679
Antipsychotic medications	0.9785	[0.7793]--[1.2285]	0.8512
Antidepressant medications	1.0277	[0.9239]--[1.1432]	0.6146
Diabetic medications	1.0118	[0.8341]--[1.2274]	0.905
Depression	1.0351	[0.9500]--[1.1277]	0.4307
Pulse pressure, mmHg	1.0004	[0.9973]--[1.0035]	0.8138
Systolic BP, mmHg	1	[0.9976]--[1.0024]	0.9747
Wave#OH40#HTN, (base no OH40, no HTN)			
No OH40, HTN	1.0302	[0.9489]--[1.1184]	0.478
OH40, No HTN	1.0025	[0.8545]--[1.1761]	0.976
OH40 and HTN	1.1821	[1.0310]--[1.3553]	0.0165
Wave# age	1.0105	[1.0063]--[1.0148]	<0.0001
Wave# Sex	0.9771	[0.9194]--[1.0384]	0.4556
Wave# Education, base primary/none			
Secondary	0.9644	[0.8934]--[1.0411]	0.3532
Third/higher	0.9829	[0.9077]--[1.0643]	0.6702
Wave# No. CVD conditions, (base 0)			
1	0.984	[0.8905]--[1.0874]	0.7521
≥2	1.0238	[0.8904]--[1.1772]	0.7412

Wave# heart failure	0.6684	[0.4514]--[0.9897]	0.0443
Wave# Diabetes	0.961	[0.7569]--[1.2203]	0.7443
Wave# CAGE score, base 0			
1	0.9484	[0.8608]--[1.0450]	0.2847
2	0.9946	[0.8887]--[1.1132]	0.9256
3	0.9605	[0.8241]--[1.1196]	0.6066
4	0.7204	[0.4315]--[1.2027]	0.2098
Wave# Smoking status, base never			
Past	1.0231	[0.9624]--[1.0877]	0.4643
Current	0.9906	[0.8957]--[1.0955]	0.8541
Wave# Anticholinesterase/Anticholinergic medication	0.963	[0.8158]--[1.1366]	0.6555
Wave# Antihypertensive medication	0.9794	[0.8824]--[1.0870]	0.6951
Wave# Anti-psychotic medication	1.2161	[0.9179]--[1.6112]	0.1729
Wave# Anti-depressant	1.1416	[1.0038]--[1.2984]	0.0436
Wave# Diabetic medication	1.0398	[0.7984]--[1.3541]	0.7724
Wave# Depression	1.0114	[0.8929]--[1.1456]	0.8584
Wave# Pulse Pressure	0.9974	[0.9929]--[1.0020]	0.2719
Wave# Mean SBP	1.0003	[0.9970]--[1.0036]	0.8724
Frailty, base not frail			
Pre-frail	1.0763	[1.0239]--[1.1315]	0.0039
Frail	1.1115	[0.8528]--[1.4487]	0.4341
Height, sm	0.9956	[0.9921]--[0.9991]	0.013
Baseline HR, bpm	1.0002	[0.9980]--[1.0025]	0.8276

Table 7. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH40, stratified by the presence of baseline supine HTN for full cohort
IRR – Incidence rate ratio; OH40 – Orthostatic hypotension sustained to 40 seconds post stand; HTN – Supine hypertension; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Table S8.

Total Errors	IRR	95% CI	P- value
Wave	0.4831	[0.3283]--[0.7110]	0.0002
OH110#HTN, (base No HTN, No OH110)			
No OH110, HTN	0.9861	[0.9179]--[1.0593]	0.701
OH110, No HTN	0.9115	[0.7453]--[1.1147]	0.3668
OH110 and HTN	0.9525	[0.8096]--[1.1206]	0.5569
Age	1.0098	[1.0064]--[1.0132]	<0.0001
Sex	0.9197	[0.8579]--[0.9860]	0.0184
Education, (base “Primary/none”)			
Secondary	0.8588	[0.8040]--[0.9173]	<0.0001
Third level/higher	0.6676	[0.6231]--[0.7152]	<0.0001
No. Cardiovascular conditions, (base “0”)			
1	1.0511	[0.9784]--[1.1291]	0.1728
2	0.9705	[0.8701]--[1.0824]	0.5907
Heart failure, (base “No”)	1.1407	[0.8880]--[1.4653]	0.3027
Diabetes, (base “No”)	1.1176	[0.9425]--[1.3252]	0.2011
Alcohol CAGE score, (base 0)			
1	0.9357	[0.8706]--[1.0055]	0.0703
2	0.8887	[0.8164]--[0.9674]	0.0064
3	0.9291	[0.8311]--[1.0388]	0.1967
4	1.1483	[0.8853]--[1.4895]	0.2973
Smoking status, (base “Never smoked”)			
Past smoker	0.9818	[0.9309]--[1.0355]	0.4985
Current smoker	1.1049	[1.0252]--[1.1907]	0.009
Anticholinesterase or Anticholinergic	1.1873	[1.0376]--[1.3586]	0.0126
Antihypertensive medications	1.0181	[0.9456]--[1.0961]	0.6338
Antipsychotic medications	0.9744	[0.7760]--[1.2236]	0.8236
Antidepressant medications	1.027	[0.9235]--[1.1422]	0.6229
Diabetic medications	1.0124	[0.8345]--[1.2281]	0.9008
Depression	1.0326	[0.9477]--[1.1251]	0.464
Pulse pressure, mmHg	1.0003	[0.9972]--[1.0035]	0.8253
Systolic BP, mmHg	1	[0.9976]--[1.0024]	0.9991
Wave#OH40#HTN, (base no OH110, no HTN)			
No OH110, HTN	1.0382	[0.9572]--[1.1259]	0.3658
OH110, No HTN	1.067	[0.8407]--[1.3542]	0.5939
OH110 and HTN	1.2731	[1.0583]--[1.5317]	0.0105
Wave# age	1.0107	[1.0065]--[1.0149]	<0.0001
Wave# Sex	0.9762	[0.9185]--[1.0376]	0.4394
Wave# Education, base primary/none			
Secondary	0.9654	[0.8942]--[1.0422]	0.3674
Third/higher	0.9853	[0.9099]--[1.0670]	0.7151
Wave# No. CVD conditions, (base 0)			
1	0.9864	[0.8926]--[1.0899]	0.7876
≥2	1.0269	[0.8931]--[1.1807]	0.7093

Wave# heart failure	0.6762	[0.4567]--[1.0011]	0.0506
Wave# Diabetes	0.9596	[0.7558]--[1.2185]	0.7353
Wave# CAGE score, base 0			
1	0.9481	[0.8605]--[1.0447]	0.282
2	0.9936	[0.8878]--[1.1121]	0.9116
3	0.9601	[0.8237]--[1.1190]	0.6023
4	0.7155	[0.4286]--[1.1945]	0.2004
Wave# Smoking status, base never			
Past	1.0245	[0.9637]--[1.0892]	0.4378
Current	0.9889	[0.8941]--[1.0936]	0.8274
Wave# Anticholinesterase/Anticholinergic medication	0.9648	[0.8174]--[1.1388]	0.6717
Wave# Antihypertensive medication	0.9757	[0.8791]--[1.0829]	0.6435
Wave# Anti-psychotic medication	1.218	[0.9191]--[1.6140]	0.1699
Wave# Anti-depressant	1.1496	[1.0111]--[1.3070]	0.0333
Wave# Diabetic medication	1.0404	[0.7989]--[1.3549]	0.7689
Wave# Depression	1.0127	[0.8941]--[1.1472]	0.8421
Wave# Pulse Pressure	0.9976	[0.9931]--[1.0022]	0.3121
Wave# Mean SBP	1.0002	[0.9969]--[1.0035]	0.9256
Frailty, base not frail			
Pre-frail	1.0769	[1.0244]--[1.1321]	0.0037
Frail	1.1068	[0.8491]--[1.4425]	0.453
Height, sm	0.9956	[0.9921]--[0.9991]	0.013
Baseline HR, bpm	1.0002	[0.9980]--[1.0024]	0.8345

Table 8. Results of Multivariate mixed effects poisson regression for IRR of errors in MOCA based on the presence of baseline OH110, stratified by the presence of baseline supine HTN for full cohort

IRR – Incidence rate ratio; OH110 – Orthostatic hypotension sustained to 110 seconds post stand; HTN – Supine hypertension; CAGE – Alcohol screening questionnaire; HTN - Hypertension; BP – Blood pressure; HR – Heart rate.

Appendix 4 – Study 5 Supplementary Data

Table 1. Baseline TSI and Atrial Fibrillation in TILDA participants - Results of multivariable regression

	B Coefficient	95% Confidence Interval	P Value
Atrial Fibrillation	0.5661	[0.1602]--[1.9999]	0.3768
Age	0.9725	[0.9450]--[1.0007]	0.056
Female	1.0552	[0.5966]--[1.8665]	0.8534
Education			
Secondary	0.7813	[0.4480]--[1.3623]	0.3841
Third/Higher	0.9393	[0.5352]--[1.6487]	0.8273
Mean SBP, mmHg	1.0117	[0.9938]--[1.0300]	0.2021
Mean DBP, mmHg	0.9966	[0.9671]--[1.0270]	0.8255
OH @ 40 Seconds	0.8529	[0.4817]--[1.5101]	0.585
Anti-hypertensive medications (not BBlocker)	0.8801	[0.5087]--[1.5228]	0.6479
Beta Blocker	0.9925	[0.5234]--[1.8823]	0.9817
Anti-depressant medications	0.6807	[0.3272]--[1.4163]	0.3034
No. of CV conditions			
1	0.9648	[0.5696]--[1.6344]	0.8941
≥2	0.7726	[0.3694]--[1.6161]	0.4931
Smoking status			
Past	0.8259	[0.5568]--[1.2250]	0.3415
Current	0.5602	[0.2889]--[1.0862]	0.0863
Depressive Symptoms	0.9744	[0.9203]--[1.0318]	0.3746
Height	1.0433	[1.0122]--[1.0753]	0.0061
Problematic alcohol use (CAGE ≥2)	0.3599	[0.1635]--[0.7925]	0.0112
Pre-frail/frail	1.3856	[0.9175]--[2.0925]	0.1209

Table 2. TSI across time points bases on AF status – results of multivariable mixed effects regression

	B Coefficient	95% Confidence Interval	P Value
Atrial Fibrillation	-0.4574	[-1.7381]--[0.8233]	0.4839
Time			
10 seconds	-1.6812	[-1.7375]--[-1.6250]	<0.0001
20 seconds	-0.2884	[-0.3446]--[-0.2321]	<0.0001
30 seconds	-0.3533	[-0.4095]--[-0.2971]	<0.0001
40 seconds	-0.5776	[-0.6339]--[-0.5214]	<0.0001
60 seconds	-0.5868	[-0.6431]--[-0.5306]	<0.0001
90 seconds	-0.6016	[-0.6578]--[-0.5453]	<0.0001
120 seconds	-0.6254	[-0.6817]--[-0.5692]	<0.0001
Time X AF			
10 seconds	-0.5237	[-0.8840]--[-0.1634]	0.0044
20 seconds	-0.245	[-0.6053]--[0.1153]	0.1827
30 seconds	0.0142	[-0.3461]--[0.3745]	0.9383
40 seconds	-0.3972	[-0.7574]--[-0.0369]	0.0307
60 seconds	-0.4031	[-0.7634]--[-0.0429]	0.0283
90 seconds	-0.2288	[-0.5891]--[0.1315]	0.2132
120 seconds	-0.1489	[-0.5092]--[0.2114]	0.4178
Age	-0.0312	[-0.0598]--[-0.0027]	0.0321
Female	-0.1503	[-0.7189]--[0.4183]	0.6044
Education			
Secondary	-0.1898	[-0.7442]--[0.3646]	0.5022
Third/Higher	-0.0398	[-0.6007]--[0.5212]	0.8895
Mean SBP, mmHg	0.0131	[-0.0047]--[0.0310]	0.149
Mean DBP, mmHg	0.0008	[-0.0291]--[0.0308]	0.9562
OH @ 40 Seconds	-0.4147	[-0.9843]--[0.1549]	0.1536
Anti-hypertensive medications (not BBlocker)	-0.1116	[-0.6582]--[0.4350]	0.6891
Beta Blocker	-0.0739	[-0.7120]--[0.5642]	0.8204
Anti-depressant medications	-0.5038	[-1.2342]--[0.2267]	0.1765
No. of CV conditions			
1	-0.156	[-0.6815]--[0.3695]	0.5608
≥2	-0.3813	[-1.1171]--[0.3544]	0.3097

Smoking status			
Past	-0.2213	[-0.6144]--[0.1718]	0.2698
Current	-0.7038	[-1.3641]--[-0.0436]	0.0367
Depressive Symptoms	-0.0305	[-0.0875]--[0.0265]	0.2946
Height	0.0395	[0.0094]--[0.0697]	0.0102
Problematic alcohol use (CAGE $\geq$2)	-0.9522	[-1.7392]--[-0.1652]	0.0177
Pre-frail/frail	0.2743	[-0.1367]--[0.6853]	0.1908