University of Dublin, Trinity College School of Medicine,

Department of Medical Gerontology

Cardiovascular Autonomic Nervous System, Blood Pressure Instability and Brain Health in Older Adults: Population-Based Perspectives

Sheila Julia O'Hare

Student ID: 00907359

Submitted in fulfilment of the requirement of the degree of Doctor of Philosophy, 2019

Declaration

I wish to certify that no part of the material contained in my thesis has been submitted by me for a degree in Trinity College Dublin or any other institution. I wish to state my independent role in the submission of this thesis: the hypotheses, statistical analysis and content of this thesis have followed my own design. The hypotheses, design and analyses in this thesis are under the direction of Professor Rose Anne Kenny.

The TILDA bioengineers, led by Dr Ciaran Finucane performed the data processing of the raw signals obtained during the haemodynamic assessments in the TILDA health assessment. Professor Caterina Rosano at the University of Pittsburgh supervised Study III based in the Health Aging and Body Composition Study. Dr. Robert Boudreau, also at the University of Pittsburgh, supervised the statistical analysis in Study III and computed the trajectories of systolic and orthostatic blood pressure in Study III. All neuroimaging processing in Study III was performed by the Geriatric Psychiatry Neuroimaging Laboratory at the University of Pittsburgh lead by Prof. Howard J. Aizenstein. Dr. Andrea Metti at the University of Pittsburgh, assisted me in the preparation of the longitudinal dataset and variable creation in Study III.

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

Sheila Julia O'Hare

Signed: _____

Date: _____

Summary

The aim of this thesis is to provide new insights into the shared pathways by which the cardiovascular autonomic nervous system underpins optimal regulation of affect and cognitive function in older adults. Ageing is characterised by an increase in sympathetic outflow and a reduction in parasympathetic tone - which may predispose to greater blood pressure instability. Based in two large population-based cohorts of ageing, this thesis presents four quantitative studies which variously employ cross-sectional, longitudinal and life course approaches to investigate associations between indices of blood pressure instability – *orthostatic blood pressure, baroreflex sensitivity and vasovagal syncope* - and markers of 'brain health' in later life: *cognition, affect and structural integrity on MRI neuroimaging.*

This thesis embraces a continuum approach to the understanding of cognitive decline and affective symptoms in later life - whereby these are overlapping presentations with shared risk factors and neural substrates that progress gradually via subclinical stages towards a clinical diagnostic threshold. In adopting this approach this thesis seeks to identify early/ sub-clinical associations between blood pressure instability and brain health, given that altering the trajectory of decline in brain health may be more successful if intervention is targeted at an early stage. A life course perspective is introduced in the final study to investigate associations between exposure to stress and blood pressure instability across the life span. A life course approach acknowledges that both cardiovascular autonomic function and brain health in older adults are underpinned by biological and environmental/ behavioural exposures occurring earlier in life; and that associations between brain health and blood pressure instability may be bidirectional across the life span.

Study I, based in the Irish Longitudinal Study on Ageing (TILDA), finds that lower orthostatic blood pressure immediately after standing, even when not meeting criteria for orthostatic hypotension, is associated with greater subjective memory impairment - a potential preclinical symptom of dementia. ***Study II*** in TILDA finds that lower baroreflex sensitivity is associated with greater affective symptoms in men, and associations are stronger in those on antidepressant treatment. To the best of my knowledge, this is the first study investigating associations between baroreflex sensitivity and both anxiety *and* depression in a population-based cohort of older adults. ***Study III,*** in the US-based Health Aging and Body Composition cohort, reports *prospective* associations between subclinical orthostatic blood pressure change and poorer brain health (poorer cognitive status and greater grey matter atrophy) up to 15 years later. To my knowledge study III is the first to incorporate MRI structural neuroimaging into the prospective investigation of orthostatic blood pressure and cognitive outcomes at the population level. ***Study IV*** investigates life course associations between stress and blood pressure instability and finds that exposure to childhood trauma may contribute to a lifelong vasovagal tendency - and therefore potentially to associations with poorer brain health in later life.

Taken together, Studies I-IV suggest that greater blood pressure instability, even at subclinical levels, and as underpinned by the cardiovascular autonomic nervous system, may be on the pathway to poorer brain health in later life; although associations may differ according to sex and medication status. Furthermore, early life exposure to stress may be a life course determinant of blood pressure instability – thus further highlighting central regulation/ integration of the cardiovascular autonomic nervous system. Recognition of an important role for the cardiovascular autonomic nervous system in regulation of affect and cognitive function in later life potentially provides new therapeutic opportunities for promoting better brain health, for longer, in older adults.

Acknowledgements

I wish to acknowledge Professor Rose Anne Kenny: a truly inspirational leader, energetic and generous at every turn. Thank you for each and every opportunity – you have broadened my horizons.

I wish to acknowledge and thank all the study members of The Irish Longitudinal Study on Ageing and The Health Aging and Body Composition Study who kindly and selflessly gave of their time to participate in these studies.

In TILDA, I wish to acknowledge the contribution of Matthew O'Connell, Cathal McCrory, Neil O'Leary and Eibhlin Hudson in helping me to understand how to analyse and interpret complex epidemiological data. I wish to thank the Health Research Board for funding my TILDA research position and research visit to the University of Pittsburgh.

I would like to thank Prof. Caterina Rosano and all those based at the wonderful eBrain group at the University of Pittsburgh for such a warm welcome and for such generosity with your time and expertise during my visit. Thank you, Pittsburgh.

I would also like to thank Ciara Rice, Lisa Byrne, Dymphna Hade, Nicola O'Doherty, Helen Fitzpatrick and Claire Dooley with whom I had the great privilege to work at the Falls and Blackout Unit in St James's Hospital.

I would like also to thank Helen O'Brien and Blaithin NiBhuachalla - thank you for your support.

I would like to thank my parents, Carl and Nan O'Hare. Thank you for encouraging me to make the most out of the opportunities I've had.

Finally, and always, thank you Luke.

Dissemination of Thesis

Peer Reviewed Publications:

O'Hare, C., McCrory, C., O'Leary, N., O'Brien, H. and Kenny, R.A., 2017. Childhood trauma and lifetime syncope burden among older adults. Journal of Psychosomatic Research, 97, pp.63-69.

O'Hare, C., Kenny, R.A., Aizenstein, H.J., Boudreau, R., Newman, A., Launer, L., Satterfield, S., Yaffe, K. and Rosano, C., 2017. Cognitive Status, Gray Matter Atrophy, and Lower Orthostatic Blood Pressure in Older Adults. Journal of Alzheimer's Disease, 57(4), pp.1239-1250.

O'Hare, C., McCrory, C., O'Connell, M.D. and Kenny, R.A., 2017. Sub-clinical orthostatic hypotension is associated with greater subjective memory impairment in older adults. International Journal of Geriatric Psychiatry, 32(4), pp.429-438.

Conference Presentations:

O'Hare, C., McCrory, C., Kenny, R.A., 2015. Childhood trauma and lifetime syncope burden, Society for Longitudinal and Life Course Studies International Conference *[Oral Presentation]*

O'Hare, C., Kenny, R.A., Aizenstein, H.J., Boudreau, R., Newman, A.B., Launer, L.J., Yaffe, K. and Rosano, C., 2015. Cognitive Status, Gray Matter Atrophy and Orthostatic Blood Pressure in Adults Aged 83+. Gerontologist (55), pp. 410-411.

Abbreviations

95%CI	95% Confidence Interval
AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
ADT	Antidepressant Treatment
AHA	American Heart Association
ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
APOE	Apolipoprotein E
ARIC	Atherosclerosis Risk in Communities Study
ASL	Arterial Spin Labelling
ASOBPR	Average Systolic Orthostatic Blood Pressure Response
BMI	Body Mass Index
BP	Blood Pressure
BRS	Baroreflex Sensitivity
CAPI	Computer Assisted Personal Interview
CBF	Cerebral Blood Flow

CES-D	Center for Epidemiological Studies-Depression Scale
CHS	Cardiovascular Health Study
CO2	Carbon Dioxide
CS	Cognitive Status
CSF	Cerebral Spinal Fluid
CT	Computed Tomography
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DLPFC	Dorsolateral Prefrontal Cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECG	Electrocardiogram
ESC	European Society of Cardiology
FI	Frailty Index
FLAIR	Fluid-attenuated inversion recovery
GAD	Generalised Anxiety Disorder
GDS	Geriatric depression scale
GM	Grey Matter
GMV	Grey Matter Volume

HADS-A	Hospital Anxiety and Depression Scale
HBP	Healthy Brain Project
Health ABC	Health Aging and Body Composition Study
HR	Heart Rate
HRS	Health and Retirement Study
HRV	Heart Rate Variability
HUNT Study	The Nord-Trøndelag Health Study
HUT	Head-up Tilt
IQR	Interquartile Range
LASA	Amsterdam Longitudinal Study on Ageing
LOC	Loss of Consciousness
MADRS	Montgomery–Åsberg Depression Rating Scale
MCA	Middle Cerebral Artery
MCI	Mild Cognitive Impairment
MDD	Major Depressive Disorder
MI	Myocardial Infarction
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging

MSNA	Muscle Sympathetic Nerve Activity
OBP	Orthostatic Blood Pressure
OH	Orthostatic Hypotension
OHT	Orthostatic Hypertension
OI	Orthostatic Intolerance
OR	Odds Ratio
PET	Positron Emission Tomography.
PPS	Psychogenic Pseudosyncope
PSWQ-A	Penn State Worry Questionnaire-Abbreviated
rCBF	Regional Cerebral Blood Flow
RCT	Randomised Control Trial
RRR	Relative Risk Ratio
SBP	Systolic Blood Pressure
SCQ	Self-Completion Questionnaire
SD	Standard Deviation
SEP	Socioeconomic Position
SMI	Subjective Memory Impairment
SNRI	Serotonin Noradrenaline Reuptake Inhibitor

SPRINT	Systolic Blood Pressure Intervention Trial
SSRI	Selective Serotonin Reuptake Inhibitor
STRIVE	Standards for Reporting Vascular changes on Neuroimaging
TCA	Tricyclic Antidepressant
TCD	Transcranial Doppler
TIA	Transient Ischaemic Attack
TILDA	The Irish Longitudinal Study on Ageing
T-LOC	Transient Loss of Consciousness
VaD	Vascular Dementia
VCI	Vascular Cognitive Impairment
VVS	Vasovagal Syncope
WHO ATC	World Health Organisation Anatomical Therapeutic Classification
WM	White Matter
WMH	White Matter Hyperintensities
WML	White Matter Lesion

List of Figures

List of Tables

CONTENTS

1. INTRODUCTION

The aim of this thesis is to provide new insights into the shared pathways by which the cardiovascular autonomic nervous system (ANS) underpins optimal regulation of affect and cognitive function in older adults. Based in two large population-based cohorts of ageing, this thesis presents four quantitative studies which variously employ cross-sectional, longitudinal and life course approaches to investigate associations between indices of blood pressure instability – *orthostatic blood pressure*, *baroreflex sensitivity and vasovagal syncope* – and markers of 'brain health' in later life: *cognition, affect and structural integrity on MRI neuroimaging.*

This thesis embraces a continuum approach to the understanding of cognitive decline and affective symptoms in later life, whereby these are overlapping presentations with shared risk factors and neural substrates that progress gradually via subclinical stages towards a clinical diagnostic threshold (Figure 1.1). In adopting this approach this thesis seeks to identify early/ sub-clinical associations between blood pressure instability and brain health, given that altering the trajectory of decline in brain health may be more successful if intervention is targeted at an early stage – ultimately allowing older people to maintain better brain health for longer.[1]

A life course perspective is introduced in the final study to investigate associations between exposure to stress and blood pressure instability across the life span. A life course approach acknowledges that both cardiovascular autonomic function and brain health in older adults

are underpinned by prior biological processes and environmental/ behavioural exposures – and that associations between brain health and blood pressure instability may be bidirectional across the life span.

Chapter summaries:

Background and literature review:

The background to this thesis is presented in **Chapter 1: Section 1.1** and provides an overview of the current state of knowledge regarding associations between usual BP and brain health in later life. **Section 1.2** and **Section 1.3** provide an overview of the proposed mechanisms linking cardiovascular autonomic function – with a focus on blood pressure instability – to brain health in later life.

Chapter 2 reviews the evidence to date linking blood pressure instability (i.e. orthostatic hypotension, reduced baroreflex sensitivity and syncope) to brain health in older adults (i.e. cognitive function, affective symptoms (depression and anxiety) and structural neuroimaging outcomes).

Quantitative studies:

Chapter 3 investigates associations between orthostatic blood pressure and potential preclinical symptoms of dementia.

Study I: ‘Sub-clinical orthostatic hypotension is associated with subjective memory impairment in older adults.’

Chapter 4 investigates baroreflex sensitivity and affective symptoms in older adults.

Study II: ‘Baroreflex Sensitivity, Depression, Anxiety and Anti-depressant use in Older Adults’

Chapter 5 investigates orthostatic blood pressure and cognitive status in older adults.

Study III: ‘Cognitive Status, Grey Matter Atrophy and Lower Orthostatic Blood Pressure in Older Adults.’

Chapter 6 investigates pathways linking stress and blood pressure instability across the life course.

Study IV: ‘Childhood Trauma and Lifetime Syncope Burden among Older Adults’

Summary, Limitations and Future Directions

Chapter 7 concludes the thesis: **Section 7.1** summarises the findings of the thesis and reviews its contribution to the literature on blood pressure instability and brain health. **Section 7.2** reviews the limitations to the investigations presented herein. Finally, **Section 7.3** discusses potential directions for future work building on the findings of this thesis.

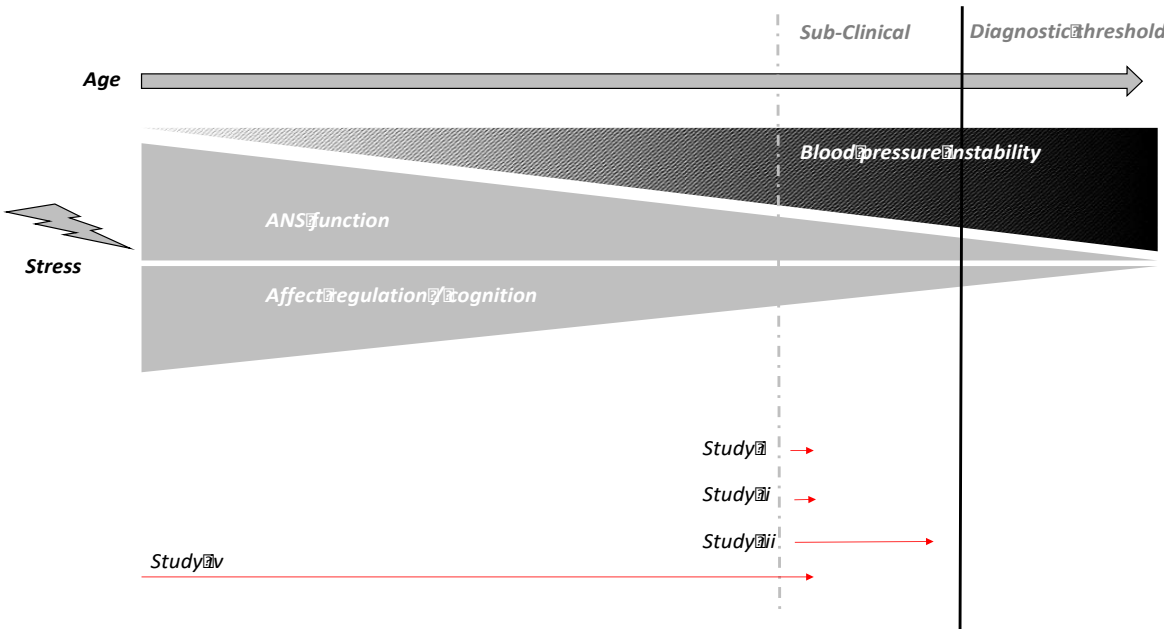


Figure 1.1: Thesis Framework. This thesis embraces a *continuum* approach to the understanding of cognitive decline and affective symptoms in older adults whereby these are overlapping presentations with shared risk factors and neural substrates that progress gradually via *subclinical* stages towards a clinical *diagnostic threshold* (e.g. Subjective Memory Impairment progresses via MCI to dementia). With increasing age there is a gradual accumulation of neuropathology (e.g. amyloid / cerebral small vessel disease), decreasing cortical function (e.g. decline in cognitive function and affect regulation) and cardiovascular autonomic function (e.g. increasing blood pressure instability – beginning with a decline in baroreflex sensitivity progressing to Orthostatic Hypotension). Peak function of the cardiovascular ANS and affect/cognition may be dictated by life course exposures including exposure to early life stress.

Study I investigates ***cross-sectional*** associations between blood pressure instability and potential preclinical symptoms of dementia. **Study II** investigates ***cross-sectional*** associations between Baroreflex Sensitivity, Depression, Anxiety and Anti-depressant use in Older Adults. **Study III** investigates ***prospective associations*** between orthostatic blood pressure and Cognitive Status in Older Adults and explores the mediating effect of Grey Matter atrophy and White Matter Hyperintensities. **Study IV** investigates ***life course*** pathways linking stress and blood pressure instability.

2. RESEARCH IN CONTEXT

2.1. Blood Pressure and Brain Health

Brain Health

Key point: ***In older adults, impaired cognition, affective symptoms (i.e. depression and anxiety) and structural change on neuroimaging may be considered markers of poor brain health.***

Peterson proposed the term *brain health* to include, "cognition and the many factors impinging on it including…. the effects of hypertension… on brain structure and function…. psychosocial challenges, and dementia".[2] While according to Sacco, "the broader spectrum of brain health encompasses stroke, dementia, vascular cognitive impairment, cognitive ageing, age-related memory loss, vascular functional impairment, and subclinical vascular diseases including white matter hyperintensities, brain atrophy, silent brain infarctions, and cerebral microbleeds".[3] Poor brain health thus represents a leading cause of population morbidity[4], reflecting often overlapping clinical presentations including dementia (e.g. Alzheimer's (AD) and Vascular Dementia (VaD)), decline in cognitive performance, and affective symptoms (e.g. late life depression and Generalized Anxiety Disorder).

Structural Neuroimaging Markers of Brain Health

Key point: ***White Matter Hyperintensities and Grey Matter Atrophy are common findings on MRI neuroimaging in older adults, and increase with age***.

Common features of cerebral small vessel disease which can be detected on MRI structural neuroimaging (as defined according to the 2013 *Standards for Reporting Vascular changes on Neuroimaging* ('STRIVE')[5]) are displayed in Figure 2.1. With increasing age, such abnormalities accumulate and may, or may not, be accompanied by clinical symptoms.[6] For more than two decades, WMH and loss of GM volume have been two of the most commonly investigated structural neuroimaging outcomes in population-based cohort studies of older adults.[7–9] WMH are a key marker of cerebral small vessel disease in older adults.[5] In the STRIVE guidelines GM atrophy has also been described as a feature of cerebral small vessel disease.[5]

GM atrophy and WMH may contribute to the neural basis of impaired cognition and affective symptoms in older adults.[7] For example, WMH and GM atrophy are associated with an increased risk of dementia and major depressive disorder[10]; in addition they may coexist with elevated amyloid.[11–13] Such overlap in neuroimaging characteristics thus mirrors the blurred clinical and neuropathological boundary between AD, VaD and affective symptoms in older adults.[5,14]

Neuroimaging acquisition and analysis

Grey matter and white matter change on MRI may be assessed visually, semi-quantitatively or entirely via automated methods.[8,9] Sensitivity of MRI neuroimaging to cerebral small vessel disease may vary: secondary to image acquisition (scanner type, magnet strength, acquisition sequence/protocol e.g. thicker slices and larger gap intervals), and/or due to the analysis protocol[15]; both may vary even within the same study.[16] Heterogeneity in the terminology used to report neuroimaging characteristics ascribed to cerebral small vessel disease however has begun to be addressed by the STRIVE guidelines.[5] Many of the most influential studies (e.g. Cardiovascular Health Study) are now decades old and thus limited by low MRI strength, variability between centres in image acquisition, analysis and reporting.[16] Such limitations extend to the majority of the investigations which have previously examined associations between blood pressure instability and structural MRI neuroimaging outcomes – these are reviewed in Chapter 2.

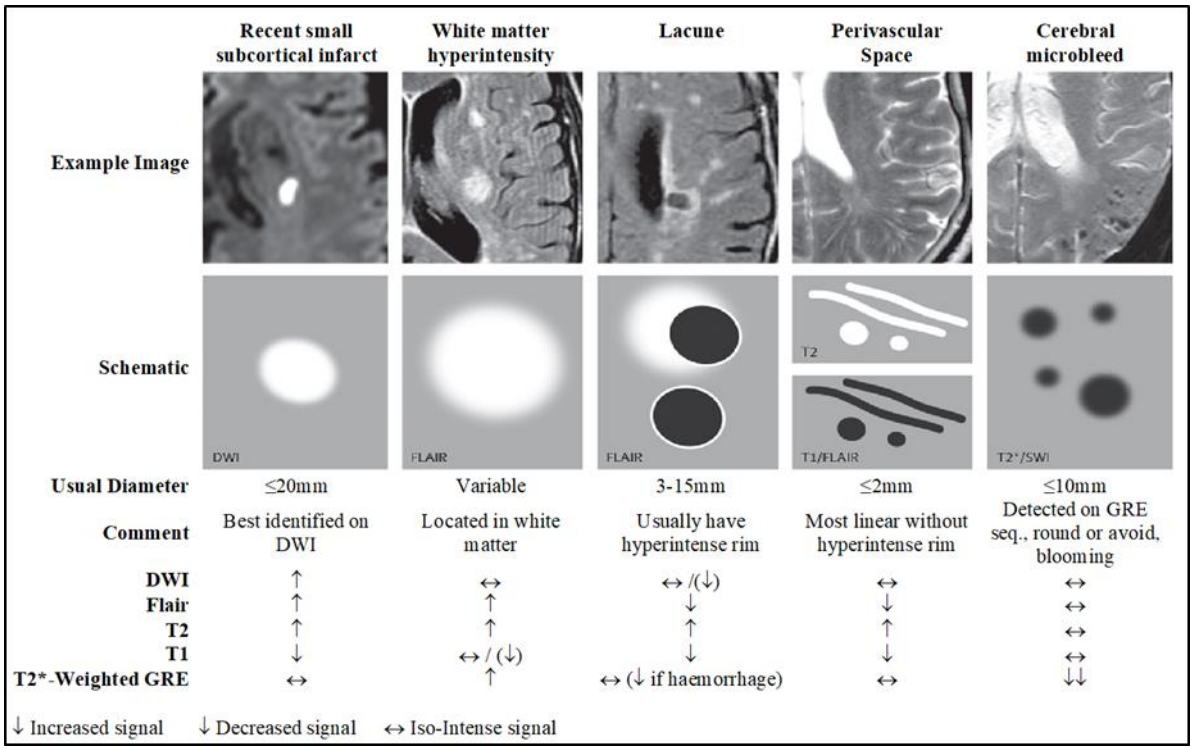


Figure 2.1: Examples of cerebral small vessel disease on MRI neuroimaging. Image from Wardlaw et al[5] as defined according to STRIVE (i.e. Standards for Reporting Vascular changes on Neuroimaging): FLAIR=fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; GRE= gradient recalled echo; SWI= susceptibility-weighted imaging.

White Matter Hyperintensity

The terminology used to describe white matter lesions visible on structural neuroimaging varies, and has often been used interchangeably in the literature. For example, the term ‘leukoaraiosis’ was initially used to describe *hypo*dense lesions visible on Computed Tomography of the brain; however the same lesions on MRI of the brain in T2 weighted sequences are *hyper*intense.[9] The most commonly used imaging techniques for the assessment of WMH burden are T2-weighted MRI, and fluid-attenuated inversion recovery (FLAIR) MRI.[17]

Although among older adults WMH are most often attributed to cerebral small vessel disease, the pathological correlates and aetiology of WMH may vary and remain incompletely elucidated.[14] Few neuropathological studies exist which make direct comparisons between lesions seen on imaging and post-mortem histopathology.[14,18] Definitive studies which would prove the neuropathological associations of WMH i.e. brain biopsy, are of course not feasible in humans and animal models remain inadequate.[18] WMH may reflect myelin degradation, however even this is uncertain.[18] WMH tend to occur in characteristic locations: as ‘rims’ around the lateral ventricles (i.e. periventricular lesions (‘PVL’)) which tend not to progress, and in the subcortical 'deep white matter' (‘deep WMH’) which tend to occur initially as punctate foci but which may progress to become confluent and involve large areas of the white matter.[9,18] WMH may also be associated with areas of infarction and may be more common in regions lacking adequate anastomosis.[18] Some may have an inherited predisposition to WMH, however specific genetic associations remain unceratin.[5]

Grey Matter

Grey matter (GM) atrophy may affect the whole brain, or be focal. The most commonly used imaging technique to visualize GM is T1-weighted MRI[17]; this provides a high degree of contrast between tissue types i.e. GM vs WM vs. CSF. Tissue segmentation in most modern analyses at population scale is automated and performed using an imaging software platform.[19] Loss of GM volume is a feature of the ageing brain and this accelerates after 50+ years.[20] GM atrophy likely reflects loss of neuronal integrity and reductions in synaptic density.[20] There may be substantial regional variation in volume loss with ageing, for example loss of GM in the frontal lobes may occur first and at the fastest rate.[21] Specific patterns of regional atrophy may be associated with neurodegenerative disorders. For example, both global and medial temporal lobe atrophy have been shown to increase risk of conversion from MCI to dementia[10]; specifically hippocampal atrophy is classically associated with impaired memory performance and risk of AD.[20,22] The STRIVE guidelines include GM atrophy as an indicator of cerebral small vessel disease however it remains uncertain as to how vascular lesions mediate secondary brain atrophy.[5]

Age Related Change in Blood Pressure and Brain Health

Key point: ***Blood pressure changes with age and hypertension is a key risk factor for poorer brain health.***

Many vascular risk factors are also risk factors for poorer brain health, although primary among these perhaps is hypertension. As noted by Hajjar, "The adverse effect of hypertension on health and ageing surpasses its effect on cardiovascular morbidity and mortality. Hypertensive individuals are at increased risk of dementia, depression, physical disability, and falls."[23]

The population surveillance definition of hypertension is BP >=140/90mmHg.[24] In industrialised nations both mean systolic BP (SBP) and diastolic BP (DBP) increase with age; this increase accelerates from the fourth decade (Figure 2.2).[25,26] Average BP however, is lower in women until the menopause after which the difference in mean BP between men and women is lost.[27] Mean population SBP continues to rise until the seventh/eighth decade.[25] Beyond 50 years however there is a *decrease* in DBP resulting from increased large vessel stiffness which is reflected in a widening of pulse pressure.[28] From the seventh/eighth decade the population mean SBP also begins to *decrease*[25]; the causes and clinical consequences of this later life *decrease* in BP are debated in particular with respect to implications for brain health in older adults.[29–31]

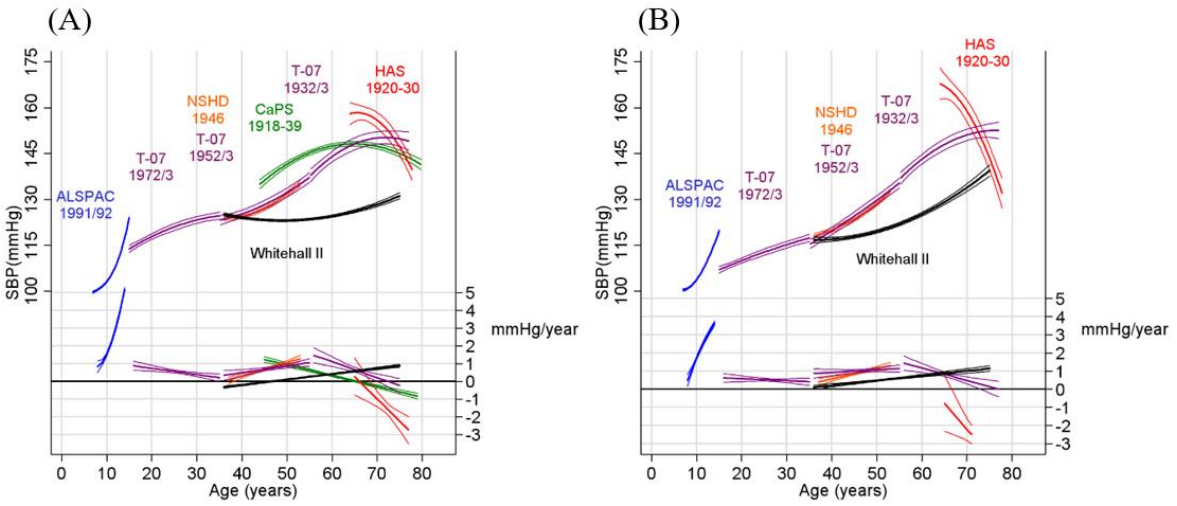


Figure 2.2: Change in Systolic Blood Pressure with Age.
Data from Wills et al[25] depicting change in Systolic Blood Pressure (mmHg) with age and rate of increase (mmHg/year) in men (A) and women (B) in eight UK cohorts. ('Life Course Trajectories of Systolic Blood Pressure Using Longitudinal Data from Eight UK Cohorts. Wills et al. PLOS Medicine 2011')

Associations between Blood Pressure and Cognition may be age-dependent

Key point: ***Mid-life hypertension has been highlighted as a key risk factor for dementia however the relationship between late life blood pressure and cognition is less clear.***

Altered BP regulation has been associated with both AD and VaD.[32,33] While AD accounts for 60-80% of all dementia diagnoses, clear boundaries between AD and VaD are increasingly questioned e.g. at post-mortem, neuropathological findings attributable to both vascular and amyloid pathology are common.[14,32] Increasingly, a 'continuum' approach is taken in dementia research. In the 2011 revision of diagnostic guidelines, the National Institute on Aging Alzheimer's Association moved from a categorical diagnostic system to a 'staging' model which reframed Alzheimer's *dementia* as Alzheimer's *disease.*[34] This reflected an improved understanding of the *gradual* accumulation of neuropathology

(beginning *decades* prior to the emergence of symptoms) and that pathological cognitive decline occurs sequentially.[35] There have also been efforts to revise diagnostic guidelines for VaD in line with a cognitive continuum approach; this is underscored by the term, 'Vascular Cognitive Impairment (VCI)' which is proposed as, "a syndrome with evidence of clinical stroke *or* subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain".[36,33]

A 2011 systematic review examined the available evidence on associations between hypertension and VaD.[37] Sharp and colleagues combined results from five longitudinal studies (providing information on 425 participants with incident VaD and 7698 controls), together with evidence from cross-sectional prevalence studies and concluded that hypertension was a 'strong' risk factor for incident VaD.[37] Among the prospective studies subjected to meta-analysis, median follow-up was less than five years and hypertension was examined only as a binary-exposure (i.e. yes/no) - ascertained either by self-report and/or a single measurement.[37]

Another 2011 systematic review and meta-analysis examined associations between hypertension and AD, however the conclusions were more circumspect.[38] No significant associations were found between hypertension and risk of AD when combining results from 18 studies on 19 populations, irrespective of the definition of hypertension used (i.e. self-report or objective measure). However, age-stratified analysis suggested a potential *age-dependent association,* such that hypertension in mid-life but *hypotension* in later life (i.e. after 65) may increase risk of AD. Notably however, 'mid-life' was considered as hypertension prior to 65 years.[38]

The first large population study to describe the link between mid-life hypertension and later life cognitive function was the Honolulu Heart Study/Honolulu-Asia Aging Study. Japanese American men who had had BP measured in the 1960's (when aged between 45-55) underwent cognitive testing and dementia ascertainment in the 1990's.[39] Follow-on investigations from the same cohort - incorporating neuroimaging and neuropathology studies - have since suggested associations between higher mid-life vascular risk and brain change, including markers of cerebrovascular small vessel disease on MRI and amyloid deposition at post-mortem.[40–42]

Similarly, recent work in the Atherosclerosis Risk in Communities Study (ARIC) investigating *change* in cognitive function has demonstrated that those with higher *mid-life* SBP (45-55years) have a steeper rate of cognitive decline into later life – a decline which occurs independently of BP in later life.[43] This has been followed by work showing similar relationships with the proposed subclinical neural markers of cognitive risk, including greater GM atrophy, white matter change, and amyloid deposition.[44–46] For example in ARIC, compared to participants with normal BP throughout follow-up, participants who had had mid-life hypertension followed by late life hypotension had substantially smaller volumes in brain regions classically affected early in AD – including the hippocampus.[45]

The AGES (Age, Gene/Environment Susceptibility study): Reykjavik Study followed 4057 participants who had BP and vascular risk factors measured in both mid (mean age 50 years) and later life (mean age 76 years).[47] The investigators reported that the relationship between late life MRI outcomes was dependent on whether the participants had been exposed to hypertension in mid-life.[47] In participants with a history of mid-life hypertension, *lower late-life* DBP was associated with smaller total brain and GM volumes and lower memory scores.

In participants without a history of mid-life hypertension, *higher* SBP and DBP in later-life was associated with an increased risk of cerebral small vessel disease: white matter lesions and cerebral microbleeds.[47]

In studies focused on later life, lower BP has often been highlighted as a risk factor for dementia.[30,31,48] For example, the Swedish Kungsholmen Project followed 1736 participants longitudinally (mean age at baseline 86 years), performing two follow-up cognitive assessments over three years, and reported an association between late life hypotension and dementia - *higher* baseline SBP and DBP were associated with *better (higher) MMSE* scores at follow-up.[49] More recently, the US based 'The 90+ Study' similarly reported an apparently protective effect of higher BP in later life.[50] 559 participants without dementia at baseline were followed every 6 months for up to 10 years, the average age at baseline was 93.2 years and the majority of the sample were women. Just under 50% developed dementia; but dementia risk was lower among those participants in whom hypertension emerged only in later in life (>80 years).[50]

Given the associations between BP and cognition, a number of studies have attempted to clarify the impact of modification of BP levels by anti-hypertensive treatment on cognitive outcomes. No conclusive evidence for a beneficial effect has been provided – as concluded by a 2009 Cochrane review of randomised double-blind placebo-controlled trials.[51] The Systolic Hypertension in Europe (SYST-EUR study), Perindopril Protection against Recurrent Stroke Study (PROGRESS) and Heart Outcomes Prevention Evaluation (HOPE) trials did suggest a potential beneficial impact on cognitive outcomes[52], however others such as the Hypertension in the Very Elderly (HYVET) trial did not.[53] Uncertain benefits on cognition in later life have been attributed variously to age at intervention (i.e. later life rather

than mid-life), duration of treatment, and neuroprotective effects specific to antihypertensive class.[52,54] For example, it has been hypothesised that calcium channel blockers may be particularly beneficial in the prevention of cognitive decline secondary to a positive impact on BP variability.[55]

Blood pressure and affective symptoms

Key point: ***Affective symptoms in older adults have been associated with both high and low blood pressure; relationships may be bidirectional across the life course.***

Depression and anxiety occurring in older adults may differ from that experienced by younger adults[56], although reviews are conflicting.[57] For example, among older adults subjective reports of low mood may be less common ('depression without sadness') and features such as somatisation and overlap with physical co-morbidity may complicate diagnosis and treatment.[56,58] *Aetiological* factors may also vary between affective disorders occurring for the first time in later life versus those with an earlier onset. Thomas et al concluded that late-life depression differs from depression in earlier life in three key ways: increased treatment resistance, associations with WMH on structural neuroimaging, and cognitive dysfunction characterised by increased impairment on tests of executive dysfunction.[57] The concept of 'early-' vs 'late-' onset depression is, however, somewhat controversial given uncertain differences in symptoms, debate over the accuracy of recall of prior episodes and a lack of studies with sufficient periods of longitudinal follow-up i.e. from early life into later life.[59]

Data from TILDA has previously shown high levels of affective symptoms among older adults in Ireland. In Wave 1, 10% of adults reported clinically significant levels of depressive symptoms, while 13% reported anxiety symptoms potentially meeting a clinical threshold.[60] Investigations of trajectories of change in depressive symptoms have suggested a decline or U-shaped relationship with age[61]; rates of worry however tend to increase among older adults.[58] In TILDA a further 18% and 29% reported 'sub threshold' symptoms of depression and anxiety respectively.[60] This is important, as despite not meeting a threshold for clinical diagnosis, such symptoms may nevertheless be associated with poor functional outcomes.[62] In the Longitudinal Amsterdam Study of Ageing (LASA), those older adults experiencing sub-clinical or subthreshold symptoms had outcomes in line with those experiencing case-level depressive symptoms; men with DSM-IV defined 'minor' depression had a higher risk of mortality.[63] Such findings are in keeping with an understanding of psychopathology as occurring along a continuum in the population; symptoms of depression and anxiety (affective symptoms) overlap and likely occur along a spectrum of severity.[62,64–67] Despite high levels of co-morbidity in later life however, depression and anxiety are often examined in isolation and/or symptoms of anxiety are neglected entirely; for example limited information is available with respect to associations between vascular risk, structural neuroimaging changes and anxiety in later life.[68] As in younger samples, both anxiety and depressive disorders in older adults are more common among women.[58,69]

Since the seminal publication by Alexopoulous 20 years ago[70], the 'vascular depression hypothesis' has been the predominant driver of research on depression in later life; it states '*cerebrovascular disease may predispose, precipitate or perpetuate some geriatric depressive syndromes'*. Multiple studies have reported associations between vascular disease and depression in later life, however the underlying mechanisms remain incompletely

understood.[71] A 2013 systematic review and meta-analysis synthesised the available evidence on the role of traditional vascular risk factors on late life depression.[72] Twenty-six studies were included and the authors concluded that there was a strong association between cardiovascular disease, diabetes, stroke, and composite vascular risk scores (whereby composite vascular risk scores from each study were summarised as reflecting low vs high levels of vascular risk) and depression in later life; but not with hypertension, smoking or dyslipidaemia. The authors suggested that further evidence from large longitudinal epidemiological studies, including neuroimaging, was required to understand the role of vascular risk in late life depression.[72]

In the Health ABC cohort study of community-dwelling older adults, although cumulative vascular risk scores (which included hypertension) were associated with depression, longitudinally higher BP (when examined in isolation) was not.[73] A prior cross-sectional report in the same cohort had suggested however that hypertension was associated with increased odds of experiencing anxiety in older adults.[74] A more recent population-based German cohort study which investigated both depression and symptoms of generalised anxiety in 3124 older adults aged 57–84, suggested that hypertension (defined by primary care diagnosis, medication use, or a home BP measurement) was related to symptoms of depression but not anxiety. The analysis did not allow conclusions to be drawn as to the temporal nature of the association.[75]

Taylor has described evidence of WMH's on neuroimaging as the 'radiological hallmark' of vascular depression in older adults.[76] A 2008 systematic review and meta-analysis of WMH in late life depression included 30 eligible studies and concluded that late life depression was characterised by more frequent white matter abnormalities, and relationships were stronger

for those with late-onset rather than early-onset depression.[77] White matter change on MRI has also been linked to subclinical depressive symptoms in later life in the Whitehall study.[78] A 2013 systematic review and meta-analysis of MRI studies investigating structural GM in late life depression, concluded that there was evidence for a small but significant difference in GM volume (i.e. greater atrophy in limbic, including the hippocampus, and frontal-subcortical regions in late life depression).[79]

There is also however, substantial evidence for *reciprocal* associations between affective symptoms and vascular risk across the life span. Meta-analyses have linked both anxiety and depression to an increased risk of CVD.[80] A meta-analysis of 37 papers (extending to studies including those 65+) including over 1 million participants, reported that anxiety was associated with a 52% increased incidence of CVD – a risk which was independent of traditional risk factors and depression.[81] With respect to BP specifically, in the Whitehall cohort when depressive symptoms and BP were assessed repeatedly over time (5 waves of follow-up spanning 24 years), recurrent depressive symptoms across mid-life were linked to an increased risk of incident hypertension.[82] In another large epidemiological study based in Norway however, symptoms of depression and anxiety were prospectively linked to future *hypo*tension over 22 years of follow-up.[83] Thus the links between affective symptoms and BP are complex and likely bi-directional.

A recent systematic review by Briggs[84] and colleagues investigated the relationship between hypotension and depression in late life depression. The authors described support in cross-sectional studies investigating hypotension and depression, however longitudinal studies were lacking.[84] Furthermore, it was noted that comparison between studies was difficult due to differences in the methods used to assess both BP and outcome variables. In TILDA

Briggs has since reported that incident case-level depressive symptoms are more common in those with baseline hypotension.[85] The analysis however did not account for variation in baseline depressive symptoms i.e. risk of incident depression may be higher in those with subthreshold level symptoms at baseline.[85]

The relationship between BP and affective symptoms in older adults may be confounded by the cardiovascular side-effects of antidepressants. Antidepressants are commonly prescribed to treat both depressive and anxiety disorders in older adults, and rates of prescription in this demographic are increasing.[86] The impact of antidepressants on BP however is controversial. For example, a 2009 cross-sectional analysis of the Netherlands Study of Depression and Anxiety, assessed both BP and affective symptoms. 2981 middle–aged participants (mean age 40.9 years; age range 18-64 years) were categorised according to affective disorder status and antidepressant treatment (ADT) i.e. controls (no history of anxiety or depression; not on antidepressants), 'cases' not on treatment: (anxiety or depression but no ADT) and 'cases' on treatment (anxiety or depression and in receipt of ADT).[87] The authors reported that participants with anxiety had higher mean DBP, while participants with depression had lower SBP. The investigators however, also reported an independent effect of ADT on BP – those on tricyclic antidepressants (TCA) or serotonergic and noradrenergic re-uptake inhibitors (SNRI) were more likely to have hypertension. The authors suggested the effects of ADT on BP were explained by their effects on the ANS, as demonstrated by lower respiratory sinus arrhythmia in those participants also on ADT.[87] In line with such findings, O'Regan and colleagues also reported that those on antidepressants in the first wave of TILDA had lower heart rate variability (HRV) but that effects varied according to antidepressant class. However, in a subsequent *prospective* study in the Rotterdam cohort

including over 11,000 participants, a negative impact on autonomic function (as assessed via HRV) was restricted to those on TCA.[88]

Blood pressure variability and brain health

Key point: ***Greater within-person variability in blood pressure may impact brain health over and above usual blood pressure***

In 2010, in a series of Lancet papers Rothwell challenged the conventional understanding of risk associated with mean BP, emphasising the associations between stroke and *blood pressure variability*.[89] Rothwell defined BP variability as, "the variation in blood pressure with time, either the overall variability during a period of time (SD or coefficient of variation) with or without adjustment for time trends in underlying mean blood pressure (residual SD) or the average absolute difference between adjacent readings (successive variation)."[89]

In a 2015 narrative review by Nagai the evidence linking within-person BP *variability* to dementia suggested that cerebral small vessel disease and arterial remodelling were shared aetiological factors for BP variability and dementia.[90] The studies highlighted in the review included a 2014 report from the Three City Study in which Alpérovitch et al[91] examined 6506 participants aged 65+ at baseline. During a follow-up over 8 years a total of 474 participants developed dementia. The majority of participants were assessed 3 times in total with an interval of two years between measures. In survival models, higher visit-to-visit SBP variability, but not mean SBP, was associated with incident dementia (1.77 times the risk in the highest decile of variability vs the lowest).[91]

The prospective Three City study has also described associations between BP and affective symptoms in the older adults. In 1454 participants (mean age 78 years) baseline GAD (as assessed at clinical interview) was associated with greater visit-to-visit variability in SBP over 8 years of follow-up but baseline depression was not.[92] However, in a study which investigated 328 patients with hypertension, those with case-level depressive symptoms (according to the CES-D) had greater day-to-day BP variability (assessed by home monitoring) over 14 days.[93] In an editorial piece discussing these findings Kario and colleagues outlined the potential role of psychological factors in determining BP variability, suggesting that variation in BP induced by psychological stress may be particularly detrimental to cerebrovascular health.[94]

Cognitive impairment and affective symptoms may co-occur in later life

Key point: ***In later life affective symptoms may be prodromal markers of dementia.***

Increased affective symptoms in later life have been proposed as occurring along the continuum towards dementia – either as a prodromal feature of an emerging neurocognitive disorder, or as an independent risk factor. The direction of causality is uncertain; impaired cognition (particularly executive dysfunction) is a common finding in older adults with depression.[76]

In a 2013 review of studies investigating associations between affective symptoms in older adults and dementia, Diniz et al reported that late-life depression was associated with an increased risk of all-cause dementia (i.e. both AD and VaD), but the risk of VaD was higher than that for AD.[95] Anxiety has also been associated with an increased risk of cognitive impairment and dementia in the community, but in at least one study did not predict

conversion to dementia from MCI.[96] Furthermore, in older adults anxiety and depressive symptoms have been associated with brain imaging changes linked to cognitive decline, including white matter change[97,98], regional GM atrophy, and higher amyloid load.[99]

A comprehensive study from the longitudinal occupational Whitehall cohort measured depressive symptoms in participants followed over 28 years.[100] Dementia diagnosis was ascertained via electronic health record linkage. Depressive symptoms began to increase, on average, over a decade prior to dementia diagnosis. The authors concluded therefore that depressive symptoms were more likely to represent a prodromal symptom rather than an independent risk factor for dementia. Results were robust to use of either the General Health Questionnaire or the CES-D to assess depressive symptoms.[100]

Subjective Memory Impairment

Subjective Memory Impairment (SMI) is a common clinical presentation which serves to further highlight the overlap between affect and cognition in older adults. Accumulating evidence suggests that an older adult's subjective report of impaired cognition - even in the setting of normal cognitive testing - may be a risk marker for future pathological cognitive decline and dementia.[101] With the move to understanding dementia as occurring along a continuum, there has been increased interest in SMI as one of the earliest and most readily identifiable features of future dementia.[102] Indeed it has been hypothesised that SMI reflects pathological processes occurring in the brain to which cognitive testing may not be sensitive - in particular among those with higher baseline cognitive function.[103]

The overlap with between SMI and affective symptoms and/or personality traits such as neuroticism, have led to debate about its validity.[104] A recent large scale study of over 40,000 participants aged 45-64 years among whom SMI was rated according to a 5-point Likert scale, reported that vascular risk factors were only weakly associated with SMI, but there was a strong association between SMI and psychological stress.[105] Vascular risk however was self-reported. Multiple studies have by contrast described associations between *objective* biomarkers and SMI, including associations with WMH[106], GM atrophy[107], and amyloid on PET imaging.[108] Furthermore, in the context of the literature on affective symptoms as prodromal symptoms of dementia, overlap between SMI, depression and anxiety may be informative. A recent meta-analysis synthesising results from 28 studies (N=29,723; mean age 71.6 years) reported that the risk of conversion from SMI to MCI, and from SMI to dementia was 2.3% and 6.6% per year respectively, over a median follow-up of 4.8 years (the longest follow-up study included spanned over 8 years).[109] Relative to those free from concerns, those with SMI had twice the risk of dementia diagnosis. Whatever the association with dementia risk, SMI is common in older adults and is associated with both increased distress and lower quality of life.[102,110]

With respect to BP, SMI has been associated with both hypertension and hypotension. In an early report from the Rotterdam cohort (N=111), significant positive associations were reported between hypertension and WMH in those aged between 65-74 years; in turn, those with WMH were more likely to experience both objective and subjective cognitive impairment.[111] More recently, in a clinical study which examined SMI (using a standardised questionnaire) in a group of patients with hypertension, those with higher levels of 'cognitive complaints' also had greater levels of cerebral microbleeds on MRI.[112] SMI, assessed using the Subjective Cognitive Failures Questionnaire, has also been linked to greater cerebral

microbleeds on MRI in the RUN DMC cohort (a cohort of participants with known cerebral small vessel disease).[113]

In a further clinical investigation of 378 hypertensive patients with SMI aged 60+ (mean age 70.4 years), those who were treated with calcium channel blockers versus other classes of antihypertensive, had higher scores on objective memory testing.[55] Patients on treatment with a calcium channel blocker also had the *highest* mean BP among the patients in the study.[55] Similarly, participants with 'moderate SBP' (i.e. 120-160mmHg seated) in the Norwegian-based Nord-Trøndelag Health ('HUNT') Study had *greater* SMI than those with 'high' SBP (>=160mmHg).[114] Furthermore, men (but not women) with the lowest SBP (<120mmHg) had the greatest levels of SMI. Amlodipine (a Calcium Channel Blocker) was the second most commonly prescribed antihypertensive during the time period of the study. In the HUNT study as a whole, SMI was more common among men than women.[115] Notably however, although the HUNT study had a comprehensive measure of SMI, no objective cognitive tests were available.

In a sample of 280 patients (mean age 78 years) with SMI, intermittent episodes of hypotension (BP<100mmHg) on 24 ambulatory BP monitoring, in combination with white matter change on CT and increased arterial stiffness, were associated with cognitive decline as assessed on MMSE over a follow-up period of 15 months.[116] SMI may indicate subclinical vascular risk; in over 9000 participants from the Rotterdam cohort who were under surveillance for stroke, Sajjad et al showed that those with greater levels of SMI at baseline were at greater risk for future stroke.[117] Interestingly, this association was strongest in those

with higher educational attainment, in whom objective cognitive impairment may be less evident on standard neuropsychological testing.[117]

Sex differences in Brain Health

*Key Point**: Sex differences in brain health are poorly understood***

The greater burden of poor brain health in older adults is borne by women: dementia, stroke and affective symptoms are each more prevalent among older women.[118,119] For example, in the Framingham study the estimated lifetime risk of stroke and/or dementia was 1 in 3 among women but 1 in 4 among men; the authors concluded that these sex differences were a function of longer survival in women.[120] Other evidence however suggests that identifying and understanding sex-differences beyond differences in life expectancy may be important in more appropriately targeting treatment and prevention strategies.[118,121] Sex differences in brain health among older adults remains poorly understood[121]; notably, many studies investigating brain health outcomes often simply correct (or 'adjust') for sex rather than investigating the potential *moderating* effects of sex.[17]

The life course accumulation of risk may be important in understanding sex-differences in brain health in older adults; exposures and/or resilience may differ as a function of *biological sex* and/or *gender*.[118,121] For example, sex-differences in psychopathology emerge from early life: disorders such as autism, ADHD and dyslexia are more common among males, while from early adolescence women are more likely to experience affective symptoms - with approximately twice the life time risk compared to men.[122] Cumulative exposure to greater affective symptoms may increase risk of cognitive impairment in later life.[123]

Sex-specific biological exposures including age at menarche, pregnancy and menopause may also impact brain health.[124–126] For example, GM change (although not necessarily pathological) has been described after pregnancy.[127] A history of pre-eclampsia has been linked to greater WMH, GM loss and both subjective and objective cognitive impairment in older women.[128–130] Furthermore, brain integrity and development is modifiable by experience, thus differences in exposure according to *gender* rather than simply biological sex may be important.[6,121] In this context, cohort effects may also be relevant; for example increasing educational attainment among women has been suggested as a possible factor in reducing incidence of dementia, in addition to better management of cardiovascular risk factors including hypertension.[118] Although in Europe rates of cardiovascular disease are similar among men and women (~one in five men and one in five women die from ischaemic heart disease), there may be gender differences in presentation, treatment received and outcomes[131,132], with potential implications for later life brain health.

Sex differences in later life brain health may also arise from life course differences in BP regulation – differences likely underpinned by reproductive hormones - the best studied of which is oestrogen.[133] In addition to putative direct neuroprotective effects, which have been consistently demonstrated in animal models but which remain unclear in women, oestrogen has positive effects on vascular function.[134,135] For example, oestrogen augments β-adrenergic activity and nitric oxide which promote endothelial function and vasodilation.[133]

While hypertension is less common among women until after the menopause, pre-menopausal women who do experience hypertension may have more significant end-organ sequelae than age-matched men.[136] For example, in a cohort of adults in whom BP was

measured twice in early mid-life, incident hypertension (by age 43 years) was associated with an increased risk of dementia in later life among women but not in men.[136]

Sex differences may also be evident on structural neuroimaging in older adults; sex differences in the prevalence of WMH have been described.[17] In a large, population-based cohort (the Mayo Clinic Study of Aging) women had a greater prevalence of WMH, but cortical infarctions were more common in men.[17] While in the Framingham study, DeCarli et al showed that the yearly rate of GM loss as a percentage of head size was faster in men than in women – in particular in the frontal and medial temporal lobes.[20] Sex differences in structural brain ageing may be mirrored by sex differences in verbal memory and search speed, with women out-performing men on these tests from mid-life.[137] Well characterised sex-differences in certain cognitive domains (i.e. men may on average have advantages in visuospatial skills and women in tests of verbal memory) present from early life may persist in older adults.[138] Advantages in verbal memory however, may render the diagnosis of AD in women more difficult, thus potentially delaying intervention.[139]

Sex differences may also be present in the preclinical and prodromal stages of dementia. Men may be more likely to report SMI, at greater levels of severity than women.[115] In men, SMI may more accurately reflect objective cognitive performance[140,141], nevertheless women with SMI may be more likely to progress to dementia.[141] With respect to MCI, some studies suggest there may be a higher prevalence and incidence of MCI in men compared to women (as shown in the Mayo Clinic Study of Ageing)[142,143], but women may have a faster rate of conversion from MCI to dementia, as demonstrated over 8 years of follow-up in the Alzheimer's Disease Neuroimaging Initiative Study.[144] After diagnosis, there may be

variability between the sexes in the presentation of behavioural and psychological symptoms of dementia; for example, men may be more likely to display aggressive behaviours relative to women.[118] Finally, women tend to live for longer with dementia regardless of diagnosis subtype.[145]

In summary:

In face of an ageing population, conditions associated with poorer brain health in later life represent an important and growing public health burden. Impaired cognition and affective symptoms may be markers of declining brain health in older adults. White Matter Hyperintensities and GM Atrophy are common findings on MRI neuroimaging in older adults; and tend to accumulate with increasing age. Blood pressure dysregulation increases with age and is a key risk factor for poorer brain health; however associations between BP and brain health may be age-dependent. Mid-life hypertension has been highlighted as a key risk factor for dementia, but the relationship between later life BP and cognition in older adults is less clear. Affective symptoms have been associated with both high and low BP in older adults and across the life span; relationships may be bidirectional. In later life cognitive and affective symptoms often overlap: SMI is an important clinical example. There are sex differences in BP change with age and in the prevalence of dementia, affective symptoms and structural changes on MRI – yet sex differences in brain health in later life remain poorly understood.

2.2. Autonomic Nervous System, Blood Pressure Instability and Brain Health in Older Adults

Blood Pressure Instability

Rothwell has defined *blood pressure instability* as:

> *'transient fluctuations in blood pressure, usually in response to a specific stimulus such as change in posture, emotional stress or pain. Instability contributes to overall variability and will often have similar clinical associations, such as arterial stiffness and baroreceptor dysfunction. However, instability differs from variability in that it refers specifically to sudden changes in blood pressure, the consequences of which might differ from more gradual fluctuations.'*[89]

In this section, I introduce the cardiovascular ANS and provide an overview of the proposed mechanisms linking cardiovascular autonomic function to brain health in later life. The focus is on the role of the baroreflex in regulation of short term BP, and BP instability as manifested in orthostatic BP fluctuations and reflex syncope.

A 'life course' framework is then introduced in Section 1.3 to provide context for the investigation of the associations between psychological stress and short-term BP instability across the life span. This acknowledges that cardiovascular autonomic function in older

adults is, at least in part, a function of biological processes and environmental / behavioural exposures occurring earlier in life.

Autonomic Nervous System

The ANS has been described by Guyenet as, 'a collection of afferent and efferent neurons that link the central nervous system with visceral effectors'.[146] It is of fundamental importance to regulation of the cardiovascular system via sympathetic and parasympathetic divisions e.g. influencing HR and BP.[147,146] Sympathetic efferents have activating functions on the cardiovascular system (e.g. increasing HR and peripheral vasoconstriction), while the parasympathetic division regulates vegetative function (e.g. decreasing HR and lowering cardiac contractility).[147]

Classically, the ANS is tasked with maintaining physiological 'homeostasis' in response to external / environmental stressors and thus (*mis*-)understood to maintain equilibrium around a single set-point. Increasingly however the ANS is understood, as per Captur, to maintain 'not stability, but adaptive variability'[148]; or as suggested by Thayer[149] its role is to promote a 'dynamic balance' e.g. lower BP when at rest overnight versus a higher day time mean; or increased BP in response to cognitive challenge.

Cardiovascular Autonomic Nervous System and blood pressure regulation

Key point: ***The ANS is of fundamental importance to blood pressure regulation.***

Blood pressure regulation involves a complex interplay between cardiovascular, renal, neural, endocrine, and local endothelial mechanisms.[150] The ANS is key in determining BP. For example, an increase in sympathetic tone has been described as a hallmark of hypertension[146]. While the mechanisms underpinning the ANS contribution to long term BP regulation remain incompletely understood, the contribution of the ANS to short term, or beat-to-beat, BP regulation has been more clearly elucidated.[150]

Baroreflex

Key point: **Short term (*beat-to-beat*) regulation of BP is facilitated by the arterial baroreflex**

The baroreflex has vascular, cardiac and central components (Figure 2.3).[151] Vascular baroreceptors are located in the intima of the aortic arch and the carotid artery. They are stretch sensitive receptors which buffer acute changes in BP.[152] A sudden drop in BP 'unloads' the baroreceptors which activates afferents via the IX (glosspharyngeal) and X (vagal) nerves to the nucleus tractus solitarius in the vasomotor centre of the medulla located in the brain stem.[153,154] Efferents relay via the nucleus ambiguous to the sinoatrial node and reduce parasympathetic (or vagal) outflow thus increasing HR, and via the rostral ventrolateral medulla to increase muscle sympathetic nerve activity thus increasing peripheral vascoconstriction.[153] There may additionally be projections to higher cortical

regions of the brain.[155] In animal, and in human clinical (e.g. post-surgery) models, baroreceptor loss is accompanied by extreme variability of BP.[152,153]

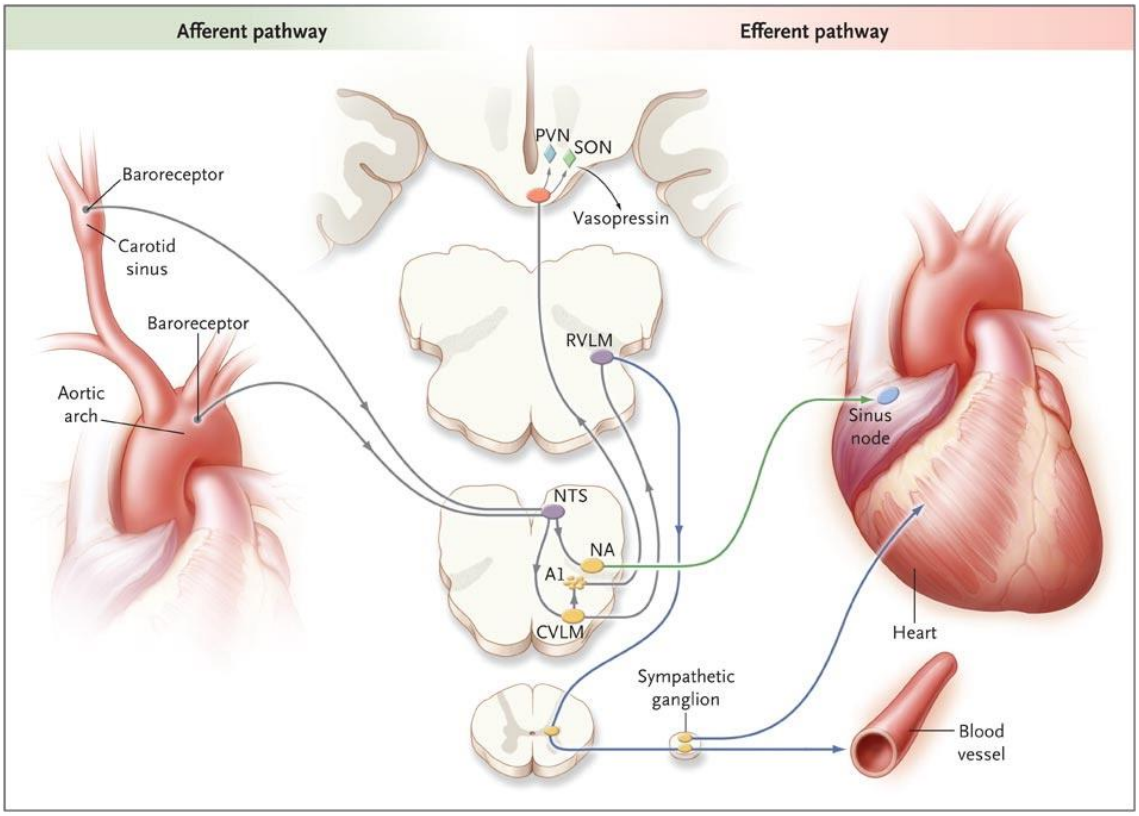


Figure 2.3: The Baroreflex.
From Freeman R et al 2008[154] depicts the baroreflex arc Blue=sympathetic neurons; Green=parasympathetic neurons; NTS=Nucleus Tractus Solitarius; NA= Nucleus Ambiguus CVLM =Caudal ventrolateral medulla; RVLM =Rostral ventrolateral medulla; A1 noradrenergic cell group; PVN = paraventricular nucleus; SON=supraoptic nucleus

Orthostasis is a physiological stressor and provides the classic example used to demonstrate the function of the baroreflex. Upon standing, the effect of gravity results in the pooling of approximately 700ml of blood in the lower limbs and splanchnic vessels.[156] An intact ANS is required to mount an appropriate BP response to maintain perfusion of the upper body, and crucially, to maintain cerebral perfusion.[154] Reduced venous return and cardiac output after standing lowers systemic arterial BP resulting in activation of the baroreflex arc which, via central integration of afferents from baroreceptors located in the intima of carotid and aortic arch, activates an effector response to increase HR and peripheral vasoconstriction thus restoring BP.[157]

Ageing and the cardiovascular autonomic nervous system

Key point: ***Blood pressure instability increases with age***

Cardiovascular ANS function is altered with increasing age. This may be precipitated by, and/or compounded by, the common features of cardiovascular ageing such as hypertension, increased arterial stiffness, reduced early diastolic filling, decreased endothelial function and neurohumoral alterations.[156,158] With ageing, there is a shift towards sympathetic predominance and reduced parasympathetic activity which may in turn affect BP homeostasis (Figure 2.4).[159]

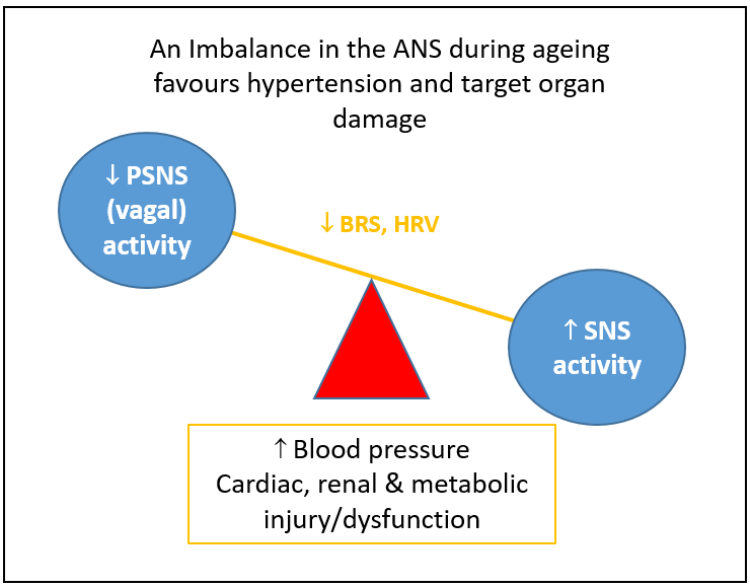


Figure 2.4: Change in the Autonomic Nervous System with Age
Adapted from Arnold et al 2013[159]: 'Schematic of proposed features associated with the imbalance in the autonomic nervous system during aging'. ANS=autonomic nervous system; SNS=sympathetic nervous system; PSNS=parasympathetic nervous system

Age related changes in cardiovascular and ANS function may lead to an impaired capacity to adapt to quotidian physiological stressors, such as orthostatic stress.[156] For example, it is proposed that chronically heightened BP induces vascular change, such as increased arterial stiffness, that contribute to the diminished baroreflex response observed in ageing (Figure 2.5).[160] Increased arterial stiffness may be accompanied by a reduction in the sensitivity of the arterial wall to stretch, thus compromising the afferent arm of the baroreflex.

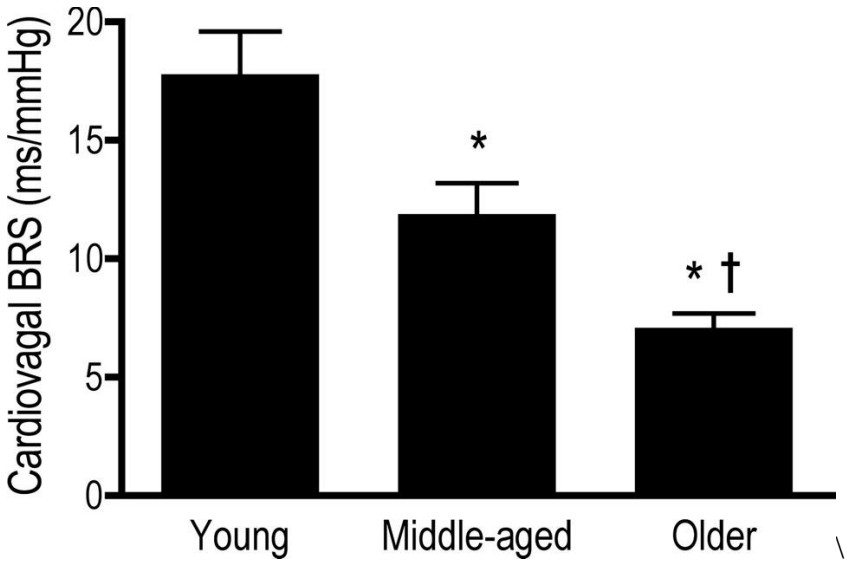


Figure 2.5: Change in the Baroreflex with Age
From Monahan 2007[160] bar chart comparing values of Baroreflex Sensitivity in volunteers aged 18–37 years ('Young') vs 38–56years ('Middle-aged') vs 57–79 years ('Older') *P < 0.05 vs. 'young'; †P < 0.05 vs. 'middle-aged'

Orthostatic hypotension

Impaired baroreflex function may underpin the clinical syndrome of Orthostatic Hypotension (OH) (an excessive reduction in BP upon standing).[156] OH is arbitrarily defined according to expert consensus criteria first established in 1996 i.e. >=20 mmHg decline in systolic BP and/or >=10 mmHg or greater decline in diastolic BP when changing from a supine to standing position.[161] The prevalence of OH increases with age and OH is more common in those with a history of hypertension.[162] OH is classically commonly observed among frail older adults.[156] Importantly, *hypertension itself* may predispose to OH[163]; the combination of supine hypertension and OH is a common presentation in older adults with impaired BP homeostasis.[164] In both clinical and epidemiological studies, OH has been associated with increased risk of stroke, cardiovascular events and mortality.[165] Measurement of the BP and HR fluctuations which accompany orthostasis have been used in multiple epidemiological cohorts of mid-life and older adults as a marker of cardiovascular autonomic reactivity.[166] Orthostatic intolerance (OI) (e.g. dizziness that occurs upon standing and symptoms of pre-syncope) is classically attributed to transient reduction in cerebral blood flow (CBF) with standing.[167]

Syncope

When there is complete failure to maintain CBF syncope may occur. Syncope is defined as a sudden, transient loss of consciousness ('T-LOC') resulting from global cerebral hypoperfusion.[168] It is associated with loss of postural tone and followed by rapid, spontaneous recovery. The aetiology of syncope in older adults is often multifactorial. Older adults may be more vulnerable to hypotension induced by age-related impairments in BP homeostasis even during quotidian stressors such as orthostasis - particularly in the setting of polypharmacy and co-morbid disease.[169]

According to the 2009 European Society of Cardiology guidelines, causes of syncope may be classified as cardiac, reflex or 'psychogenic'.[168] Cardiac causes of syncope include structural or conduction abnormalities of the heart which are associated with increased risk of sudden cardiac death. In the young these are a rare cause of syncope but are more prevalent with ageing given corresponding increases in ischemic coronary heart disease.[170]

Reflex syncope

Reflex causes of syncope include vasovagal syncope (VVS), carotid sinus syncope and situational syncope (i.e. related to triggers including cough, laughter or micturition syncope).[168] Reflex syncope is the most frequent cause of syncope in any setting, including among older people; it is unusual however for an adult to experience a first vasovagal episode after the age of 35.[171]

The precise pathophysiology of VVS (or the 'common faint') is unknown. The ESC guidelines describe VVS simply as an 'inappropriate' autonomic reflex.[168] The afferent limb of the vasovagal reflex may include higher cortical involvement.[172] The final common pathway is hypotension with or without bradycardia (due to sympathetic inhibition and parasympathetic activation) which leads to cerebral hypo-perfusion and LOC.[173]

Some theories suggest an abnormal baroreflex may be key in VVS, given the role of the baroreflex in regulation of the BP response to orthostasis. VVS is often preceded by orthostasis and/or prolonged standing. An alteration in baroreflex function may be the 'hallmark' of the VVS as evidenced by concurrent bradycardia and hypotension, suggesting that baroreflex-mediated compensatory control of BP and HR has failed.[174] Both under *and* over sensitivity of the baroreflex have been implicated.[174] Some studies investigating the baroreflex in those with Head Up Tilt (HUT)-induced syncope have reported lower BRS in un-medicated, otherwise healthy patients.[175,176] Moreover, lower BRS predicted syncope-recurrence: those participants with lower BRS after 5 minutes of passive HUT were more likely to experience recurrence of syncope during 24 months of follow-up.[175] An older study from the same group however, which had followed 312 patients (mean age 36 years) with unexplained syncope, revealed higher BRS and greater HR response to low BP in those with VVS relative to controls.[177]

Other theories on the pathophysiology of VVS include the 'Ventricular theory'. This holds that contraction of the ventricle in the setting of severely reduced filling secondary to reduced venous return leads to the 'Bezold-Jarisch reflex' which induces bradycardia, hypotension and ultimately syncope.[178] Others describe maladaptive neurohumoral responses to hypotension.[179] Skoog et al showed similar lower limb blood pooling in young women with

VVS versus age-matched controls, but greater resting plasma noradrenaline and a blunted increase during hypotension in those with VVS in addition to slower mobilisation of peripheral blood to the central circulation.[180]

Potential cortical contributions to VVS have also been described, particularly within the context of the ANS response to stress; these are discussed in Section 1.3.

Sex Differences in Blood Pressure Instability

*Key point**: Cardiovascular Autonomic Function and Blood Pressure Instability may vary according to sex***

Young women have both the lowest BP and lowest sympathetic nerve activity.[133] By contrast, in young men BP is supported by a greater relative peripheral sympathetic pressor effect.[27,133] Indeed, greater sympathetic predominance is commonly described in men, while women, in general, demonstrate higher parasympathetic tone.[131] A meta-analysis of 172 studies (with data from >60,000 participants) investigating sex-differences in autonomic function, as reflected in HRV, demonstrated a consistent parasympathetic advantage in women.[181] The authors hypothesised that in addition to a hormonal basis (e.g. oestrogen, oxytocin) for such differences, higher parasympathetic tone may also reflect higher cortical influences on peripheral BP regulation e.g. socialised female coping strategies to stress i.e. to 'tend and befriend' rather than the classic male 'fight or flight' response which may be reflected in higher sympathetic tone.[181] Koenig and Thayer suggest such a hypothesis is supported by sex differences in GM volume of regions implicated in the Central Autonomic Network including the amygdala, hippocampus and insula.[122,181]

Disorders of orthostatic intolerance including VVS and Postural Orthostatic Tachycardia Syndrome ('POTS') are more prevalent among young women[182]; sex-differences in BRS may be important. For example, one study investigated sex-differences in baroreflex responses to HUT and suggested women have reduced sympathetic peripheral sympathetic nervous activity, greater parasympathetic activity and lower plasma noradrenaline in response to passive HUT compared with men - thus rendering women more vulnerable to OH and VVS.[183]

Sex differences were also evident in age-related change in orthostatic BP in the first wave of TILDA. The maximum change in orthostatic BP from supine to standing (i.e. 'delta' SBP and DBP) continued to increase, and supine DBP decreased, from age 50+ in men; however in women there was no age gradient.[184] In line with this perhaps, older men have previously been shown to have higher rates of OH related hospital admission, and potentially to demonstrate poorer cerebral auto-regulation in response to orthostasis than women.[185]

Consequences of intermittent hypotension

*Key point**: Recurrent episodes of cerebral hypoperfusion may occur with Orthostatic Hypotension and Vasovagal Syncope***

Repeated episodes of cerebral hypoperfusion may occur with increased BP instability e.g. with OH, syncope and/or in the setting of altered baroreflex function. Failure to maintain BP in response to orthostasis may have important consequences for the cerebral circulation.

Cerebral Blood Flow

The main function of the systemic circulation is to maintain perfusion to vital organs. The brain has the highest metabolic demands of any organ – receiving up to 20% of the cardiac output in the resting state.[186] Blood supply to the brain is via the internal carotid and vertebral arteries. The internal carotid arteries branch to form the anterior cerebral and middle cerebral arteries which supply the anterior circulation.[187] The right and left vertebral arteries merge to form the basilar artery which then joins the Circle of Willis along with the anterior and middle cerebral arteries.[187] The posterior cerebral arteries arise from this anastomosis to join the posterior circulation, which is also contributed to by branches arising from the basilar, and vertebral arteries.[187] The posterior circulation of the brain supplies the posterior cortex, the midbrain, and the brainstem.[187] Lenticulostriate arteries branch from the middle cerebral artery to supply the basal ganglia and thalamus[187].

Cerebral autoregulation

*Key point**: Cerebral autoregulation is poorly understood but may buffer acute episodes of high blood pressure better than acute episodes of low blood pressure***

The cerebral circulation is relatively protected from excess variation of the systemic BP by cerebral autoregulation. The extent of this regulation or how it changes with age and in disease states however remains uncertain. Mechanisms involved in determining the extent of cerebral autoregulation likely include compliance of the large intracranial arteries, neurovascular coupling, and chemoreceptors monitoring partial pressures of oxygen and carbon dioxide.[188]

The classic understanding of cerebral autoregulation suggested a wide range of perfusion pressure over which the brain is buffered against peripheral change in BP.[189] In 1959, Lassan reported that there was a large plateau over which perfusion pressure to the brain was constant despite change in peripheral BP i.e. ranging from 60mmHg to 150mmHg.[189–191] Hypertension has been understood to shift the range of autoregulation rightward, thus ensuring stable regulation at higher BP but increasing vulnerability to cerebral under-perfusion in the setting of intermittent hypotension.[191] Recent research however, has strongly challenged the concept of a wide range of peripheral BP over which the cerebral circulation is buffered. Writing in 2014 in a review of the physiology of cerebral autoregulation, Willie and colleagues stated, 'CBF regulation is often assumed to be so efficacious that it is treated separately, instead of as an integral component of the cardiovascular system… its efficacy is not perfect and is dependent on the severity and direction of change in perfusion pressure'.[192] They argue that a contemporary understanding suggests that the range of

peripheral BP across which cerebral autoregulation acts is narrow, and moreover that there is asymmetry in the ability of cerebral autoregulation to buffer change in peripheral BP - with an enhanced ability to respond to higher rather than lower BP (Figure 2.6).[192]

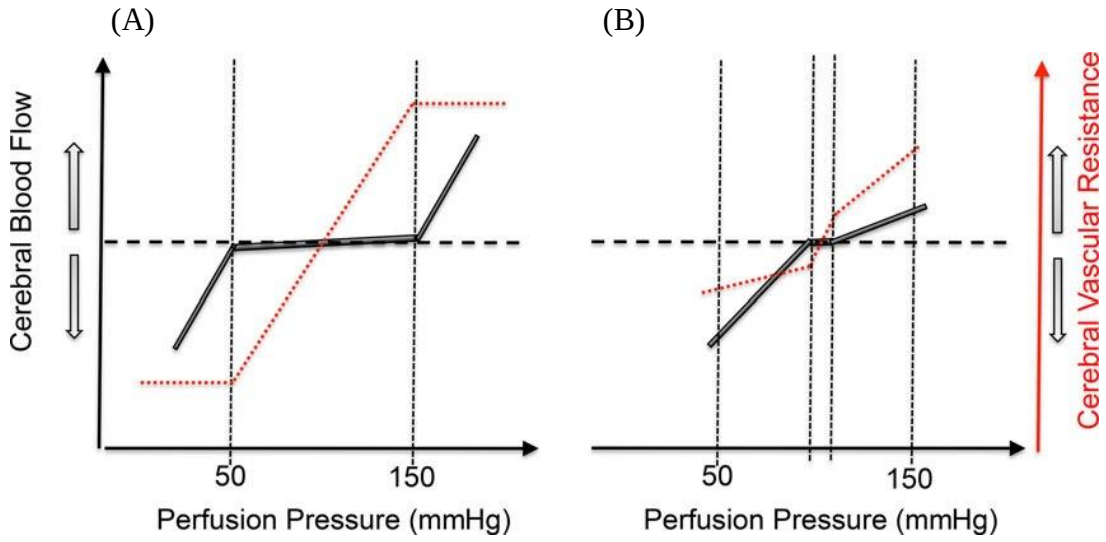


Figure 2.6: Cerebral Autoregulation.
Adapted from Willie et al 2014[192]: a representation of the classic (A) and modern (B) understanding of the association between peripheral mean arterial pressure and cerebral blood flow.

Impaired cerebral autoregulation has been described in ageing[193], OH[194], white matter change and increased beta-amyloid[195]; although evidence is conflicting.[196] Willie et al argue however that there is a need to better understand the normal physiology of cerebral autoregulation prior to investigating how this may be affected in various disease states.[192] If however, cerebral autoregulation operates only across a narrow plateau with asymmetry, even in health the brain will be vulnerable to hypoperfusion from peripheral BP instability in the setting of altered baroreflex function, OH and syncope.

Border zone arterial areas

*Key point**: Border zone regions may be particularly vulnerable to cerebral hypoperfusion***

Brain regions which lack adequate arterial anastomosis i.e. occurring at the distal region between two arterial supplies of the brain, are referred to as border zone regions.[197] Such areas may be particularly vulnerable to hypoperfusion during hypotension. The stroke literature describes 'border zone infarcts' which are ischemic lesions that occur in characteristic locations at the junction between two main arterial territories, and which may account for up to 10% infarcts.[197] There are two types: external (cortical) and internal (subcortical); internal are the most common. They occur between superficial and deep arterial systems emerging from the middle cerebral artery, and may be more likely to result from haemodynamic impairment.[197] External border zone infarcts (occurring anteriorly between the territory of the anterior cerebral artery and the middle cerebral artery, and posteriorly between territory of the middle cerebral artery and the posterior cerebral artery) may be more likely to result from embolism in combination with hypoperfusion ('impaired washout' of emboli).[198] It is important to note that considerable between-person variability exists in cerebral arterial anatomy and this has hampered classification of border zone regions.[199] Postural symptoms classically attributed to cerebral hypoperfusion may precede 'border zone' stroke - it has been hypothesised therefore, that BP instability in the setting of postural change, may play an aetiological role.[198]

According to Pantoni, subcortical white matter may be particularly susceptible to injury resulting from decreases in CBF.[191,200] Cerebral arterial small vessels arise from the

subarachnoid circulation as terminal vessels of medium sized arteries, which in turn have stemmed from larger arteries; at the base of the brain they arise as arterial perforators directly from the large vessels[200]. Where these systems merge there is a border zone area thus rendering the subcortical white matter vulnerable to hypoperfusion injury.[200]

Cerebral Hypoperfusion and Cognition in Alder Adults

*Key point**: Cerebral hypoperfusion is a key pathogenic mechanism in dementia***

Cerebral hypoperfusion has been widely implicated in neurodegenerative disorders, including associations with white matter change, GM atrophy and increased amyloid deposition. Love has described cerebral hypoperfusion as 'the dominant pathogenic process' in white matter change in dmentia.[201] In AD transient ischaemia has been implicated in the overexpression of amyloid-β precursor protein mRNA (i.e. messenger Ribonucleic acid) and increased β-secretase activity and hence in the over production of amyloid-β peptide.[201] Excess amyloid-β in turn may increase the production of local vasoconstrictors thus further exacerbating ischaemia – therefore associations between cerebral hypoperfusion and AD pathology may be bidirectional.[201]

Importantly, reduced cerebral perfusion may be evident even in the earliest preclinical and prodromal stages of AD, as demonstrated in the Amsterdam Dementia Cohort by Binnewijzend et al.[202] CBF was investigated using MRI arterial spin-labelling in 177 participants across the stages of cognitive impairment i.e. patients with SMI, MCI and AD. Diagnostic categories were assigned based on clinical evaluation and cerebrospinal fluid

analysis of amyloid beta and tau. CBF was observed to reduce along the continuum of AD disease severity.[202]

In the Rotterdam cohort, Wolters et al[203] observed that cerebral hypoperfusion *preceded* neurodegeneration, cognitive decline and dementia. 4759 participants (mean age 61.3 years at baseline; 55.2% women) were followed prospectively over a median 6.9 years. 123 participants developed dementia; 97 were diagnosed with AD. At baseline mean total CBF was estimated non-invasively using MRI ('2-dimensional phase-contrast'). In survival models adjusted for age, sex, cardiovascular risk and APOE, lower estimated CBF was associated with higher dementia risk. Lower baseline CBF was also associated with lower scores on cognitive testing at follow-up.[203]

Another study from the Rotterdam cohort however, described a *bidirectional* relationship between brain atrophy and CBF.[204] In participants who were followed over an average of 3.9 years, associations between CBF and brain volume differed according to age: in those over 65 lower baseline CBF was associated with greater brain atrophy, however in those younger than 65 brain atrophy *preceded* a decrease in CBF.[204]

As noted by Taylor, cerebral hypoperfusion need not be severe enough to cause ischemia in order to disrupt brain activity.[76] Transient and, crucially, *reversible* effects of posture on cognition have been described in patients with Parkinson's disease (among whom OH is a common non-motor feature). 18 patients with Parkinson disease and OH performed cognitive testing in the supine position, when tilted passively upright, and again when returned to the supine position, and were compared to 19 patients without OH and healthy

controls.[205] Relative to the patients free from OH and the healthy controls, cognitive scores were lower in patients with OH in the upright position but the deficits resolved when the participants were returned to the supine position. These effects were attributed to cerebral hypoperfusion occurring with posture.[205] It is therefore plausible that transient cerebral hypoperfusion – via acute or cumulative effects – may lead to the earlier manifestation of clinical deficits (or *unmask* deficits) in a vulnerable brain i.e. in which neurodegenerative processes are already established and thus compensatory mechanisms compromised.

Cerebral Hypoperfusion and Affective Symptoms in Older Adults

*Key point**: Cerebral hypoperfusion may play an aetiological role in affective symptoms in late life although results are conflicting.***

Several studies have suggested a role for regional deficits in CBF and CBF regulation, in the aetiology of affective symptoms in older adults. Indeed, in 2013 Taylor proposed a 'hypoperfusion hypothesis' of late life depression which suggests that deficits in cerebral perfusion may impair cortical function and thus impact brain circuits involved in the regulation of cognition and affect.[76] Results in studies investigating CBF in late life affective symptoms have been conflicting, however study sample size, characteristics and methods of CBF assessment have been heterogeneous.

Perhaps the largest study to examine the role of CBF in affective symptoms in older adults is the Rotterdam cohort. Cross-sectional and longitudinal findings support a role for lower CBF and reduced cerebral reactivity in depressive symptoms in older adults.[206,207] In two

studies, CBF velocity in the middle cerebral artery was assessed using Transcranial Doppler (TCD) and cerebrovascular reactivity was assessed during mild hypercapnic challenge (i.e. inhalation of 5% CO2). Hypercapnic challenge provides a measure of the ability of the cerebral vasculature to respond to varying metabolic requirements.[208] CBF and cerebrovascular reactivity tend to decrease with age and vary according to sex; older women tend to have higher CBF velocity than older men.[208] Depression was assessed via a two-step process which initially included screening using the CES-D and subsequently administration of the Schedule for Clinical Assessment in Neuropsychiatry ('SCAN' - a more detailed semi-structured interview administered by clinicians)[206]. Cross-sectional results showed that lower CBF was associated with greater depressive symptoms[207], and longitudinal follow-up over a mean of 4.1 years demonstrated that lower baseline CBF was associated with greater incident depressive symptoms, subthreshold depression and depressive disorder.[206] Whereas cross-sectionally reduced vasomotor reactivity was associated with greater depressive *symptoms* on CES-D, longitudinally it was associated only with incident depressive disorder.[207]

Dotson and colleagues[209] followed 61 older adults in a neuroimaging sub-study of the Baltimore Longitudinal Study of Aging. Resting state regional CBF was measured using PET both at baseline and after 8 years of follow-up. Depressive symptoms were assessed annually using the CES-D.[209] The authors reported that, on average, those with greater depressive symptoms over time had lower regional CBF at the end of follow-up and had larger decreases in regional CBF. Further, the authors reported that there were sex differences in the associations seen; men had more extensive reduction in fronto-temporal regional CBF than women. In women, longitudinal associations were limited to the right inferior frontal gyrus and inferior parietal lobule, whereas multiple frontal and temporal

regions were effected in men. The authors assert that their findings lend support to the continuum hypothesis of depressive symptoms in older adults and that there are potentially different aetiological factors underlying depressive symptoms in older men and women.[209]

More recent clinical studies have also examined regional CBF in older adults with late life depression using MRI arterial spin labelling (ASL). A 2012 investigation compared regional CBF in grey and white matter in patients aged 60+ with a history of a current or prior major depressive episode to regional CBF in healthy controls.[210] Current depressive symptoms were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) and Geriatric Depression Scale. No differences between patients and controls were found in regional grey matter CBF, however those with depression had higher regional CBF in white matter; a difference which appeared to be driven by those patients who were in remission (i.e. had lower current depressive symptoms on the MADRS). Although the accuracy of regional CBF in white matter as assessed by ASL has been questioned[211], the authors suggested that the increase in regional CBF may have reflected the effect of successful treatment in the older adults who were in remission .[210]

Abi Zeid Daou et al[212] explored regional CBF differences in 21 patients aged 60+ with major depressive disorder in response to a 12 week open label trial of sertraline treatment. The authors hypothesized that those with lower regional CBF (measured using pseudocontinous ASL) in frontal and temporal regions, in addition to lower cerebrovascular reactivity (assessed with hypercapnic challenge during ASL) would have a poorer response to treatment. However, contrary to their hypothesis those with higher baseline regional CBF in fact had a poorer response to treatment - higher regional CBF in the lateral orbitofrontal

cortex and caudal anterior cingulate cortex was associated with *less* change in depressive symptoms over the course of treatment, with a similar relationship seen with greater cerebrovascular reactivity. The authors acknowledged the small sample size and that results were not adjusted for multiple comparisons, but speculated that hypoperfusion in late life depression may be of more prognostic significance in the context of co-occurring cognitive symptoms.[212]

Differences in regional CBF have additionally been described among older adults with anxiety disorders; although with complex findings of both higher and lower regional CBF in patients. Two small clinical studies from the Geriatric Psychiatry Neuroimaging group in Pittsburgh investigated regional CBF using ASL during rest and during a worry induction task in older adults with Generalised Anxiety Disorder.[213,214] In common with TILDA, current symptoms of worry were assessed using the Penn State Worry Questionnaire. In the first study seven older adults with GAD were compared with 10 healthy controls.[214] In those with excessive worry CBF was lower in regions implicated in worry suppression. In a larger follow-up study, older adults with GAD had *higher* CBF than healthy controls in multiple regions during worry induction (visual and parietal cortex, middle and superior frontal cortices). Patients however had *lower* CBF during reappraisal in the supplemental motor area, middle cingulate gyrus, insula and putamen – regions the authors note have also been implicated in late life depression thus potentially explaining overlapping symptoms.[213]

Central Autonomic Network

*Key point**: Overlapping brain regions are involved in the regulation of cognition, affect and cardiovascular autonomic function***

The involvement of brain stem regions in autonomic function is accepted, however the advent of advanced non-invasive neuroimaging (in particular functional neuroimaging) has increased understanding of higher cortical regions involved in autonomic regulation.[215] Notably, many of the areas implicated in cortical control of cardiovascular autonomic function are understood to have overlapping function in the regulation of cognition and affect.[215] Benarroch has described the brain regions hypothesised to be involved in central control of autonomic function as the 'Central Autonomic Network'.[216] As per Palma and Benarroch, '*Areas distributed throughout the neuraxis, including the anterior insula, anterior cingulate cortex, amygdala, hypothalamus, periaqueductal grey matter, parabrachial nucleus, and several regions of the medulla, exert a beat-to-beat control on cardiac function. These areas are critically involved in emotional behaviour, stress responses, and homeostatic reflexes and exert their influence on HR and cardiac contractility via the sympathetic and parasympathetic nervous systems'*.[215]

Clinical evidence for the involvement of cortical regions in the regulation of cardiac function is provided by syndromes such as stroke and epilepsy. For example, tachycardia occurs in 80% of patients experiencing temporal lobe seizure while Takotsubo cardiomyopathy may be triggered by insular and vertebrobasilar stroke.[215] Moreover, electrical stimulation of the

insula may induce vomiting, respiratory arrest, as well as changes in HR and rhythm and BP; right-sided strokes may have a greater impact on cardiac activity.[215]

A 2013 meta-analysis entitled, 'The Autonomic Brain'[217] synthesised recent research using functional MRI, PET and SPECT neuroimaging to assess cortical regions active during affective (e.g. fear conditioning, appetitive or aversive videos, pictures, music or words), cognitive (e.g. stroop, colour word interference) or somatic motor (e.g. hand grip, acupuncture) tasks – tasks which are understood to activate the ANS. Forty-three studies met inclusion criteria, involving a total of 615 participants among whom 571 neural foci had been investigated.[217] The meta-analysis identified four main brain regions which were consistently activated during tasks including the left amygdala, right anterior and left posterior insular, and mid-cingulate cortices. The authors concluded therefore that these regions form the 'core' neural substrates of the Central Autonomic Network.[217] Notably however, the sample size of the individual studies involved were small (the largest number of participants in any single study was 41) and the age range of participants included in the studies was not reported.

Central neuropathology

Key point: ***Brain regions involved in central autonomic function may also be vulnerable to ageing related neurodegeneration.***

Many regions involved in central autonomic function may also be vulnerable to ageing-related neurodegeneration. Damage to these areas via central neurodegenerative processes

may thus be reflected in changes in both peripheral autonomic indices and cognitive and affective symptoms. In 2006, Royall[218] hypothesised that right insular dysfunction may be a marker of *pre-clinical* AD based on the understanding that AD neuropathology affects the insular cortex at an early Braak stage, thus potentially causing autonomic dysfunction in older adults at a *preclinical* phase of the disease process. The insula has been implicated in a large number of functions; in addition to regulatory functions linked to cardiovascular autonomic function it may also contribute to cognitive and emotional control. Indeed, according to Nieuwenhuys, together with other cortical areas the insula forms part of, 'a highly interconnected cognitive control network' which may underpin the experience of emotions such as happiness, sadness, fear, and disgust.[219]

Udow et al[220] reviewed the potential contribution of OH to cognitive impairment in the α-Synucleinopathies, which are often characterised by impaired BP regulation and include Parkinson's disease, Multisystem Atrophy and Lewy Body Dementia. Although these disorders are less prevalent at population level, they may provide a model for understanding associations between BP instability and cognitive decline. Udow et al[220], among others including Royall[218], theorise that central neurodegeneration may cause *both* OH and cognitive impairment. OH may then cause cognitive impairment via the impact of cerebral hypoperfusion (either acutely or chronically). Finally, Udow et al[220] proposes a 'synergistic' model whereby both these processes interact to accelerate decline in brain health (Figure 2.7). Such a model may perhaps also be reasonably applied to associations between BP instability and cerebrovascular small vessel disease and amyloid pathology at the population level. At a given level of amyloid/ neurodegeneration, those with greater BP instability may show greater decline in brain health because they are less resilient to the effects of recurrent exposure to acute/transient cerebral hypoperfusion.

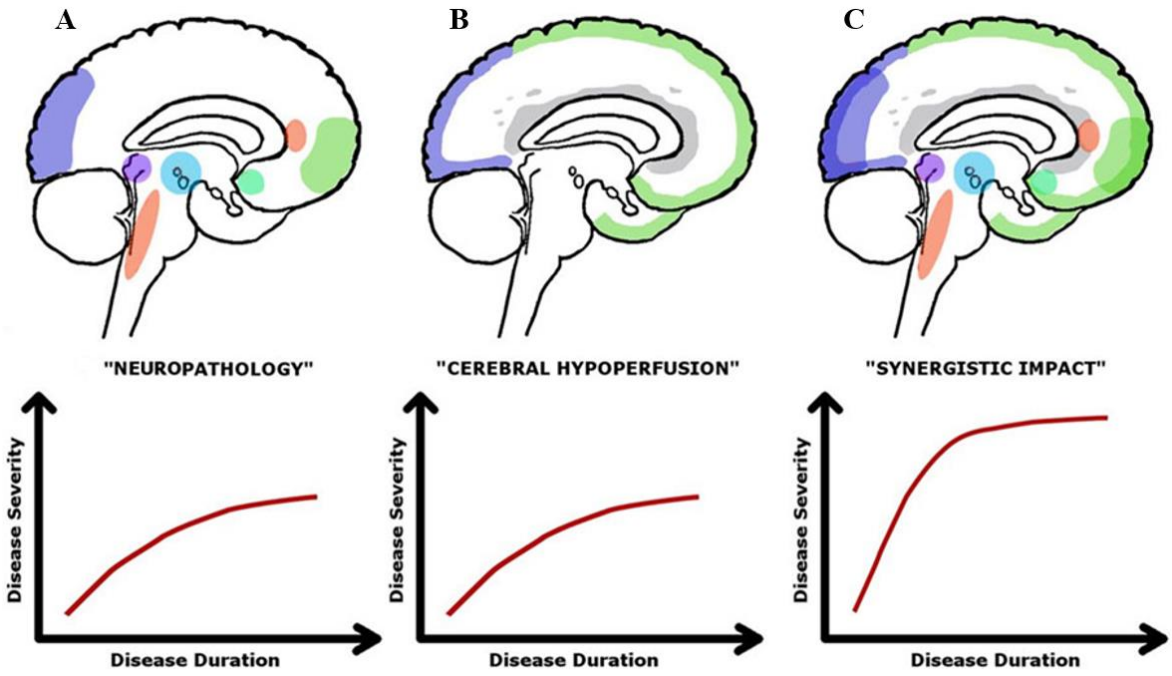


Figure 2.7: 'Synergistic Model' of Orthostatic Hypotension and the Brain.
Adapted from Udow et al, 2016[220]: (A) neuropathology causes Orthostatic Hypotension and cognitive impairment; (B) Orthostatic Hypotension contributes to cognitive impairment and to worsening of neuropathology (C) In combination these processes act synergistically to increase the rate and severity of cognitive decline

Summary:

The ANS is of fundamental importance to BP regulation. Short term (beat-to-beat) regulation of BP is facilitated by the arterial baroreflex. Baroreflex function decreases with age; BP instability increases with age. There may be sex-differences in cardiovascular autonomic function and short term BP regulation and how these change with age. Recurrent episodes of cerebral hypoperfusion may occur with OH and syncope. Cerebral autoregulation is poorly understood but does not act across a wide plateau of peripheral BP as classically described. Cerebral autoregulation may buffer acute episodes of high BP better than acute episodes of lower BP. Border zone regions of the brain may be particularly vulnerable to cerebral hypoperfusion. Cerebral hypoperfusion has been associated with greater affective symptoms and impaired cognition in later life. Overlapping brain regions are involved in the central regulation of cognition, affect and cardiovascular autonomic function. The brain regions involved in central autonomic function may also be vulnerable to ageing-related neurodegeneration. There may thus be bidirectional, and synergistic, relationships between brain health and peripheral BP instability.

2.3. Stress, Blood Pressure Instability and the Life Course

A life course perspective

Key point: ***In older adults, cardiovascular autonomic function is underpinned by biological processes and environmental/ behavioural exposures occurring earlier in life.***

The American Heart Association / American Stroke Association have emphasised the importance of the life course to maintaining optimal brain health in later life.[221] Life course epidemiology has been defined by Kuh as, *'the study of long term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life. The aim is to elucidate biological, behavioural, and psychosocial processes that operate across an individual's life course, or across generations, to influence the development of disease risk.'*[222]

A life course perspective emphasises that cardiovascular autonomic function in older adults is underpinned by biological processes and environmental / behavioural exposures occurring earlier in life. Exploring life course associations between exposure to childhood stressors, BP instability and later life outcomes may thus help to explain individual differences in brain health in older adults.

As previously discussed in Section 1.2 relationships between the brain and BP regulation may be bidirectional; indeed the brain has been described as the *'essential'* in the aetiology

of hypertension.[223] It is increasingly understood that exposure to psychological stress may alter BP regulation across the life course. Autonomic pathways have long been hypothesised to act as a mediator in such 'biological embedding' of psychological stress.[224] According to Chris Power and colleagues, '*Biological embedding, or embodiment, refers to the processes through which extrinsic factors experienced at different life stages "get under the skin," i.e., alter the body's biological functions or structures*'.[225] While according to McEwen[226] 'stress' may be defined as, *'a transactional process arising from real or perceived environmental demands that can be appraised as threatening or benign, depending on the availability of adaptive coping resources to an individual'*; and thus a 'stressor' is a *'salient environmental stimuli that [is] unpredictable, uncontrollable, conflictual, aversive, and thus labelled as psychologically stressful'*.[226] A key life course psychological stressor measured in the TILDA study is exposure to childhood adversity – specifically childhood trauma: childhood sexual and physical abuse prior to 18 years.

The impact of exposure to psychological stress on the ANS may vary across the life course. Exposure to psychological stress in childhood may be particularly important, as the physiological systems involved in the stress response develop across childhood. It has therefore been hypothesised that differential exposure to stress may alter maturation of the ANS and continue to underpin response to stress across adult life.[227] For example, the ability to self-regulate emotion in response to stress may be determined by the balance of the cardiovascular ANS.[228] In a population-based study of Dutch adolescents it was demonstrated that there was an interaction between lower HR (a marker of greater vagal tone) and exposure to stress, such that those teens with lower HR were less likely to suffer from affective symptoms following stress exposure.[229]

Hypertension and stress

Key point: **Psychological stress is a poorly understood risk factor for hypertension.**

Transient hypertension may occur in response to acute psychological or physiological stress (e.g. pain, exercise, and mental stress) and is adaptive in the short term.[150] Cumulatively however, prolonged and/or repeated BP elevations, even if transient, may contribute to hypertension via, for example, small vessel injury.[150]

Multiple studies have linked the acute cardiovascular response to stress with an increased risk of cardiovascular disease.[230] In laboratory settings, standardised stressors can be used to investigate between-individual differences in haemodynamic response; for example the magnitude of any BP increase ('stress reactivity') and the time taken for BP to recover to pre-stress levels ('stress recovery').[230] In a 2010 meta-analysis Chida and Steptoe reviewed 36 prospective cohort studies detailing 175 associations between cardiovascular responses to laboratory mental stress and future cardiovascular risk.[230] Greater stress reactivity at baseline was associated with incident hypertension, and both greater stress reactivity and poor stress recovery were observed in those with subsequent elevations in SBP or DBP. As noted by Lovallo, the effect sizes described for risk of hypertension were notable i.e. a 23% increased risk of future hypertension and were in line with those from the Framingham study - where an increase of 20 mmHg in resting systolic BP was associated with a 25% increase in carotid stenosis.[231]

Baroreflex and Stress

Key point: **Baroreflex activity may be altered by psychological stressors.**

During stressful situations there may be a concurrent elevation in BP and HR to meet increased metabolic demands.[232] According to Gianoros, *'A key mechanism by which the processing of psychological stressors evokes acute cardiovascular reactions (e.g., simultaneous BP and HR rises) involves the central nervous system suppression of the arterial baroreflex'*.[232] Reductions in parasympathetic tone and increases in sympathetic vascular resistance allow the baroreflex set-point to be exceeded, thus allowing HR and BP to rise simultaneously.[232]

Brain regions, including those thought to form part of the Central Autonomic Network, may be involved in the autonomic response to psychological stressors. For example, building on evidence from animal studies that had suggested higher brain regions were involved, Gianaros et al investigated the role of the barorflex in mediating the cardiovascular stress response.[232] In 97 adult volunteers Gianaros and colleagues measured beat-to-beat BP and HR during a standardised psychologically stressful task. During the task both BP and HR increased while the sensitivity of the baroreflex reduced. The participants then repeated the task during functional magnetic resonance neuroimaging. The measured reduction in BRS correlated with greater brain activity during stress in regions important for central autonomic and cardiovascular control including the cingulate cortex, insula, amygdala, and midbrain periaqueductal grey.[232]

Childhood exposure to stress and blood pressure

Key point: **Early life stressful experiences may affect blood pressure regulation into adult life.**

The experience of adversity in childhood is common. The Sexual Abuse and Violence in Ireland survey collected information on exposure to sexual abuse in childhood.[233] In this study the term sexual abuse was used to describe, 'sexual offences committed against a person aged under 17 years (the legal age for consent to sexual relations in Ireland)'; 20% of women reported they had experienced 'contact abuse'.[233] In the Growing Up in Ireland cohort, an epidemiological survey of Irish children, by age nine years approximately 5% of children had experienced two or more adverse events.[234]

While the psychological sequelae of childhood adversity are accepted it is increasingly understood that there may also be consequences for physical health, including poorer cardiovascular health.[235] The seminal 1998 US-based Adverse Childhood Events study collected information from 9508 participants (including over 2600 participants aged 65+) on exposure to potentially traumatic events in childhood via postal questionnaire. Questions captured information on 'childhood abuse' (psychological, physical, sexual) and exposure to 'household dysfunction' in childhood (e.g. parental mental illness, substance misuse, domestic violence).[236] Over 52% endorsed a history of at least one category of childhood traumatic event. Moreover associations were reported in a dose-response fashion with multiple physical health outcomes - including ischemic heart disease and stroke as ascertained via medical record interview.[236]

In the Irish context, TILDA has further demonstrated the potential lasting negative physiological consequences of childhood trauma in older adults. McCrory and colleagues reported a graded association between exposure to increasing childhood adversity and greater risk of poor physical health in later life - including associations with cardiovascular disease.[235] Notably, the physical health consequences of exposure to stressful events in childhood are not fully explained by negative health behaviours nor childhood socioeconomic position.[235]

With respect to BP, compelling evidence for an effect of childhood adversity on adult BP regulation comes from the 2015 study in the US-based Georgia Heart Study cohort (Figure 2.8). 394 participants were prospectively followed from childhood into early mid-life.[237] Over 5000 observations of BP were collected among individuals followed over 22 years. In participants who had experienced adverse life events before the age of 18 – including a history of sexual or physical abuse – a steeper increase in the trajectory of SBP and DBP into early mid-life was observed relative to those who were not exposed. The risk increased in a dose-response fashion, with a steeper BP trajectory observed in those with a higher number of adverse events.[237]

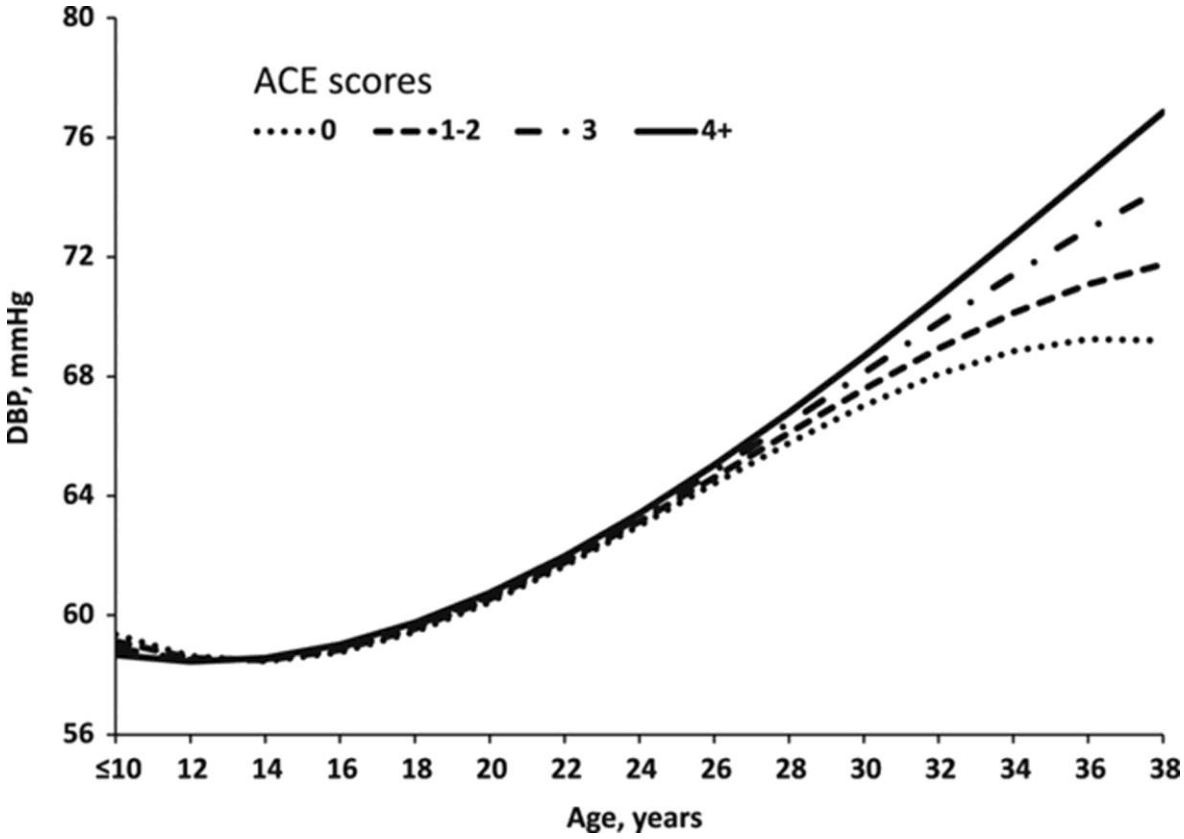


Figure 2.8: Childhood Adversity and Adult Blood Pressure.
From Shaoyong Su[237], estimated diastolic blood pressure (DBP) change with age (in the Georgia Stress and Heart Study) according to exposure to adverse childhood experiences ('ACEs'): 1 to 2 ACEs, 3 ACEs, and ≥4 ACEs

Blood pressure instability and stress

Key point: **Psychological stress may also precipitate lower blood pressure.**

Orthostatic Hypotension and Psychological Stress

In older adults, Feeney and colleagues reported an association between the cumulative number of stressful life events experienced, including a history of childhood adversity, and BP response to orthostasis in the TILDA sample.[238] A linear 'dose-response' relationship was reported between greater prior exposure to stressful life events and a larger systolic

orthostatic BP drop. These findings were in line with studies from younger adults suggesting an association between orthostatic BP response and exposure to stress. For example, Oddone[239] and colleagues recruited 222 volunteers and US veterans ranging in age from 18 to 39, of whom just under 50% (n=102), met criteria for Post-Traumatic Stress Disorder (PTSD) on diagnostic interview. During active stand those with a diagnosis of PTSD were over 4 times more likely to have excessive orthostatic BP drops even after adjustment for psychotropic medication and alcohol intake.[239]

A further small clinical study suggested that Cambodian refugees with orthostatic panic (a panic-attack triggered by orthostasis more common among Cambodian refugees possibly as a function of cultural beliefs) had an impaired systolic BP response to orthostasis.[240] Follow-on work from the same group reported that those who had undergone Cognitive Behavioural Therapy for symptoms of trauma-related PTSD had an improved BP response to orthostasis post-treatment. Interestingly lower parasympathetic activity and reduced baroreflex sensitivity have also been described in PTSD.[241]

Vasovagal Syncope and Psychological Stress

VVS predominantly affects young women, and a VVS tendency may persist through life.[242] Sheldon et al[243] compared 443 patients with a confirmed history of VVS and positive HUT (mean age 42 SD 18; 64% women) to 88 patients with a syncopal episode secondary to a cardiac cause (e.g. ventricular tachycardia, complete heart block). Those with a diagnosis of VVS were younger and had had a median of 8 syncopal episodes over a 10 year period prior to study entry. Those with a cardiac aetiology were older and reported a median of two episodes of syncope over one month at baseline. Age of onset of syncope <44 years (the

median age of syncope onset in the sample was during adolescence) was 81% sensitive and 81% specific for a diagnosis of VVS. The findings were robust to comparisons across the six countries in four continents from which the sample had been recruited. As Sheldon concluded a, "predisposition to vasovagal syncope starts early and lasts for decades… individuals may be predisposed to syncope for decades, perhaps as a lifelong phenotypic trait."[243]

Psychiatric disorder is a known long term effect of exposure to childhood trauma.[235] Psychiatric disorder is more common in those with VVS.[244,245] Skeldon[246] (unpublished; thesis) performed a systematic review of the literature on the frequency of psychiatric disorder in those <60 years but > 17years with a confirmed history of VVS or unexplained syncope i.e. as diagnosed on HUT. A total of nine studies met inclusion criteria and were subject to qualitative review. Although the quality of the studies varied and cross-study comparison was difficult due to varying methodologies used to assess the psychiatric disorder, studies consistently reported a high prevalence of psychiatric disorder (variously defined) in VVS. In one study 95% of participants (64/67) met criteria for at least one psychiatric diagnosis.[246]

Bracha has framed the vasovagal reaction in humans within the fight vs flight function of the ANS suggesting that 'trait faintness' is missing from the commonly understood spectrum of responses to stress/fear in humans and may thus have conferred an evolutionary advantage.[247] Indeed Porges and Alboni have drawn parallels between VVS in humans and the freezing/tonic immobility stress response in animals which likely evolved as a means to escape predation.[247,248] In his 'Polyvagal' theory Porges proposes social engagement as the

most adaptive and most recently evolved stress response in humans, which he suggests is promoted by high parasympathetic tone.[249] In situations of extreme stress however *excess* parasympathetic tone may also be observed, leading to profound bradycardia and/or hypotension which in humans may culminate in LOC.[250] This is mirrored by the fear/threat bradycardia in animals amongst whom however LOC is rare.[173] Humans are rendered more vulnerable to LOC by virtue of their bipedal stance and larger brain with a greater CBF requirement.[173] Following a review of the literature of vasovagal-type reactions in animals Alboni concluded nevertheless that VVS in humans and tonic-immobility in animals may share an evolutionary and physiological basis.[173]

A common presentation in specialist syncope clinics is the functional psychiatric disorder (conversion disorder) 'psychogenic pseudosyncope' (although this terminology has been debated).[251,252] There is a small literature suggesting that patients with a diagnosis of psychogenic pseudosyncope, and children with unexplained/recurrent syncope, may have been more likely to have history of childhood adversity.[253,254] A meta-analysis however investigating 'somatic' health outcomes of childhood sexual abuse specifically highlighted the absence of information on associations with syncope.[255]

Summary:

Life course exposures may be important in determining later life brain health outcomes. In older adults cardiovascular autonomic function is underpinned by biological processes and environmental / behavioural exposures occurring earlier in life. Psychological stress affects BP regulation and is a risk factor for hypertension, although the mechanisms are poorly understood. Altered baroreflex activity may be key in facilitating haemodynamic change during an acute psychological stressor. Exposure to stressful experiences in early life may affect BP regulation into adult life and alter development of the cardiovascular ANS. VVS may be underpinned by alterations in baroreflex function. Psychological stress may precipitate episodes of VVS. Vasovagal syncope is increasingly understood as a life course disorder, beginning in adolescence but potentially persisting into later life. Stress disorders (e.g. PTSD), and exposure to stressors in childhood, have been associated with BP instability including VVS and OH. Only limited information is available on the associations between exposure to childhood adversity and VVS.

3. LITERATURE REVIEW: Blood Pressure Instability and Brain Health in Older Adults

This chapter reviews prior studies investigating blood pressure instability (i.e. orthostatic hypotension, reduced baroreflex sensitivity and syncope) and brain health in older adults (i.e. cognitive function, affective symptoms (depression and anxiety) and structural neuroimaging outcomes). An electronic search was conducted using Pubmed and Google Scholar; last updated in January 2017. The search terms used included combinations of 'orthostatic hypotension', 'postural hypotension', 'baroreflex', 'baroreflex sensitivity', 'syncope', 'vasovagal syncope' AND 'subjective memory', 'white matter', 'grey matter', 'atrophy', 'brain', 'MCI', 'dementia', 'cognition', 'depression', 'anxiety' AND 'elderly', 'older adults'. Studies were restricted to those involving human subjects and preference was given to findings in community based healthy populations (e.g. investigations restricted to patients with a primary diagnosis of an alpha-synucleinopathy were not included). References from selected studies were hand searched and relevant articles retrieved. Data are summarised below in a narrative format.

3.1. Orthostatic Blood Pressure and Brain Health in Older Adults

3.1.1. Assessment and Definitions

Assessment of Orthostatic Blood Pressure

The ***active stand*** (Figure 3.1 (A)) is the simplest procedure to evaluate orthostatic BP: after a period of rest in the supine position (*usually* at least 5 minutes) the subject is then asked to stand quietly (*usually* for at least three minutes)[256]. BP and HR are measured in each position before and after standing.

Head-up Tilt Testing (HUT) (Figure 3.1(B)) allows assessment of orthostatic BP moving from supine-to-standing *passively*. HUT thus provides a more controlled measurement of orthostatic BP[256] i.e. removing variation in time-to-stand, assistance required while standing and also reducing lower limb muscular contraction to counteract venous pooling. The initial fall in BP characteristic of the haemodynamic response to active stand may be reduced or entirely absent when a subject is passively tilted to the upright position; thus the active stand may be a better representation of the quotidian orthostatic response.[257] HUT is most often used to evaluate BP response to prolonged orthostatic stress – as a diagnostic procedure for reflex syncope and delayed OH.[258]

Traditionally measurement of the BP response to orthostasis is made at pre-defined intervals before and after standing e.g. using a mercury sphygmomanometer or oscillometric device, and accompanied by measurement of the HR response to standing - measured either by

palpation or automated recording. The introduction of continuous orthostatic BP measurement has facilitated more detailed assessment of the changes in BP and HR which accompany orthostasis.[257] Plethysmography devices such as the Finapres as used in TILDA allow continuous non-invasive BP measurement i.e. BP is measured on a heartbeat to heartbeat basis.[257] BP measurements using finger arterial plethysmography have been validated against measurements collected via intra-arterial devices.[259] Investigators have applied various methods to summarize beat-to-beat data to derive clinically meaningful haemodynamic parameters. In TILDA, algorithms were applied to the raw signal using a five second averaging method, and summarised as mean SBP and DBP in 10-second bins over two minutes of standing.[184,260]

Measurement of the BP response from ***seated-to-standing*** (Figure 3.1(C)) has been used in some cohorts rather than supine-to-stand.[261] Evaluation of the BP response from the seated position may be a more pragmatic approach in an older frail population, particularly if assessment is taking place outside of the clinical setting e.g. in home assessments in TILDA.[262] There is debate however around the ability of the seated-to-stand manoeuvre to invoke a sufficient postural BP change to diagnose OH according to current consensus criteria, with recent reports suggesting low sensitivity for consensus OH.[263] It is of note however that TCD assessment of the change in middle cerebral artery blood flow with posture are usually performed from the seated-to-stand position, and are sufficient to induce change in CBF.[264]

Test	Baseline	Orthostasis	Advantage	Disadvantage
(A) Active Stand			Reflects usual physiological response to standing	May prolong time to achieve upright position
(B) Head up Tilt			Controlled conditions and timing provides support for people unable to stand	Does not replicate everyday situation. Equipment required. Not suitable for initial OH.
(C) Sit-to-stand			Reflects every day activity. Simple with little assistance required	Venous pooling in legs and pelvis during baseline

Figure 3.1: Assessment of Orthostatic Blood Pressure
Adapted from Frith 2015[256], 'Diagnosing orthostatic hypotension: a narrative review of the evidence'.

Definitions of abnormal Orthostatic Blood Pressure

Classical/ consensus OH

Defined according to the Committee of the American Autonomic Society and the American Academy of Neurology 1996 consensus criteria as: *a sustained drop of >=20mmHg in SBP/>=10 in DBP within three minutes of moving from the supine to the standing position.*[265]

Initial OH

Defined according to Weiling[266] as a transient orthostatic BP decrease within 15 s of standing: >=40 mmHg SBP and/or >=20 mmHg DBP accompanied by symptoms of cerebral hypoperfusion. Continuous orthostatic BP measures are required to capture the earliest orthostatic BP drops <30 seconds after standing.

Delayed OH

Defined as OH occurring after three minutes standing (as may occur in syndromes associated with autonomic failure). This will be missed by BP measurements ceasing at 3 minutes.[161]

Complexity in the interpretation of the orthostatic blood pressure response.

Consensus definition

The 1996 expert panel consensus statement defined OH as a *sustained* orthostatic BP change from supine within three minutes, however guidance is not provided regarding numerous parameters which may impact findings e.g. duration of supine rest, timing or number of seated and standing BP measures, measurement device, position of the BP measuring cuff relative to the heart at standing measure, support provided to the hand during standing measure, nor what is meant by 'sustained'. Moreover BP changes which occur with standing may vary according to the baseline (seated/supine) measurement e.g. the degree of hypertension. OH may be more common in the setting of supine hypertension.[267] Alternate cut-points for an abnormal orthostatic BP drop have been proposed, depending on the pre-stand measure e.g. lower in the setting of hypotension but higher in the setting of hypertension.[268]

Symptomatic OH

Clinically, OH may be symptomatic or asymptomatic.[269] Symptoms which accompany OH include transient dizziness and light-headedness, and are often referred to as 'Orthostatic Intolerance (OI)'. OI is generally attributed to cerebral hypoperfusion resulting from transient reductions in systemic BP induced by the orthostatic manoeuvre.[270] There may be considerable between-individual variability in the expression of symptoms and the degree of BP drop required to induce symptoms.[271] OI may occur in the absence of any detectable orthostatic BP change. Traditionally, treatment of OH has been based on the presence or otherwise of symptoms, and some OH syndromes (e.g. initial OH) require that a BP drop is

accompanied by symptoms for diagnosis.[266] Some reports describe associations between OH and clinical outcomes (e.g. depression) only in the presence of symptomatic OH[272], however the reliability of depending on symptoms to drive investigation/treatment has been questioned[269], including among patients with dementia who may be less able to report symptoms.[273]

Orthostatic Blood Pressure Recovery (or 'Stabilisation')

TILDA has provided the first population-representative data measuring orthostatic BP using continuous best-to-beat methods and demonstrated that a reduction in BP from supine levels upon standing is universal in adults aged 50+.[184] The magnitude of this drop and the time taken for BP to return to supine BP levels varies; BP takes longer to return to supine levels with increasing age.[184] Finucane and O'Connell et al. describe the return of BP to pre-standing levels as time to 'stabilisation'[184]; this has also been described as BP '*recovery*'.[274] 'Recovery' is a term often used to denote the return to baseline levels of a peripherally measured biological marker after a stressor - be that physiological (e.g. HR recovery after exercise stress testing[275]) or psychological (e.g. BP recovery after a public speaking task[276]). Recovery/stabilisation indices of the haemodynamic response to orthostatic stress thus provide an index of the relative change i.e. the change in standing BP is *conditioned* on supine BP.

Allan et al[277] examined continuous orthostatic BP in older adults with dementia and defined 'recovery' as the return of the standing BP to within one Standard Deviation above or below the supine reading. Elmsthal et al[278] accounted for baseline orthostatic BP in associations with future cognitive status (CS) by calculating the orthostatic BP 'quotient' i.e. dividing the

standing measure by the supine BP measure. Romero et al[274] examined associations between continuous orthostatic BP measures and falls and frailty in a convenience sample of 442 community-dwelling older adults. Romero described the relative change in orthostatic BP from supine to standing, and the subsequent return of BP to supine levels as 'percentage recovery', whereby the standing measurement at each time point after stand is expressed as a percentage of the supine measure.[274] Lagro et al[279] subsequently calculated percentage orthostatic BP recovery when investigating associations between continuous orthostatic BP measures and mortality. The same metric has since been applied in investigations of associations between orthostatic BP and cognition in older adults by Hayakawa[280] and Feeney[281] in both clinical and epidemiological settings.

Orthostatic Hypertension

A proportion of the population may also experience an increase in standing orthostatic BP relative to pre-stand levels. When standing BP is significantly elevated above the supine measure – usually defined as >=20mmHg above pre-stand levels – this is referred to as orthostatic hypertension (OHT), although no formal (consensus) definition of OHT is agreed.[282] OHT has been described as an 'unchartered' cardiovascular risk marker given associations with hypertension, cognitive impairment and stroke.[282] An investigation in the middle-aged Atherosclerosis Risk in Communities study reported that both OH and OHT were associated with increased risk of lacunar stroke.[283,284]

Orthostatic Blood Pressure Variability

Some investigators have argued that rather than absolute or relative change in orthostatic BP, overall patterns (i.e. markers of within-person variability) in orthostatic BP may

determine end-organ outcomes.[285] In a convenience sample of community-dwelling older adults Romero et al[274] used cluster analysis to summarise orthostatic BP patterns measured using beat-to-beat devices and described three distinct patterns: 'small-drop, fast over-recovery'; 'medium drop, slow recovery'; and 'large drop, non-recovery'. These clusters were later echoed in findings by Cooke et al. in a clinical sample attending a falls clinic.[271]

Drawing parallels with the extensive literature on short (e.g. 24 hour ambulatory BP) and long term (e.g. visit-to-visit BP) variability and increased risks of end organ damage, NíBhuachalla[286] investigated patterns of orthostatic BP response across two minutes of continuous recording in the TILDA sample. The authors described a phenotype of orthostatic BP variability where both OHT and OH occur in 25% of participants. NíBhuachalla and colleagues subsequently related this orthostatic BP variability to poorer visual acuity within the TILDA cohort.[286,287] More recently, the Rotterdam group reported that *within*-person variability at baseline assessment increased dementia risk (i.e. greater variability around the mean of repeated systolic orthostatic BP measures taken during a single active stand procedure).[288]

3.1.2. Orthostatic Blood Pressure and Cognition in Older Adults

Prospective Studies

An increasing number of large epidemiological cohorts have assessed prospective associations between orthostatic BP and cognition in older adults with the duration of follow-up ranging from 1-2 years to a median of 15 years (reviewed below in Table 3.1). The majority of studies have investigated consensus OH as the primary predictor of interest, have measured orthostatic BP at a single time point, and used traditional BP measurement techniques.

The most comprehensive study to date investigating the association between orthostatic BP and cognition used data from the population-based Rotterdam longitudinal cohort.[288] 6204 participants in the Dutch general population aged 55+ (mean age 68.5 ± 8.6) at baseline, were followed over a median of 15.3 years. The investigators found that those participants who met criteria for consensus OH on active stand had an increased risk of dementia diagnosis during follow-up (1,176 received a diagnosis of dementia). Multiple measurements of BP during active stand (once in the supine position and three in the standing position) allowed calculation of the coefficient of variance – a measure of the within-person variability in systolic orthostatic BP (defined as the ratio of the SD to the mean of all measurements i.e. measurements in supine and upright position combined). Greater within-individual variability in systolic orthostatic BP also increased the risk of dementia. No association was found with OHT. Results were similar for all-cause dementia and a subgroup analysis investigating AD.[288] Dementia case ascertainment was comprehensive

within the cohort: by a three-step screening protocol at each follow-up visit with subsequent consensus panel adjudication of CS, and additionally by continuous monitoring of the cohort using computerised medical-record linkage. MCI, however, was not investigated.

Only one prospective population-based study has investigated associations between orthostatic BP and preclinical/prodromal dementia i.e. SMI or MCI. In a Swedish population-based sample Elmsthal et al[278] reported that those with OI, irrespective of orthostatic BP change, were more likely to report subjective memory deficit even in the absence of objective cognitive impairment i.e. SMI. The investigators also reported an association between baseline OH and MCI, although objective cognitive assessment within the cohort was limited to the MMSE.[278]

Studies using beat-to-beat measurements

An increasing number of studies have additionally incorporated beat-to-beat measurements of orthostatic BP in investigations of associations with cognition in older adults. Early clinical studies include that by Ballard et al, which reported that consensus OH was a common finding in those with AD and Lewy Body Dementia when measured using a beat-to-beat device.[289] In 2007, a follow-up study from the same group reported that the maximum drop in systolic orthostatic BP within 30 seconds of standing was greater in those with dementia relative to controls i.e. AD: *45.4 mmHg*; VaD: *40.9 mmHg*; Parkinson's Dementia: *48.2 mmHg*; Lewy Body Dementia: *43.2 mmHg vs* controls: *26.6 mmHg.*[277] The median time to recovery (defined as orthostatic BP within one SD of the baseline BP) was

16 seconds (IQR 12-19) in controls, contrasting with 20 seconds (IQR 12-70) in patients with AD, and 23 seconds (IQR 16-73) in those with Parkinson's Dementia.[277]

In a clinical cohort of patients with MCI attending a memory clinic, Collins et al[290] reported larger drops in systolic orthostatic BP in patients with MCI relative to controls (mean 47mmHg vs 38 mmHg; p=0.007). Hayakawa et al[280] subsequently followed this clinical sample longitudinally (n=150 with MCI; n=75 controls), reporting that those with a slower time to recovery (defined as a SBP deficit greater than 30% at 30 seconds after standing) were twice as likely to convert to dementia (Hazard Ratio = 2.77 (1.02–7.50)) over 3years of follow-up relative to those in whom SBP had recovered closer to supine levels.

To date, two epidemiological investigations have used beat-to-beat BP measurements to investigate associations between orthostatic BP and cognitive function – each based in the TILDA study.[164,281] Frewen et al reported no overall association between OH and cognitive performance, but participants who had both supine hypertension and OH meeting consensus criteria within the first thirty seconds of standing, scored lower on screening tests of global cognition and executive function.[164] Longitudinally, after two years of follow-up in the same cohort, Feeney reported no statistically significant association with change in cognitive function when applying both consensus OH criteria and 'percentage recovery' parameters to the orthostatic BP data.[281]

Studies describing U-shaped Associations

Several studies have reported that there may be a U-shaped association between orthostatic BP and cognitive function among older adults. In a large prospective Italian based study Curreri et al[291] reported that baseline OHT was associated with lower MMSE scores (a decline of >=3 points on MMSE) after 4-years of follow-up. However, when investigating orthostatic BP according to quintiles of orthostatic BP change, both higher and lower systolic/diastolic orthostatic BP were associated with declining scores on MMSE. This was in line with prior findings of a U-shaped cross-sectional relationship in Japanese older adults, however Kario investigated a clinical cohort all of whom had a diagnosis of hypertension. It is of note however that no relationship was found with OHT and future dementia diagnosis in the Rotterdam cohort.

Table 3.1: Prospective Population-Based Studies Investigating Orthostatic Blood Pressure and Cognitive Outcomes									
Author, year	**Setting**	**Sample Characteristics**	**Orthostatic Test**		**Timing of OH measurements**	**OBP parameter investigated**	**Follow-up**	**Outcomes**	**Finding**
Viramo[292], 1999	Oulu, Northern Finland, All persons in locality born before 1920 (Study began in 1991)	N=907 cross-sectional (63.8% female) N=651 longitudinal (65.7% female)	Supine 5min	Stand 3 min	1 min 3 min	cOH @ 1 min and/or 3 min	2.5 years (1994)	MMSE at baseline and at follow-up *(*shorterned 0-25 with exclusion of calculation and spelling tasks)*	***No longitudinal association*** *Cross-sectional association between cOH and lower MMSE*

Table 3.1: Prospective Population-Based Studies Investigating Orthostatic Blood Pressure and Cognitive Outcomes									
Author, year	**Setting**	**Sample Characteristics**	**Orthostatic Test**		**Timing of OH measurements**	**OBP parameter investigated**	**Follow-up**	**Outcomes**	**Finding**
Yap[293], 2008	Chinese older adults, Singapore longitudinal studies cohort (Baseline 2004/5)	N=2321, Age 65.5y +/- 7.4 65.8% female N=1347 followed up 1-2 y *(those without baseline cognitive impairment only)*	Supine *to seated* 10 mins	Stand 3 mins	BP was measured for each of four different positions *(supine, sitting,* ***immediate standing****, and standing),* up to three times **at 3-min** intervals, using a standard mercury sphygmomanometer	cOH @ 3 min	1-2 years (2005/6)	***Cognitive Impairment*** =MMSE<24 ***Cognitive Decline***= MMSE decline >=1	***No longitudinal association*** *Cross-sectional* analysis stratified according to baseline SBP/DBP status: *Hypotensive* (SBP <120 mm Hg or DBP <70 mm Hg) OH increased risk of cognitive impairment *but* *Hypertensive* (SBP ≥140 mm Hg or DBP ≥90 mm Hg) OH reduced risk *Normotensive* (SBP 120–139 mm Hg and DBP 70–89 mm Hg) no relationship

Table 3.1: Prospective Population-Based Studies Investigating Orthostatic Blood Pressure and Cognitive Outcomes									
Author, year	**Setting**	**Sample Characteristics**	**Orthostatic Test**		**Timing of OH measurements**	**OBP parameter investigated**	**Follow-up**	**Outcomes**	**Finding**
Rose[294], 2009	ARIC, USA, 4 US communities	N=12,702 Age: 45-64 y at baseline Biracial cohort: African American and white	Supine 20 mins Every 30s for 2 min (2–5 measures ; 90% >=4)	Stand 2 min Every 30s for 2 min (2–5 measures ; 91% >=4)	Avg standing – average supine (excluding first standing measure) Standing BP measured every 30s for 2 min	cOH	6 years (Yr 2 1990-1992 Yr 4 1996-1999)	Cognitive scores at visit 2 **Change** Between 2nd and 4th year visits *(Cognitive Screening Tests: Delayed Word Recall, Digit Symbol Substitution test(DSST), Word fluency test(WFT))*	***Longitudinal association*** ***But did not survive adjustment for demographics, established CHD*** Age Adjusted relationship: At 2 years: lower DSST & WFT At 6 years: Decline in DSST

Elmstahl[27][8], 2014	Swedish Good Aging in Skåne study (GÅS-SNAC), randomly invited community-dwelling older adults; Baseline 2001-04	N=1480 Age:60-93y Sex=56% female	Supine 10 min	Stand 10 min	BP Immediately, 1, 3, 5, and 10 minutes of standing	cOH and OI *orthostatic BP quotient*	6years after baseline; 82% attended follow-up 2007/10	**MCI** defined as cognitive complaint + objective cognitive decline in the absence of dementia **Dementia** defined according to the DSM-IV based on clinical examination, medi-cal records, and proxy information **Cognitive complaint** self-reported scale **Cognitive decline** was defined as a score of 0 or 1 on the MMSE three-word later recall test. **Subjective memory loss** was defined as a score of 28 on the Crook scale in the **absence** of objective memory loss, dementia, or an MMSE <24. **Objective memory loss** was defined as a score of 0 or 1 on the MMSE three-word later recall test in the absence of subjective memory loss, dementia, or an MMSE <24	***Longitudinal association*** *(NB associations adjusted for age only)* OI associated with MCI: OR 1.84 (1.20–2.80) cOH associated with dementia: OR=2.18(1.24-3.84) OI associated with subjective memory impairment: OR =1.55 [95% CI: 1.07–2.25]).

Table 3.1: Prospective Population-Based Studies Investigating Orthostatic Blood Pressure and Cognitive Outcomes									
Author, year	**Setting**	**Sample Characteristics**	**Orthostatic Test**		**Timing of OH measurements**	**OBP parameter investigated**	**Follow-up**	**Outcomes**	**Finding**
Feeney[281], 2016	Population-based longitudinal cohort of ageing TILDA Baseline 2009-11	N=3417 Age 50 + Mean age: 65.4y (SD9.1) 57.8% female	Supine 10 min	Stand 120s	<u>*Beat-to-beat OBP*</u> measurements; estimated at 10 second intervals and supine measure as 60 seconds average prior to stand	'*OBP recovery'* at 40 seconds after standing i.e. cOH applied at 40 seconds post stand	2 years	MMSE; Verbal fluency 10-word recall task-immediate and delayed recall	***No longitudinal association*** *after considering effect of other co-variates on change*
Curreri[291], 2016	Progetto Venetto Anziani ('Pro.V.A.') Population-based cohort (two towns in Northern Italy) Baseline 1995-97	N= 1421 836 female Age: 65y+ (mean 71.4y +/- 5.2)	Supine 5 min (x3 in the right arm with 30 sec intervals to estimate supine measure)	Stand 1 min 3 min	1 min 3 min	cOH (at 1 min and/*or* 3 min) OHTN (Increase in SBP >20mmHg) Quintiles Mean OBP at 1 & 3 mins using predefined cut-point (mmHg): SBP: -11, -3, +2, +9 DBP: -1, +2, +6, +10	4 years (Mean 4.4 years)	MMSE Crude scores normalized to the population (age and formal education) **Cognitive impairment (CI):** <=24 MMSE **Cognitive decline (CD):** decrease >= 3points on MMSE	***Longitudinal association*** *OHT associated with CD at follow-up:* *OR:1.5 (CI95% 1.26-1.78)* *Using quintiles of orthostatic BP values <u>both decreases and increases</u> in systolic and diastolic BP raised the risk of CD, but not of CI*

Table 3.1: Prospective Population-Based Studies Investigating Orthostatic Blood Pressure and Cognitive Outcomes

Author, year	Setting	Sample Characteristics	Orthostatic Test		Timing of OH measurements	OBP parameter investigated	Follow-up	Outcomes	Finding
Wolters[288], 2016	Rotterdam Prospective cohort study, Baseline 1989, 1993	N=6204 Age: 68.5+/-8.6y Sex:59.7% female	Supine: 5 mins	Stand 3 mins	1 min; 2mins & 3 min Information on symptoms collected	cOH; SBP variability; (co-efficient of variability); Orthostatic HR; Delta SBP/DBP	25 years (Median follow-up 15.3 years)	Dementia: VaD AD	***Longitudinal association*** *cOH & orthostatic SBP variability predict Dementia modelled using COX proportional hazards* *Linear effect with SBP variability including after exclusion of those with severe rises in OBP when standing*

cOH=Consensus Orthostatic Hypotension; OHT=Orthostatic Hypertension; OI=Orthostatic Intolerance; OBP=Orthostatic Blood Pressue; VaD=Vascular Dementia; AD=Alzheimer's Dementia; MMSE=Mini Mental State Examination; DWR=Delayed Word Recall; DSST=Digit Symbol Substitution Test, WFT=Word Fluency Test; CD=Cognitive Decline; CI=Cognitive Impairment; SBP=Systolic Blood Pressure

3.1.3. Orthostatic Blood Pressure and Affective Symptoms in Older Adults

Associations between lower BP, including orthostatic BP, and depression in older adults have recently been subject to systematic review.[84] Three small cross-sectional studies from Newcastle University have reported that systolic orthostatic BP is lower in older adults with Major Depressive Disorder relative to controls when measured using beat-to-beat devices – the most comprehensive of these additionally incorporated MRI neuroimaging and is discussed below (Section 2.1.4).[84,295]

O'Regan et al[272] extended such findings to the population setting using a seated-to-stand protocol; orthostatic BP was assessed intermittently using an oscillometric device with a single standing BP measure at one minute. O'Regan reported an association between lower sit-to-stand BP and greater depressive symptoms in TILDA.[272] Of note however, these associations were restricted to those with symptomatic OH – findings which the authors suggest may provide support for Taylors[76] cerebral hypoperfusion hypothesis of late life depression.

The literature search did not identify studies investigating associations between orthostatic BP and anxiety disorders in older adults. As previously noted in Section 1.3 however, prior findings in TILDA point to associations between exposure to psychosocial stressors and lower orthostatic BP in later life.[238] Feeney et al reported that greater self-reported stressful life events, including a history of childhood trauma, were associated with a slower recovery of systolic orthostatic BP.[238] Exposure to traumatic events may be associated with

development of the anxiety disorder Post-Traumatic Stress Disorder – which has in turn been associated with OH and OI (although such findings were reported in younger samples).[239,296]

3.1.4. Orthostatic Blood Pressure and Structural Neuroimaging in Older Adults

Studies which have investigated associations between orthostatic BP and structural neuroimaging (i.e. CT or MRI) are summarised in Table 3.2. Investigations completed in patients with a primary diagnosis of an alpha-synucleinopathy are not included (but have been reviewed elswhwere).[220] Firstly studies based in clinical samples are reviewed and then population-based samples.

Clinical Studies

Dementia

In a retrospective case note review of 204 patients, Raiha[297] et al reported that a history of OH was more common among patients with WMH on Computed Tomography scanning. Ballard et al also reported that in a clinical sample of patients with dementia, WMH were more common in those with a systolic orthostatic BP decrease in response to Carotid Sinus Massage (CSM) or Active Stand, however most participants (N=29/30) had a larger fall in response to CSM rather than Active Stand.[289] In a more recent cross-sectional clinical study of patients with 'mild dementia', Soennesyn et al reported no relationship between consensus OH and WMH on MRI.[298] Several participants however underwent a seated-to-stand procedure rather than supine-to-stand, and a period of rest prior to measurement of the standing BP was not required.[298]

Hypertension

Japanese investigators have reported cross-sectional U-shaped associations between orthostatic BP and visual ratings of cerebral small vessel disease on MRI brain in three clinical studies in older participants with hypertension.[299–301] In each study, participants with exaggerated increases or decreases in orthostatic BP (variously defined) were compared to those participants with an intermediate or 'normal' postural response. Matsubayashi et al[301] reported that lacunes and periventricular WMH on 0.5T MRI were more common in participants with either OHT (N=15) or OH (N=15) compared to those with an 'intermediate' orthostatic BP response (N=30). Kario[299], from the same group, extended these finding to 241 participants in whom hypertension had been identified on 24-hour ambulatory monitoring; participants underwent HUT to assess orthostatic BP and 1.5T brain MRI. Silent cerebral infracts (defined as lesions >3mm-20mm) were more common in those participants with either OHT or OH – a finding mirrored when systolic orthostatic BP response was summarised into quintiles. Moreover, WMH were more common in those with OHT relative to those with either OH or a 'normal' postural systolic orthostatic BP change. Eguchi[300] reported similar findings in the third study, although cut-points for OHT and OH differed from prior studies i.e. an elevation in systolic orthostatic BP of >=10mmHg was used to defined OHT, and OH was defined as a decrease of systolic orthostatic BP >=10mmHg.[300]

Late life Depression

Colloby et al[295] investigated associations between orthostatic BP as measured with beat-to-beat technology and changes on brain MRI in patients with Major Depressive Disorder (MDD), relative to age and sex matched controls (N=60; 30 patients and 30 controls). WMH and regional GM volumes were estimated according to a fully automated quantitative

method. In the group with MDD, WMH volume in parietal and temporal lobes was associated with the magnitude of change systolic orthostatic BP, but in the healthy controls there was no correlation. There were no associations between orthostatic BP and regional GM volumes of subcortical structures chosen a priori (based on potential relationships to depression in older adults).[295] The authors acknowledged differences between the groups with respect to the burden of antidepressant medication but argued that treatment with TCA was an exclusion criteria, and therefore ADT were unlikely to affect their findings as TCA are the ADT most likely to cause OH.[295] Interestingly, an association between TCA and WMH volume had previously been reported in the Cardiovascular Health Study.[302] This association was attenuated after adjustment for OH in analyses, suggesting that the impact of TCA may have been mediated via OH i.e. as a side-effect of ADT (although the authors cautioned that this may also have been due to the drop in sample size when OH was added to models).[302]

Epidemiological Studies

The Cardiovascular Health Study (CHS) is a longitudinal study of 5201 adults aged 65+ randomly selected from four communities in the United States, 62% of whom also underwent MRI neuroimaging.[16] In the CHS, orthostatic BP was assessed using a mercury sphygmomanometer. Participants lay in the supine position for twenty minutes after which a supine BP reading was recorded; a subsequent BP measurement was recorded after three minutes in the standing position.[303] The prevalence of asymptomatic OH was 16.2% in the total population which increased to 18.2% when symptomatic OH (defined as ‘"dizziness" or "lightheadedness" upon questioning such that the procedure was aborted’) was included.[303] In cross-sectional analysis of 2981 participants, consensus OH was associated with a higher grade of white matter lesions[16], however this relationship although did not

survive correction for 'clinically silent stroke' in models. The authors suggested that the relationship may thus have been mediated by known associations between OH and stroke and/or stroke – as both white matter change and stroke may share similar pathophysiology.[16]

In a prospective, follow-up study of the same cohort, the presence of OH at time of initial MRI was not related to progression of white matter lesions grade on repeat MRI brain 5 years later[304], nor in a separate report to incident infarction.[305] Although in bivariate analysis OI was related to progression of white matter change, this association did not survive multivariate adjustment.[304] The CHS studies however were limited by use of visual rating scales to assess brain MRI, varying MRI magnet strength (0.35 – 1.5 T) across four centres, and measurement of orthostatic BP at a single time point.[16,304,305]

The Honolulu-Asia Study[306] followed a cohort of 575 Japanese-American men from mid-life for approximately three decades: from 1965-1974 (age range 45-64yrs) until 1994-1996 (mean age 82 years). Orthostatic BP was measured at examination 4 (1991-1993) prior to a 1.5 T MRI brain at examination 3-5 years later. MRI outcomes were measured using the same protocol as the CHS, and scans were obtained at a single centre. In addition to WML grade, ventricular enlargement was also rated using a semi-quantitative (visually-rated) protocol. OH was not related to any of the brain MRI endpoints.[306] Notable limitations to this study include the male only design, ethnic homogeneity and low-resolution scanning.

The National Heart, Lung, and Blood Institute Twin Study (NHLBI)[307] was a large epidemiological sample which followed 418 twin males; it reported a cross-sectional association between a greater absolute change in systolic BP (measures from supine-to-

standing) and a larger volume of abnormal white matter signal.[307] This study however was also limited by a male-only design and low-resolution scanning. Associations with regional GM change were not investigated.

Table 3.2: Orthostatic Blood Pressure and Structural Neuroimaging									
Author, year	**Setting**	**Characteristics**	**Orthostatic Test**		**Timing/No of measurements**	**OBP parameter investigated**	**Follow-up**	**Outcome ix**	**Finding**
Longstreth, 1996[16]	Cardiovascular Health Study Random sample four medicare lists in the US USA baseline 1989/90	N=3301 Age 65+ 62 % had an MRI	Supine 20 min	Stand 3 min	**One** measure at 3mins	cOH OI	Cross-sectional MRI in 5 & 6 (except N=303 @ yr4) OBP at year 5 or baseline	**Brain MRI** 1.5 T (or 0.35 T) 1. Visual Rating 1-8 of total volume of white matter signal abnormalities	***Cross-sectional association*** OH (no=0; yes=1) associated with increased white matter grade - survived multiple variable adjustment when stroke not included in the model
Matsubayashi, 1997[301]	Community-dwelling sample those with dementia and neurological disease excluded	N=60 with neuroimaging Age 75+	Supine 5 min	Stand 2 min	1 and 2 mins after standing (**mean of two measurements of BP in each position**)	Continuous delta SBP divided into: OH <=20mmHg OHT>=20mmHg NormoT: 20<dSBP<20 mmHg N=15 OH N=15 OHT N=30 NormoT	Cross-sectional	**Brain MRI** 0.5 T 1. Number of Lacunes 2. Four grades of PVH WML's	***Cross-sectional association*** OHT and OH associated with greater number of Lacunes <0.001 ANOVA and Periventricular white matter hyperintensities <0.01 on Chi ^{2}

Table 3.2: Orthostatic Blood Pressure and Structural Neuroimaging									
Author, year	**Setting**	**Characteristics**	**Orthostatic Test**		**Timing/No of measurements**	**OBP parameter investigated**	**Follow-up**	**Outcome ix**	**Finding**
De Carli ,1999[307]	Longitudinal Population-based Observational Cohort Study, National Heart, Lung, and Blood Institute Twin Study, USA baseline 1969–1972. 47.2+/-3 years at baseline	N=414 All men 72.5 +/- 2.9 years at final follow-up	Supine Not reported	Stand 3-5 mins	**One** measure after 3 to five minutes of standing	Delta SBP and DBP	Cross sectional OH and BRAIN MRI measured at fourth examination only 1995-1997	**Brain MRI** 1.5 T 1. Total brain volume 2. Volume of abnormal white matter signal (WMHI) 3. Volume of stroke	***Cross-sectional association*** Magnitude of orthostatic SBP change was significantly associated with WMHI volume in multivariate adjusted regression models

Table 3.2: Orthostatic Blood Pressure and Structural Neuroimaging									
Author, year	**Setting**	**Characteristics**	**Orthostatic Test**		**Timing/No of measurements**	**OBP parameter investigated**	**Follow-up**	**Outcome ix**	**Finding**
Longstreth, 2002[305]	Cardiovascular Health Study Random sample four medicare lists in the US USA baseline 1989/90	N=1433 participants underwent 2 MRI scans separated by 5 years *and had no infarcts on initial MRI.* Age 65 + with two scans ~15% black ~59.5 % women	Supine 20 min	Stand 3 min	**One** measure at 3 min	Delta SBP Delta DBP Dizziness on standing cOH	Prospective follow-up MRI 5 years later	**Brain MRI** **1.5 T** 1. Incident infarct on MRI *(all infarcts ≥3 mm; Lacunes were defined as subcortical infarcts 3 to 20 mm in size)*	***No association*** with incident infarct 65+

Table 3.2: Orthostatic Blood Pressure and Structural Neuroimaging									
Author, year	**Setting**	**Characteristics**	**Orthostatic Test**		**Timing/No of measurements**	**OBP parameter investigated**	**Follow-up**	**Outcome ix**	**Finding**
Havlik, 2002[306]	Japanese-American men in Hawaii long-term study of cardiovascular disease, baseline 1965 to 1974.	N=575 men Age 82 yrs 1994-1996	Supine 15 min	Stand 3 min	**One** measure at 3 min	cOH @ 1991 to 1993 (examination 4)	*Prospective :* Brain MRI @ 5th examination 1994 to 1996	**Brain MRI** 1.5T *1.* WML grade: end-point for was set at grades 5 to 9 *(mild or greater confluence of WMLs in the periventricular or broader regions)* 2. Atrophy set at grades 6 to 9 *(borderline or definite increase in ventricular volume)*	***No association*** No association with **either MRI** end point

Table 3.2: Orthostatic Blood Pressure and Structural Neuroimaging									
Author, year	**Setting**	**Characteristics**	**Orthostatic Test**		**Timing/No of measurements**	**OBP parameter investigated**	**Follow-up**	**Outcome ix**	**Finding**
Kario, 2002[299]	Elderly hypertensives; outpatient's HTN based on 24 ambulatory monitoring April 1996-August 2000 no Anti-HTN meds x 14 days prior to study	N=241 Age 60+ ~40%male *(Patients with symptomatic OHYPO with SBP decrease >=30 mm Hg 1 min after active standing were excluded)*	HUT Supine 10 min	Passive stand 70° 15 min	Average of BP measured at 6-10 mins stand *minus* average BP supine 1- 5 min **(BP measured at one minute intervals)**	Continuous delta SBP divided into: OH <=20mmHg OHT>=20mmHg NormoT: 20<dSBP<20 mmHg *N=26 OH* *N=23 OHT* *N=192 NormoT* Quintiles of SBP change	*Cross-sectional*	**Brain MRI** 1.5 T 1. Silent Cerebral Infarct *Multiple SCIs were defined as >=3 infarcts/person* 2. Advanced Deep white matter lesions: *hyperintense multiple punctate lesions or such lesions at the early confluent stage or those that had reached confluency*	***Cross-sectional association*** Silent cerebral infarcts > OHTN (3.4/person) & OH (2.7/person) vs. NormoT=1.4/person Advanced DWM OHTN > NormoT & OH group Quintiles OBP: U-shaped relationship for SCI and multiple SCIs (after adjusting for demographics and ambulatory BP)

Table 3.2: Orthostatic Blood Pressure and Structural Neuroimaging									
Author, year	**Setting**	**Characteristics**	**Orthostatic Test**		**Timing/No of measurements**	**OBP parameter investigated**	**Follow-up**	**Outcome ix**	**Finding**
Eguchi, 2004[300]	Older patients with HTN, Japan 1996-7 Hypertensive patients age 40+ *No patient had taken any antihypertensive medication for at least 14 days before the HUT and ambulatory BP monitoring (ABPM) study.*	N=86 outpatients (mean age, 67.6 years; range, 48–86 years) N=59 dx HTN N=27 normotensive. Brain MRI 41 of the 59 hypertensives (69%) and in 13 of the 27 normotensives (48%)	HUT Supine 10 min	70 degree tilt 15 mins	BP at **1 min intervals** Average value over the 2 to 9 min during tilting (8 points) *minus* average in the supine position during the 1 to 5 min just before the tilting (5 points).	Hypertensives spilt into three groups: OHT=increase >=10mmHg OH= decrease >=10mmHg Normal Postural BP change & Normotension group	*Cross-sectional*	Brain MRI 0.5T 1. Silent cerebral infarct (SCI) was defined exclusively as a low signal intensity area (≥ 3 mm-15mm) 2. Multiple SCIs ≥ 3 3. Periventricular hyperintensity (PVH) 4. Advanced PVH was defined as a PVH grade ≥ 3, as described previously	***Cross-sectional association*** Total Number SCI/ Any SCI /Multiple SCIs highest in the OHT group compared to the normotension group OH more likely multiple SCU compared to normotn No statistically sig difference in PVH

Table 3.2: Orthostatic Blood Pressure and Structural Neuroimaging									
Author, year	**Setting**	**Characteristics**	**Orthostatic Test**		**Timing/No of measurements**	**OBP parameter investigated**	**Follow-up**	**Outcome ix**	**Finding**
Longstreth, 2005[304]	Cardiovascular Health Study Random sample four medicare lists in the US USA baseline 1989/90	N=1919 Age 74; Men ~ 40%	Supine 20 min	Stand 3 min	One measure at 3 min	Delta SBP Delta DBP OI cOH	*Prospective* (Mean 5 years)	**Brain MRI** 1.5T 1. Worsening white matter grade (0, 1grade, >=2 grades)	***No association*** [OI associated with Worsening WM grade: None(1.7%) *vs* 1 grade (2.7%) *vs* >= 2 grades (5.1%) *p=0.035* *but* did not survive multivariable adjustment] No association with delta SBP or DBP, cOH

Table 3.2: Orthostatic Blood Pressure and Structural Neuroimaging									
Author, year	**Setting**	**Characteristics**	**Orthostatic Test**		**Timing/No of measurements**	**OBP parameter investigated**	**Follow-up**	**Outcome ix**	**Finding**
Soennesyn, 2012[298]	Secondary care outpatient clinics in geriatric medicine and old age psychiatry in western Norway. Consecutive referrals Norway 2005-2007 160 patients with MMSE>=20	N=160 Median age= 76.9% (71-81) 57% female (data from parent cohort of n=246)	Supine* *No set protocol	Stand 3 min	Once in the supine position and one measure at 3min	cOH Low Standing SBP <110mmHg	*Cross-sectional* (MRI median interval of 2 months from the baseline clinical examination)	**Brain MRI** 1.5T 1.WMH automated (Volumetric) & visual Scheltens scale (semi-quantitative): *highest vs. lowest WMH quartile*	***No association***
cOH=Consensus Orthostatic Hypotension; OHT=Orthostatic Hypertension; OI=Orthostatic Intolerance; 'NormoT': 'normal' orthostatic BP response; SCI=Silent Cerebral Infarct; DWM=Deep White Matter; MMSE=Mini Mental State Examination; WMH=White Matter Hyperintensity; PVHV=Periventricular Hyperintensity; T MRI= Tesla Magnetic Resonance Imaging									

3.1.5. Summary

In 1996 OH was defined by expert consensus however guidelines as to the optimal manner of assessment of orthostatic BP were not included. There is variation between studies in the measurement of orthostatic BP both at the clinical and epidemiological level, thus limiting comparison of findings across investigations. The introduction of continuous beat-to-beat orthostatic BP measurement has facilitated the analysis of early changes (<30seconds) in BP after standing but has also added complexity to the interpretation of the orthostatic BP response.

Increasing numbers of studies have described prospective associations between orthostatic BP and cognition in older adults. The most comprehensive study to date followed participants over an average of 15 years. Consensus OH at baseline was associated with dementia risk; as was a novel sub-clinical orthostatic BP parameter i.e. within-person variability in orthostatic BP at a single time point. The authors, however, did not investigate brain MRI outcomes nor MCI. Only one prior study has investigated associations between orthostatic BP and potential preclinical dementia symptoms; reporting associations between OI (but not orthostatic BP) and SMI at population level.

TILDA is the first population-based study of older adults to incorporate beat-to-beat orthostatic BP measures. Varying methods have been employed to summarise data into clinically meaningful measures and to account for conditional change from the pre-stand measurement. Slower 'percentage' orthostatic BP recovery has been associated with increased risk of conversion to dementia in a sample of older adults with MCI. Few studies

have investigated orthostatic BP and affective outcomes. A small clinical study has described associations between beat-to-beat orthostatic BP, WMH and depression in older adults.

Population-based studies which have examined associations between orthostatic BP and structural MRI outcomes are limited by MRI magnet strength (and thus low-resolution scanning) and use of visual rating scales. Although cross-sectional associations between orthostatic BP and WMH have been described, to date there have been no prospective associations found. Prospective associations have been described been OI and WMH although these did not survive multivariable adjustment. Associations with regional GM volume have not been investigated at the population level. Only small clinical studies have investigated orthostatic BP and cognition in older adults and incorporated brain MRI, producing conflicting results.

3.2. Baroreflex Sensitivity and Brain Health in Older Adults

3.2.1. Assessment and Definitions

Definition

Baroreflex sensitivity (BRS) is defined according to Swenne as, 'the change in the interval between heart beats in milliseconds per one unit change in blood pressure'.[308] For example, if BP increases by 10 mmHg and the HR interval then increases by 100msec, BRS is calculated as 100/10 = 10 msec/mmHg[308]. In the seminal Autonomic Tone and Reflexes After Myocardial Infarction, 'ATRAMI' study, BRS was measured post-myocardial infarction and patients were followed over 24months – lower BRS was a significant predictor of ventricular arrhythmia, ventricular fibrillation and death.[309] The ATRAMI investigators defined low BRS as <3 msec/mmHg.[309]

Assessment

Invasive

Measurement of BRS by the modified Oxford method, by which change is HR is induced by intravenous administration of a pressor agent such as phenylephrine or a peripheral vasodilator such as nitroprusside, is regarded as the gold standard.[27,310] Change in HR is calculated and regressed against the change in SBP; the slope of the regression line is interpreted as sensitivity of the baroreflex[153] i.e. a steeper regression slope reflects a closer relationship between SBP and HR. The modified Oxford method has limited applicability beyond clinical samples.

Non-invasive

Non-invasive measurements capture the activity of the baroreflex without the introduction of a vasoactive agent.[311] For example, continuous BP and HR recordings during SBP and HR change induced by the Valsalva manoeuvre may be used to provide an estimation of BRS.[310] In the epidemiological setting however, BRS is most often estimated from spontaneous fluctuations in SBP and HR during supine rest.

Sequence Method

In TILDA, the sequence method is used to estimate BRS and is calculated in the time domain. SBP is measured peripherally using beat-to-beat plethysmography at the finger. HR is measured using an electrocardiogram. Successive, spontaneously occurring change in SBP during supine rest is mapped to successive change in HR (Figure 3.2).[312] BRS, as estimated using the sequence method, has previously been demonstrated to provide a close approximation to BRS measured using invasive techniques.[313] In older adults with hypertension, BRS assessed during spontaneous fluctuation in BP may better reflect BRS function than an invasive measurement.[311]

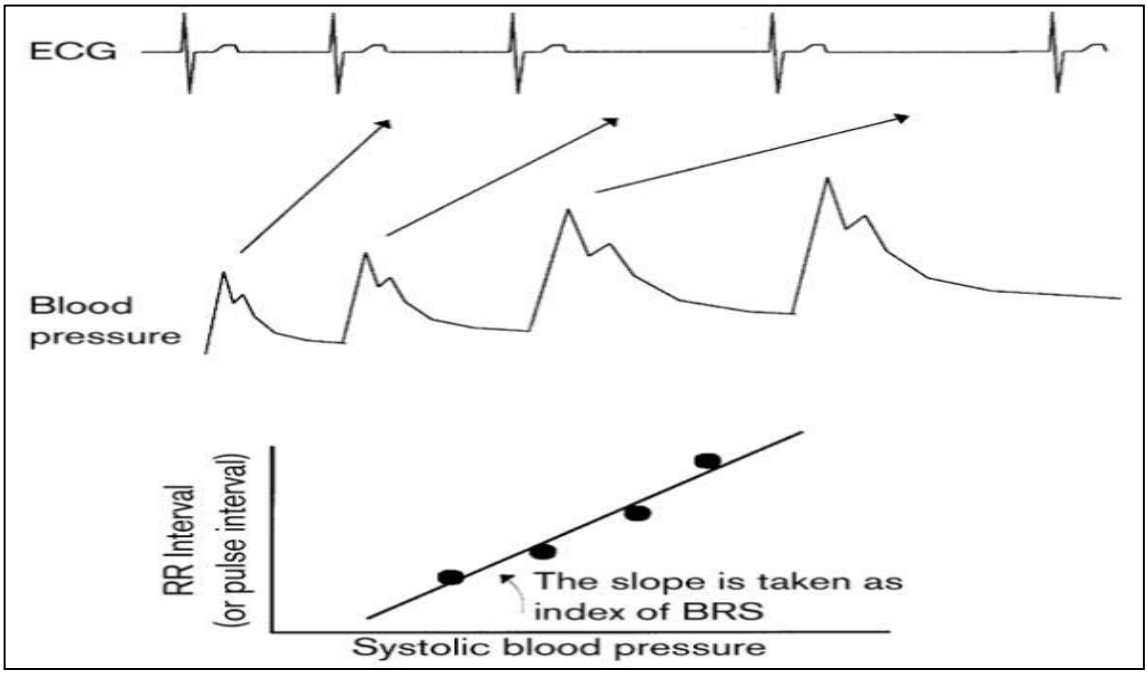


Figure 3.2: Baroreflex Assessment: Sequence Technique.
From Persson et al. 2001[312]**:** Schematic of the sequence technique for the estimation of baroreflex sensitivity (BRS); ECG= electrocardiogram.

Frequency Domain

BRS may also be assessed in the frequency domain via the calculation of the alpha co-efficient (Figure 3.3). Here, the association between the variability of SBP and the variability of HR is mapped via spectral analysis. Spectral analysis breaks down haemodynamic recordings of HR and BP according to their frequency components before quantifying the power of each.[183] The sensitivity of the baroreflex thus provides an indication of relative association between oscillations in BP and oscillations in the R-R interval at the same frequency or the 'transfer magnitude'.[183]

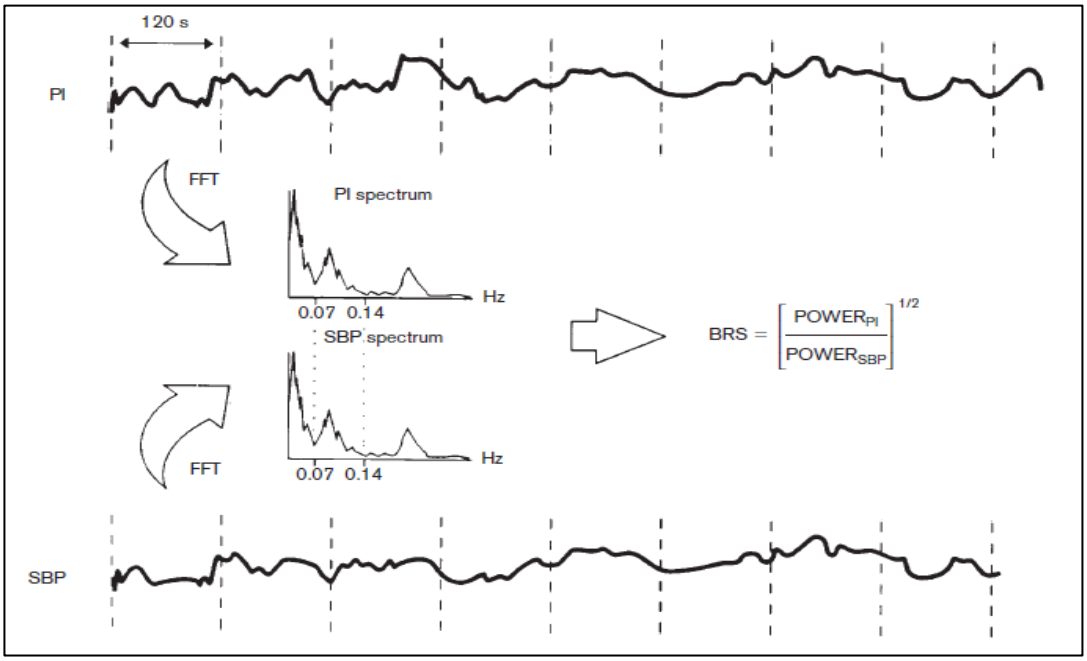


Figure 3.3: Baroreflex Assessment: Spectral Analysis .
Diagram from, 'How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life', Parati et al. Journal of Hypertension 2000, 18:7-19[311] illustrating how BRS can be assessed in the frequency domain using spectral analysis. PI=pulse interval (or R-R interval); SBP=systolic blood pressure; FFT =fast Fourier transformation'

3.2.2. Baroreflex Sensitivity and Cognition in Older Adults

The literature review identified a small number of studies which have investigated the association between cardiac BRS and cognition in older adults (Table 3.3).

In clinical samples, investigators have reported lower BRS in patients with AD and MCI.[151,314] For example, Dutch investigators reported that they were able to distinguish those with AD vs controls using BRS; BRS varied according to severity of cognitive impairment in a graded fashion i.e. BRS in Controls>MCI>AD.[151] These findings were consistent with those from another small clinical study in which BRS was lower in patients with AD and Parkinson's disease relative to healthy controls.[314]

Two publications from the French based PROOF study ('PROgnostic OF cardiovascular and cerebrovascular events') have examined the association between BRS and cognitive function in older adults at population level.[315,316] The PROOF cohort baseline sample was randomly selected and at inception was representative of the French population aged 65 (i.e. according to sex and socioeconomic position); those with existing cardiovascular disease were excluded. The first report details a cross-sectional investigation with a second extending the findings longitudinally.[315,316] In both, BRS was assessed non-invasively using the sequence method, and cognition was assessed using a battery of screening tests validated for use in a French speaking sample. BRS was lower in those with lower cognitive performance. In the longitudinal follow-up, the investigators described 'parallel' change in BRS and in cognition over time i.e. in participants followed over 8 years, those with lower BRS at both time points (baseline and follow-up) also had a greater decline in memory.[316] It is of note however that

the statistical methods used did not take into account correlation between repeated measures nor loss to follow-up.

Table 3.3: Baroreflex Sensitivity and Cognition in Older adults.						
Author, year	**Setting**	**Sample Characteristics**	**BRS investigated**	**Follow-up**	**Outcome**	**Finding**
Szili-Torok[314], 2001	Clinical Case-control	N=23 w/PD 65yrs +/-9.3; N=24 w/AD 72.3yrs +/- 7.2 N=22 controls age & sex matched	Non-invasive: Continuous	Cross-sectional	AD, PD vs control	***Graded association*** BRS lower in AD & PD vs. controls
Meel-van den Abeelen[151], 2012	Clinical Case-control	N=34 patients with AD; 29 patients with MCI; 37 healthy controls Age:60+ Sex:50:50	Non-invasive: Continuous	Cross-sectional	AD,MCI vs control	***Graded association*** BRS was lower in AD (1.4 +/- 0.8 msec/mmHg) vs. control subjects (6.4 +/- 2.7 msec/mmHg) ($p < 0.01$) BRS in MCI **between** the values for AD and control subjects
Saint Martin[315], 2013	Population-based cohort PROOF STUDY	N=916 Age 66.9yrs +/- 0.9 Sex: 65.5% female	Non-invasive: Continuous and cut-point	Cross-sectional	**Cognitive domains**: Attention /Executive /Memory	***Linear association*** Lower BRS associated with increased odds of lower cognitive function compared to normal BRS (BRS >6): $3 < BRS \leq 6$: OR = 1.82 (1.13–3.17; $p = 0.02$) $BRS \leq 3$: OR = 2.65(1.40–5.59; $p = 0.006$)

Table 3.3: Baroreflex Sensitivity and Cognition in Older adults.						
Author, year	**Setting**	**Sample Characteristics**	**BRS investigated**	**Follow-up**	**Outcome**	**Finding**
Saint Martin[316], 2015	Population-based cohort PROOF STUDY	N = 425 at baseline Age 66.9yrs +/- 0.9 58% female	Non-invasive: Continuous and cut-point – *measured twice at baseline and follow-up*	Longitudinal 7.8 +/- 0.9 y follow-up	**Cognitive domains:** Attention /Executive /Memory – *measured twice at baseline and follow-up*	***Prospective association*** Participants with greatest reduction in BRS over follow-up also had greater change in memory relative to those with stable BRS No significant association with attention and executive dysfunction.
AD=Alzheimer's Disease; PD=Parkinson's Disease; MCI=Mild Cognitive Impairment						

3.2.3. Baroreflex Sensitivity and Affective Symptoms in Older Adults

There is a larger literature on associations between BRS and affective symptoms in older adults (Table 3.4). Early studies in cardiac patients suggested that BRS may be reduced in patients with depression and anxiety.[317,318] Another study in patients attending psychiatric services, demonstrated that BRS was lower in patients with depression relative to a control group of volunteers.[319] At the population level, it is again the French investigators based in the PROOF study who reported that lower BRS – as measured using spontaneous BRS assessment – was associated with greater depressive symptoms in older adults.[320] The investigators examined depression in three ways: i) self-reported history of depression ii) depressive symptoms on a validated questionnaire and iii) use of psychoactive medications.

Another large French cohort study composed of volunteers and their families recruited from an occupational health screening service, investigated the association between BRS and depression.[321] Depression was categorised as a binary outcome based on case-level depressive symptoms assessed using a validated screener.[321] They reported that case level depressive symptoms were not associated with BRS, but ADT (in particular treatment serotonin and norepinephrine reuptake inhibitors (SNRI's)) was associated with *lower* BRS. The authors acknowledged limitations to the study: they were unable to adjust for symptoms of anxiety and only 38% of the cohort were women. Notably however, they highlight their use of an alternative non-invasive measurement of BRS ('echo tracking-derived neural BRS') which they report removes the confounding effect of arterial stiffness on BRS measurement.[321]

Table 3.4: Baroreflex sensitivity and Affective Symptoms in Older Adults						
Author, year	**Setting**	**Sample Characteristics**	**BRS investigated**	**Follow-up**	**Outcome**	**Finding**
Watkins[318], 1999	Clinical Patients with stable Coronary Artery Disease	N=66 *(n = 14:low depression;13 men; age 62 +/- 8 years)* *(n=16 high depression; 13 men; age 63 +/- 8 years)*	Non-invasive Continuous	Cross-sectional	Beck Depression Inventory: Quartiles of scores used to define groups with low vs. high depressive symptomatology - *lower (scores <3, n = 14) and upper (scores >9, n = 16)*	***Lower BRS associated with higher depressive symptoms*** Low vs High depressive symptoms: (BRS 6.5 ± 2.8 msec/mmHg vs. 4.5 ± 2.7msec/mmHg; *P* <0 .05).
Watkins[317], 2002	Clinical Post- Acute Myocardial Infarction (AMI)	N=204: 167 completed anxiety measure 37 with depression 60% male Age: 56+-13years	Non-invasive Continuous	Cross-sectional	Structured clinical interview inpatient setting (6 ± 3 days post AMI). 20-item Spielberger State Anxiety Inventory	***Lower BRS associated with higher anxiety*** *BRS not associated with depression* Low vs High anxiety (based on median split): BRS 4.7 +/- 3.2 msec/mmHg in patients with high anxiety vs. 5.7 +/-3.3 msec/mmHg in patients with low anxiety; p<0.05
Vasudev[319], 2011	Clinical Case- Control: (i.e. Secondary care psychiatric services; dx ***major depressive episode (current or previous)*** vs healthy control)	N=42 depressed cases (74.0 +/- 5.9 years; n=31 women) *vs.* N= 31 controls (Age:74.6 +/- 6.3 years; n=20 women)	Non-invasive Continuous : **BRS extractable from n=35 depressed and n=23 controls*	Cross-sectional	Montgomery–Asberg Depression rating scale (MADRS) Geriatric Depression Scale (GDS) Hospital Anxiety and Depression Scale (HADS)	***BRS lower in depressed group*** (natural log mean (SD) Control: 2.05 +/-0.57 vs Depressed 1.70 (+/- 0.66); p=0.032) *(Modified by Co-varying for age and sex (ANCOVA F3,54=3.983, p=0.051))*

Dauphinot[320], 2012	PROOF population-based cohort – excluded at baseline participants with existing CVD	N= 823 subjects were included in the analyses. Age =65 yrs +/ 1.2 Men=41.19%	Non-invasive Continuous	Cross-sectional	History of depression: (depressive status defined by both self-report history of depression and a depression QD2A score higher than the threshold 7, and use of psychoactive treatment.)	**BRS lower in case-level depressive symptoms vs those without case level symptoms not on treatment (ADT)** lnBRS 1.82+/-0.51 Not Depressed; No Rx (n=712) lnBRS 1.67+/-0.46 Not depressed; Rx (n=44) lnBRS 1.72+/-0.51 depressed; no Rx (n=52) lnBRS 1.90+/-0.31 depressed; Rx (n=15) No significant difference between groups defined by self-reported hx of depression
Empana[321], 2016	PARIS PROSPECTIVE STUDY III Population-based cohort	N=9213 Age= 50-75 years Women=38.6%	Non-invasive Continuous *(Low nBRS defined as a value below the median, which was calculated in the entire participant population)*	Cross-sectional	A total score >=7 Questionnaire of Depression 2nd version, Abridged (QD2A) =depression Information on ADT use was obtained on a face-to-face interview with a medical doctor who checked the most recent medical prescriptions and/or medical package.	***No significant association* between high depressive symptoms and lower (neural) BRS**: OR 1.02 (95% CI: 0.84- 1.23) p=0.870 **ADT (SNRI in particular) associated with low BRS:** ADT OR 1.27 (95% CI: 1.04-1.54) SNRI OR 1.94; (95% CI: 1.16-3.22).
ADT=Antidepressant Treatment; lnBRS= natural logarithm transformed baroreflex sensitivity; rx=treatment; SNRI= Serotonin Noradrenaline Reuptake Inhibitor ; AMI=acute myocardial infarction ; dx=diagnosis; hx= history						

3.2.4. Baroreflex Sensitivity and Structural Neuroimaging in Older Adults

A number of studies of modest sample size have investigated associations between BRS and structural MRI outcomes. Of most interest perhaps to older adults, Laosiripisan[322] and colleagues (Table 3.5) investigated BRS (as assessed during the Valsalva manoeuvre) and relationships with regional cerebral perfusion using Arterial Spin Labelling. This study was performed in a sample of adults aged 49+/-1 year – thus similar to the youngest participants in the TILDA sample. Hippocampal perfusion was higher among participants with higher BRS.[322] No associations were found with other regions of interest which included the insula and caudate. No correction was made for multiple comparisons in analyses.

Tarumi and colleagues[310] investigated the association between BRS and white matter neuronal fibre integrity in 54 participants (65 +/- 6years) using 3T Diffusion Tensor Imaging MRI (Table 3.5). BRS was measured invasively using the modified Oxford protocol, with both the response to hypotension and hypertension recorded. There were stronger correlations between lower BRS and lower white matter integrity when BRS was assessed during hypotension, than with BRS assessed during hypertension. The authors conclude that BRS during hypotension may thus be important in determining white matter neuronal fibre integrity in older adults.[310]

Table 3.5: Baroreflex sensitivity and Neuroimaging in Older Adults

Author, year	Setting	Sample Characteristics	BRS methods	BRS investigated	Follow-up	Outcome	Finding
Laosiripisan, 2015[322]	Healthy volunteers	N= 52 middle-aged normotensive adults Age: 49yrs ± 1	Non-invasive (Valsalva manoeuvre; Phase IV)	Continuous and tertiles	Cross-sectional	BRAIN MRI: 3T Arterial Spin labelling	***Hippocampal perfusion was correlated with BRS*** i.e. significantly lower in the lowest BRS tertile vs highest tertile No association was observed between BRS and cerebral perfusion in other brain ROI
Tarumi, 2015[310]	Clinical & volunteers University of Texas Southwestern Medical Center Alzheimer's Disease Center. Normal cognitive vs MCI	N=54 Age= 65±6 yrs	Invasive Modified Oxford protocol sodium nitroprusside (100 µg) followed 60 seconds by phenylephrine hydrochloride (150 µg).	Continuous ('Up slope' & 'down slope' BRS)	Cross-sectional	BRAIN MRI: 3-T WM DTI diffusion metrics: FA and RD,AD	***BRS assessed during hypotension was correlated with lower WM microstructural integrity***

MCI=Mild Cognitive Impairment; DTI=Diffusion Tensor Imaging; WM=White Matter; FA= fractional anisotropy; RD= radial diffusion; AD= axial diffusion

3.2.5. Summary

Cardiac BRS can be assessed non-invasively at population level. Lower cardiac BRS has been associated with poorer cognition in older adults in both cross-sectional and longitudinal population-based studies. To date, only cross-sectional associations have been reported between lower BRS and depressive symptoms at population level; associations may vary according to ADT. No study has investigated associations between BRS and both depression and anxiety at population level, although associations between lower BRS and greater anxiety have been reported in small clinical samples comprised predominantly of male patients. Cross-sectional associations between BRS and advanced neuroimaging parameters in older adults have been reported but only in small samples. Findings suggest associations between lower BRS and poorer brain health e.g. lower hippocampal perfusion and lower white matter microstructural integrity.

3.3. Syncope and Brain Health in Older Adults

3.3.1. Assessment and Definitions

The AHA syncope guidelines describe reflex syncope as, 'Syncope due to a reflex that causes vasodilation, bradycardia, or both'.[323] Reflex syncope is the most common cause of syncope in any setting, including among older people; it is unusual however for an adult to experience a first vasovagal episode after the age of 35.[243,323]

Clinical Diagnosis

According to the AHA the diagnosis of VVS is made, 'primarily on the basis of a thorough history, physical examination, and eyewitness observation, if available'.[323] VVS most often occurs secondary to stereotyped triggers e.g. prolonged standing or 'emotional stress'. It is characterized by a classic prodrome of diaphoresis, pallor and nausea. The National Institute for Clinical Excellence (NICE) guidelines suggest an assessment which focuses on eliciting key presyncopal, syncopal and post-syncopal features of an event. The guidelines highlight potential 'red flags' which may suggest a cardiac (e.g. arrhythmic) aetiology e.g. syncope during exercise, a family history of sudden death.[324] A collateral witness history is also emphasized as useful in diagnosis to confirm the presence of features classically accompanying VVS.[323] Older patients however may be less likely to report prodromal features of VVS and be more likely to have unwitnessed episodes, rendering diagnosis more difficult.[178,325]

In a specialist setting a HUT may be used to confirm a vasovagal tendency[323]; after a period of supine rest the patient is tilted passively upright to approximately 70 degrees[323], although protocols may differ. A provoked test may involve the administration of vasoactive agent (e.g. sublingual nitroglycerin) or venepuncture.[323] Reproduction of symptoms and/or T-LOC accompanied by haemodynamic change confirms a VVS tendency which is then sub-classified as vasodepressor, cardio-inhibitory or both, according to the BP and HR response.[168]

Vasovagal syncope is classically considered a benign diagnosis, particularly on the basis of the favourable outcomes of isolated syncopal events in the Framingham study[326], however syncope, particularly when recurrent, may be associated with high levels of morbidity and reduced quality of life.[327]

Ascertainment of Syncope Prevalence in population-based studies

Population-based studies which have estimated the lifetime prevalence of syncope suggest that up to 40% of the population will experience at least one episode of syncope.[323] Many studies however have estimated syncope prevalence in unrepresentative samples i.e. medical students or pilots.[328] Estimating the true population prevalence of syncope however is difficult as many of those who experience syncopal events will not seek medical treatment, thus estimates of syncope prevalence based on medical record linkage are likely to underestimate the true population prevalence.[170] TILDA assesses syncopal events using a self-reported questionnaire which elicits information on 'frequent' syncope in youth and the number of syncopal events within the last year.[329,330]

The ‘Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis (CAMERA)’ study aimed to assess features of autonomic dysfunction in patients with migraine. A population-based control sample was additionally selected in which the syncope prevalence was ascertained.[331] VVS was ascertained by self-report via a questionnaire administered by telephone to participants. The defining features of a vasovagal event (e.g. such as T-LOC preceded by a prodrome and/or occurring after prolonged standing) were explained to participants who were asked to endorse (or not) a history of similar events. Those who had had episodes with features suggestive of a TIA or seizure were excluded. The lifetime prevalence of VVS was 31% in a sample of 153 participants with mean age 48 years.[331]

Ganzeboom et al[332] examined the frequency of fainting in the ‘Cardiovascular Risk profile of native Dutch people in the Netherlands (‘CRANS’)’ study. The CRANS cohort also formed the control group to another study (the SUNSET study ‘Surinamese in the Netherlands: Study on Ethnicity and Health’) so included only those of ‘Dutch heritage’.[332] Participants were aged 35-60 years and were asked to report a history of syncope, its frequency, age at initial onset and age at recurrence, in addition to any identifiable triggers.[332] Participants who reported episodes with features suggestive of intoxication, traumatic injury or stroke, or who had a history of epilepsy were excluded. The investigators reported an overall lifetime prevalence of 35%. Commonly reported triggers of syncope included orthostasis. Syncope was more common in young women, with a first peak in incidence at around 15 years; it was rare to experience a first faint after the age of 35.[332] The lifetime cumulative prevalence of syncope was greater among women than men (41% vs 28%), only 37 % of participants had sought medical attention.[332]

In the US-based Olmsted County study (set within a larger study evaluating ventricular dysfunction) Chen et al[328] estimated syncope prevalence at 19% (N=1925). All participants were aged 45+ (median 62years); 47% were men. Participants were asked "Have you ever experienced a blackout (fainting, complete loss of consciousness)?". Participants were asked about age at first syncopal episode, recurrence, and injury during syncopal events. The frequency of comorbid conditions was similar in individuals with and without syncope. Women reported a higher overall prevalence at 22% and while the median age at onset of syncope in the sample was 25 years, a first episode tended to occur earlier among women.[328]

The Framingham Heart Study reported an incidence of syncope of 6.2/1000 person-years, however syncopal events prior to entry to the study were excluded.[333] In Framingham the incidence of syncope rose sharply after 80 years to an incidence to 16.9/1000 person years in men and 19.5/1000 for women.[178] In a retrospective analysis of institutionalised adults aged 80+, the 10 year cumulative prevalence of syncope was 23% with the majority (approximately 70%) either unexplained or diagnosed as VVS.[334]

3.3.2. Syncope and Cognition in Older Adults

The literature search identified few studies which have specifically investigated associations between syncope and brain health. Two recent studies however focused on syncope and cognitive function in older adults (Table 3.6).

In TILDA, Frewen et al described lower global cognitive function (as assessed using the MoCA) in patients with a greater frequency of self-reported syncopal episodes.[330] This effect was restricted to those older adults with recurrent syncope in the last year. Interestingly, the authors also highlighted the potential role of misclassification of syncopal events as falls in older adults. Associations with global cognitive performance were strongest with self-reported 'non-accidental falls' i.e. a fall not related to a trip, which were therefore categorized as syncopal events.[330] Amnesia for LOC has been demonstrated in patients undergoing assessment for VVS on HUT (including in those <40 years though rising with age).[325]

A recent paper from a Dutch Falls clinic sample reported a high prevalence of cognitive impairment in older adults with syncope.[335] Given the clinical setting, the authors were more confidently able to assign study members to diagnostic groupings i.e. falls vs syncopal events. A higher prevalence of cognitive impairment was found among syncope patients when assessed using the MoCA versus assessment using the MMSE i.e. the MMSE was less sensitive to cognitive impairment than the MoCA. The authors emphasize the importance of cognitive assessment in older patients presenting with syncope.

Table 3.6: Syncope and Cognition in Older Adults							
Author/ year	**Setting**	**Sample Characteristics**	**Method of assessment**	**Syncope definition**	**Follow-up**	**Outcome**	**Finding**
Frewen[330], 2015	Observational population-based cohort TILDA, 09-12	N=5846; Age=median 62 y 54% female	Retrospective self-report	Self-reported syncope in last twelve months 1 vs none; 2+ vs none	Cross-sectional	Cognitive function assessed using MoCA	***Aassociation between syncope &/or unexplained falls history and lower MoCA score*** Patients with >=2+ syncope events in the past 12 months scored significantly lower on MoCA than subjects with no syncope history however, this was largely explained by confounders.
De Ruiter[335], 2016	Outpatient fall and syncope clinic; observational clinical cohort	N=200; Age= Mean 79.5 +/-6.6 y 70 % female	Retrospective case-note review	Clinical diagnosis of syncope (*T-LOC according to the definition of the European Society of Cardiology).*	Cross-sectional	Cognitive function with the MMSE and MoCA.	***High prevalence of cognitive impairment in older adults with syncope*** Cognitive impairment in the syncope on MMSE 16.8% but 60.4% using MoCA *(general population aged >=75 years prevalence of cognitive impairment 19%)*
MoCA= Montreal Objective Cognitive Assessment; MMSE=Mini Mental State Examination ; T-LOC=Transient Loss of Consciousness; TILDA=The Irish Longitudinal Study on Ageing; y=years							

3.3.3. Syncope and Affective Symptoms in Older Adults

Two recent studies have investigated associations between syncope and affective symptoms in older adults (Table 3.7). In a cross-sectional analysis of the first wave of the TILDA cohort, Bhangu and colleagues found an association between higher depressive symptoms (as measured using the CES-D) and self-reported syncope during the preceding year.[329] The authors also reported an association between ADT and syncope – specifically a higher risk of syncope in older adults prescribed TCA.[329] These findings are in line with those from an Italian clinic-based study which followed older adults with syncope over 24 months: at the end of follow-up, depressive symptoms (as measured using the Geriatric Depression Scale) had risen among the sample with syncope.[336]

VVS has been associated with high levels of psychiatric co-morbidity (although notably investigations have predominantly studied young adults).[244,337] For example, using diagnostic interviews to identify psychiatric disorder, a 1995 report from Kapoor showed a 20% prevalence of psychiatric disorder in those aged 16+ presenting to a hospital-based practice with syncope (i.e. emergency department, inpatients and out-patient clinics). [244]

Table 3.7: Syncope and Affective Symptoms in Older Adults

Author/ year	Setting	Sample Characteristics	Method of assessment	Syncope definition	Follow-up	Outcome	Finding
Ungar[338] 2011	Italian Group for the Study of Syncope in the Elderly Clinical diagnosis consecutively referred to the participating centres for T-LOC were enrolled in a multicentre 2-year longitudinal observational study	N=242; Age 65 + Mean Age: 78,7 +/- 6.8 Sex: 57.7 % female	Clinical Diagnosis Specialist Clinic	Syncope was clinically diagnosed	*Prospective* (24 mnths)	Geriatric Depression Scale (GDS) *(Mortality and syncope recurrence was recorded and multi-morbidity evaluated at 6, 12, 18 and 24 mnths)*	***Depressive symptoms increased in patients with syncope*** GDS score significantly increased from baseline of 3.73 ± 3.67 to 5.59 ± 5.76 at last evaluation (P < 0.001). % GDS score ≥6 increased from 28.3% at baseline to 41.4% (P < 0.001). *{MMSE score remained stable throughout the study (26.1 ± 9.5 versus 26.9 ± 3.8; P = 0.321).}*
Bhangu[329] 2014	TILDA, 2009-12	N=7993 Age: 50+	Self-report	Self-reported syncope in last twelve months 1 vs none; 2+ vs none	Cross-sectional	CES-D ADT: selective serotonin reuptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs)	***Depressive symptoms and TCA associated with syncope*** Higher score on CES-D associated with increased risk of single and multiple syncopal events (relative risk ratios [RRR]: 2.78 and 2.84, respectively, P < 0.05) Participants treated with TCA were also at greater risk for single and multiple syncopal episode in the last year (RRR: 2.31, P = 0.062; RRR: 2.95, P < 0.05)

CES-D= Center for Epidemiological Studies–Depression; ADT=Antidepressant Treatment; Mnth=Months; TCA= Tricyclic anti-depressants; RRR=Relative Risk Ratio; T-LOC=Transient Loss of Consciousness; TILDA=The Irish Longitudinal Study on Ageing ;SSRI= selective serotonin reuptake inhibitors; GDS=Geriatric Depression Scale

3.3.4. Syncope and Structural Neuroimaging in Older Adults

Repeated episodes of syncope may expose the brain to repeated episodes of hypoperfusion[330], and recurrent syncope has been linked to structural brain changes in younger adults.[339] The literature search did not identify studies investigating brain neuroimaging outcomes (structural MRI) in older adults with syncope. It is of note, however, that given the potential overlap between syncope and falls in older adults, that higher levels of WMH are a consistent finding on neuroimaging of older adults who have experienced falls.[340] Furthermore, conditions associated with syncope including carotid sinus hypersensitivity and OH have been associated with greater WMH on neuroimaging.[289]

In younger adults, higher levels of WMH on MRI brain have been described in participants reporting syncope in the CAMERA study (Table 3.8).[339] This association was seen in those participants with recurrent syncope (defined by the investigators as 5+). Even though this was an investigation based within a larger study designed to investigate the neuroimaging correlates of migraine, the authors note that their finding were not confined to participants with migraine but equally extended to controls with a history of recurrent syncope.[339]

I identified two studies which had investigated regional GM volumes in younger adults with VVS (Table 3.8). Both used voxel-based morphometry and reported differences in GM volumes of regions potentially associated with autonomic control, including the caudate[172] and right insula in those with VVS.[341]

Table 3.8: Syncope and Structural Neuroimaging							
Author/ year	**Setting**	**Sample Characteristics**	**Method of assessment**	**Syncope definition**	**Follow-up**	**Outcome**	**Finding**
Beacher[172], 2009	Non-clinical sample of eighteen individuals with a history of VVS	N=18 case (Mean age 28.6 years; 14 F, 4 M) N=19 control (mean age 27.6 years; 14 F, 5 M)	Self-report : detailed participant interview, confirming onset in childhood or early adulthood, family history and the presence of characteristic triggers e.g. emotional stress or exposure to blood stimuli	Self-report VVS	Cross-sectional	Brain MRI 1.5T Regional grey and white matter volumes assessed using voxel-based morphometry	***Inverse association – greater syncope associated with reduced brain integrity:*** Lower regional brain volume within medulla and midbrain in participants with VVS Lower GM volume in contiguous regions of left caudate nucleus associated with frequency of syncope
Kruit[339], 2013	Population-based, cross-sectional CAMERA (Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis) cohort (aged 30–60 years, and free of other neurologic symptoms)	N=291 pts N=140 controls Mean age: 47.4 =/- 7.8 Sex:94% female	Self-report: Structured telephone interview including questions on frequent syncope (>=5/lifetime) and OI Ccategorized as “syncope ever” (at least once) and “frequent syncope” (5 or more episodes/lifetime). OI was defined as the syncope or presyncope upon standing or the avoidance of prolonged standing	Frequent syncope and OI	Cross-sectional	Brain MRI Whole-brain MRI scans from a 1.0- and a 1.5-tesla Semiquantitative WML -rating *: deep white matter lesions & high periventricular white matter* Infarcts or infratentorial lesions.	***Inverse association – greater syncope associated with reduced brain integrity:*** In patients with migraine *and* in controls : Frequent syncope (odds ratio [OR] = 2.7; 95% confidence interval: 1.3–5.5) and OI (OR = 2.0 [1.1–3.6]) were independent risk factors for high load of deep white matter lesions. OI had higher prevalence of high periventricular white matter lesion load (OR = 1.9 [1.1–3.5]). Syncope and OI were *not* related to subclinical infarcts or infratentorial lesions.

Table 3.8: Syncope and Structural Neuroimaging							
Author/ year	**Setting**	**Sample Characteristics**	**Method of assessment**	**Syncope definition**	**Follow-up**	**Outcome**	**Finding**
Kim[341], 2014	Consecutive patients with 'neurocardiogenic syncope (NCS)' were prospectively recruited from the outpatient clinic at the Neurology Department, Korea University Guro Hospital, from January 2010 to April 2012.	N=64 Age 24.1 +/-6.9 N= 32 patients with neurocardiogenic syncope N=32 controls who had no history of syncope Age =24.8 +/-5.2	Head-Up Tilt Test	Positive HUT	Cross-sectional	MRI 3T scanner voxel-based GM volume morphometry	***Inverse association –syncope associated with reduced brain integrity:*** Significant reduction in the GM of right insular cortex in patients with neurocardiogenic syncope compared with controls
VVS= Vasovagal Syncope; OI=Orthostatic Intolerance; HUT=Head up Tilt; NCS=Neurocardiogenic Syncope; WML= White Matter Lesion; GM=Grey Matter							

3.3.5. Summary

Vasovagal syncope can be diagnosed on clinical history alone. VVS most often first presents in teenage years and it is rare to experience a *first* episode of VVS after 35 years. VVS may be a *persistent* tendency across the life course (VVS is the most common cause of syncope at any age) and may occur in response to emotional stress. A small number of studies have additionally pointed to associations between syncope in later life and brain health in older adults, including associations with greater cognitive impairment and depressive symptoms. In younger adults recurrent syncope (i.e. a vasovagal tendency) has been linked to structural MRI change, including WMH and regional GM change; the direction of association is uncertain.

4. STUDY I - Sub-Clinical Orthostatic Hypotension is Associated with Greater Subjective Memory Impairment in Older Adults

Study I investigates orthostatic BP as the independent variable of interest and SMI as the outcome of interest. Subjective Memory Impairment may be an early risk marker for dementia while orthostatic BP may be on the pathway to poorer CS, but is most often investigated as consensus OH. Orthostatic Intolerance, but not lower orthostatic BP, has been prospectively associated with SMI using standard orthostatic BP measures. Standard intermittent orthostatic BP measurement however is not sensitive to early (i.e. <30seconds) post-stand haemodynamic change. There may be sex differences in autonomic function and brain health in later life; while OI is classically more common among women, in men SMI may be more prevalent, and a better reflection of objective cognitive function.

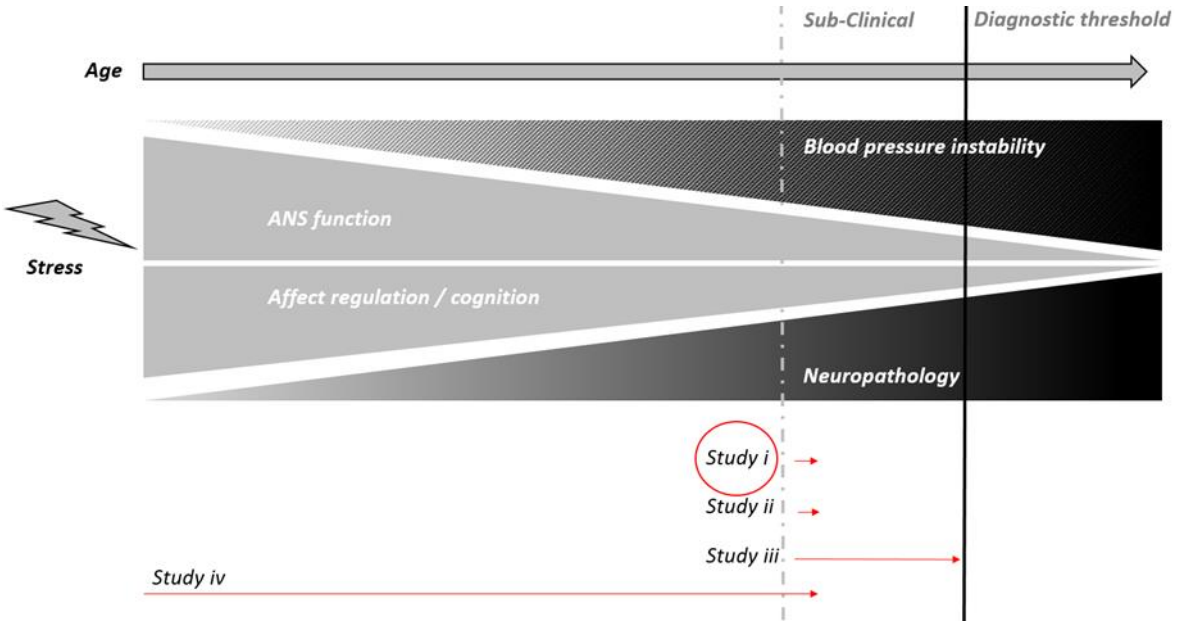


Figure 4.1: Thesis Figure: Study I
Study I investigates ***cross-sectional*** associations between blood pressure instability and potential preclinical symptoms of dementia.

Sub-Clinical Orthostatic Hypotension is associated with Greater Subjective Memory Impairment in Older Adults

4.1. Abstract

Introduction: Orthostatic BP is a measure of cardiovascular autonomic function. Orthostatic BP dysregulation may lie on the causal pathway to dementia. Subjective memory impairment is commonly reported by older people some of whom may progress to dementia. This study tests the hypothesis that sub-clinical OH is associated with SMI, and that associations may vary according to sex.

Methods: Cross-sectional analysis of data from 4340 participants aged 50 and over collected during the first wave (2009-2011) of the TILDA cohort study. Subjective memory was rated according to a 5-point scale ranging from 'poor' to 'excellent'. BP was measured during orthostatic stress using continuous non-invasive beat-to-beat recording over 2 minutes.

Results: 2% reported 'poor' subjective memory, 12.3% 'fair', 38% 'good', 33% 'very good' and 14.6% 'excellent'. After controlling for some potential confounding factors including cardiovascular risk, objective cognition, and depressive symptoms, mean systolic orthostatic BP was lowest in those with 'poor' subjective memory: 92.2mmHg (95%CI 87.1; 97.3) vs. 'excellent' 99.3mmHg (95%CI 97.4; 101.2); p=0.011. Further adjustment for supine systolic BP suggested that men with 'poor' subjective memory reached the lowest average systolic orthostatic BP and had the greatest impairment in systolic orthostatic BP stabilisation to baseline levels at 10 seconds post-stand (-6.64 mmHg; 95%CI -11.49; -1.79; p=0.007).

Conclusions: Sub-clinical OH is associated with SMI and there are sex-specific associations evident in this population-based cohort. Subtle cardiovascular autonomic dysfunction may represent a modifiable risk marker at an early stage of cognitive decline in older adults.

4.2. Introduction

Despite controversy stemming from conflicting associations with objective cognitive deficits and overlaps with psychiatric disorder, SMI remains one of the sole means by which the earliest stages of cognitive decline may be identified.[102] SMI in the absence of objective cognitive dysfunction in older adults has been conceptualized as a potential 'pre-clinical' phase of dementia.[103] Multiple longitudinal studies have confirmed that SMI, even in the absence of baseline deficits on cognitive testing, is associated with an increased risk of future dementia.[104,342] The reasons for this are poorly understood.

Orthostasis invokes a re-balance of the sympathetic and parasympathetic output from the Central Nervous System. Measurement of orthostatic BP assesses cardiovascular autonomic balance on a peripheral basis.[266] OH is the clinical syndrome defined as a drop in systolic BP of >=20 mmHg and/or diastolic BP of >=10mmHg drop within 3 min of standing and in the clinical setting is most often measured using an oscillometric sphygmomanometer.[161]

SMI and OH become increasingly common with ageing [102,184] and both have been linked to sub-clinical vascular risk factors for dementia, including reductions in CBF and higher levels of WMH's on neuroimaging.[106,295,343,344] Both OH and SMI have been associated with ischemic heart disease and stroke.[117,345]

Cross-sectional studies have reported a higher prevalence of OH in dementia syndromes.[346,347] It has been postulated that OH may be on the causal pathway to dementia either as a peripheral marker of central autonomic dysfunction or via repeated episodes of

cerebral hypoperfusion during orthostatic stress.[293] TILDA, among others, has described associations between deficits on formal cognitive testing and OH in an epidemiological setting [164,294,348]; however neither SMI nor sub-clinical OH was explored until recently. Elmståhl and Widerström reported an association between baseline OH and SMI six years later.[278] Although this relationship did not survive correction for age, they did describe prospective associations between OI (defined as symptoms of cerebral hypoperfusion on standing) and both SMI and Mild Cognitive Impairment (MCI). Orthostatic intolerance may have arisen from baseline sub-clinical orthostatic BP drops that the authors suggest were not detectable by traditional BP measurement using a sphygmomanometer.

Continuous beat-to-beat non-invasive orthostatic BP measurement is a novel addition to epidemiological studies of ageing and has been used to explore sub-clinical patterns of orthostatic BP dysregulation.[274] Investigation of OH at arbitrary cut-points may miss important information on sub-clinical OH and thus the earliest stages of autonomic function. It has been hypothesized that subtle cardiovascular autonomic dysfunction may occur early on the continuum towards dementia as brain areas involved in central cardiovascular autonomic control may be among those first affected by neurodegeneration.[218] If orthostatic BP dysregulation is on the causal pathway to dementia, then sub-clinical OH may accompany the earliest phases of cognitive decline such as SMI.

To the best of the authors knowledge, no study has previously investigated the impact of continuous measures of orthostatic BP on SMI. This study tests the hypothesis that sub-clinical orthostatic BP dysregulation, measured using continuous beat-to-beat monitoring and reflecting early cardiovascular autonomic dysfunction, will be more common in those

with SMI, a potential preclinical phase of dementia. Given prior findings of differing patterns of orthostatic BP regulation and implications of SMI in men and women[140,182], this study secondly tested the hypothesis that these associations may differ between men and women.

4.3. Methods

Sample

This study uses data collected during the first wave (2009-2011) of The Irish Longitudinal Study on Ageing (TILDA) that includes 8175 participants. The sampling procedure produced a representative sample of the community-dwelling Irish population aged 50 and over in Ireland. The household response rate was 62.0%. Data collection included a face-to-face in-home computer-assisted structured interview that was used to capture health related, social and demographic information. Each participant was also invited to attend a detailed physical health assessment. Further details of the sampling procedure, in-home interview and health assessment are available elsewhere.[349]

Ethics

Trinity College Dublin Health Research Ethics Committee granted Ethical Approval for the study. Each participant provided written informed consent prior to enrolment in the study. Those unable to give informed consent were excluded.

Measures

Subjective Memory Impairment

Subjective memory was assessed using the question: "How would you rate your day-to-day memory at the present time?". Participants were invited to respond according to the options 'poor, 'fair', 'good', 'very good' and 'excellent'. This measure was used in the Health and Retirement Study (HRS) and The Aging, Demographics, and Memory

Study sub-study.[350,351] 'Impairment' in subjective memory was investigated by comparing those who reported their memory as very good *or* good *or* fair *or* poor to those who reported excellent subjective memory.

Orthostatic Challenge

Each participant performed a supervised lying-to-standing test ('Active Stand') while BP was recorded peripherally using a beat-to-beat plethysomnography device (Finometer® MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands, www.finapres.com). Participants lay quietly for ten minutes to capture a stable resting supine measurement of BP. Participants then stood as quickly as possible (receiving assistance as necessary) while BP monitoring continued for two minutes. Further details of the processing and extraction of BP readings (at 10-second intervals) are available elsewhere.[184] Participants were asked to report symptoms of dizziness, presyncope or light-headedness after standing coded as 'Orthostatic Intolerance' (Yes/No).

Orthostatic BP Variables of Interest

'Nadir' was used to denote the lowest BP recorded at any point during the 120 seconds of recording. Subsequent analysis focused on *10 - 30 seconds* after standing as this is the period of maximum orthostatic BP change.[184] Relative orthostatic BP 'stabilisation' was investigated by accounting for differences in supine BP.

Other measures

Objective cognitive function was assessed using the MoCA[352] which is an interviewer-administered paper and pencil test with scores ranging from 0-30. Higher scores indicate better cognitive function; a cut-point of >=26 has been proposed for detection of MCI.[352]

Depressive symptoms over the previous week were recorded using CES-D[353] and a cut point of ≥ 16 was used to identify clinically significant depressive symptoms.[354]

Self-reported doctor-diagnosed conditions (diabetes, lung disease, asthma, arthritis, osteoporosis, cancer, peptic ulcer, and hip fracture) were summed to give an indication of chronic co-morbidities. Cardiovascular / cerebrovascular conditions were also summed to include a history of TIA, stroke, high cholesterol, heart failure, heart 'murmur', cardiac arrhythmia and MI. Smoking history was coded as 'current', 'past' or 'never'.

Antidepressant use was identified using the first four digits of the World Health Organization's Anatomical Therapeutic Chemical code ("N06A"). Antihypertensives were identified using the codes "C02*" (anti-adrenergic agents) "C03*" (diuretics), "C07*" (beta-blockers), "C08*" (calcium-channel blockers), "C09*" (angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers) and combinations of the above "(C02*)". Binary variables (no/yes) were coded to indicate antihypertensive and antidepressant use.

Statistical Analysis

Statistical analysis was conducted using Stata v12 (StataCorp LP, Texas, USA). The sample was described by subjective memory category according to demographic and health-related characteristics. ANOVA was used to test for linear trends according to categories of subjective memory in SBP and DBP at the Nadir and at time points of interest. Linear regression analysis was used to estimate differences in SBP and DBP between subjective memory categories adjusting for covariates. Separate models were fit for each outcome variable (SBP or DBP) at the Nadir and at 10-30 seconds post stand. Initial models (adjusting for age, age squared and sex - 'Model 1') regressed mean SBP or DBP at the Nadir and at 10-30 seconds post-stand against subjective memory. Further multivariate analysis then adjusted for potential confounders: Model 2= Model 1 + education, BMI, depressive symptoms, objective cognitive deficits (MoCA), physical co-morbidities (chronic conditions and cardiovascular disease), medications (antidepressants and anti-hypertensives) and a history of smoking. In sensitivity analysis these models were re-estimated excluding those with low scores on the MoCA (i.e. <26).[352]

To assess hemodynamic stabilisation after orthostasis, models were further adjusted for the appropriate supine BP measure (Model 3= Model 2 + supine BP). If significant relationships with subjective memory remained after adjustment for supine BP, the associations according to sex were also estimated using a regression model now including the interaction terms between subjective memory and sex. Where significant interactions occurred, subsequent analyses were stratified by sex.

Adjusted marginal means with 95% confidence intervals for the SBP and DBP variables for each level of subjective memory at the Nadir and each time-point across 120 seconds were estimated (i.e. the values of these variables holding all other variables in the models constant) and plotted to allow interpretation of patterns of orthostatic BP across all time points collected after standing.

4.4. Results

5035 participants attended a health assessment and 4475 had usable continuous beat-to-beat orthostatic BP measurements. Participants missing data on any variable of interest were excluded as were those with a history of Parkinson's disease (n=57) giving a final analytical sample of 4340. Descriptive statistics are shown in Table 4.1. Sensitivity analysis using logistic regression suggested those included in the final sample relative to the TILDA cohort as a whole were younger, more likely to be women, have better cognition and have less co-morbidity.

Table 4.1: Descriptive statistics by Subjective Memory

	Total Sample	**Excellent**	**Very Good**	**Good**	**Fair**	**Poor**	***p***
	***n*= 4340**	635 (14.6)	1431 (33.0)	1651 (38.0)	535 (12.3)	88 (2.0)	
Demographic Characteristics							
Age (mean (SD))	61.5 (8.3)	59.6 (7.5)	61.0 (8.0)	62.2 (8.5)	63.1 (8.3)	62.5 (9.3)	**<0.001**
Body mass index (kg/m2), mean SD	28.5 (4.8)	28.8 (4.9)	28.5 (4.9)	28.4 (4.7)	28.4 (5.0)	29.4 (5.8)	**0.14**
Education *n* (% primary only)	913 (21.0)	72 (11.3)	232 (16.2)	402 (24.4)	170 (31.8)	37 (42.1)	**<0.001**
Gender *n* (% female)	2334(53.8)	325 (51.2)	770 (53.8)	922 (55.8)	281 (52.5)	36 (40.9)	**0.029**
Orthostatic Intolerance *n* (%)	1661(38.3)	191 (30.1)	535 (37.4)	649 (39.3)	239 (44.7)	47 (53.4)	**<0.001**
Affective Symptoms & Cognition							
Depressive symptoms (median (IQR))	3 (7)	2 (5)	3 (6)	4 (7)	5 (10)	8 (13.5)	**<0.001**
Antidepressants Treatment *n* (%)	254 (5.9)	22 (3.5)	55 (3.8)	94 (5.7)	63 (11.8)	20 (22.7)	**<0.001**
MoCA (median (IQR))	26 (4)	26 (4)	26 (4)	26 (5)	25 (4)	23 (6)	**<0.001**
Physical Comorbidity & Cardiovascular Risk							
Chronic conditions *n* (% ≥1)	2203 (50.8)	268 (42.2)	681 (47.6)	877 (53.1)	315 (58.9)	62 (70.5)	**<0.001**
Current Smoker *n* (%)	641 (14.8)	82 (12.9)	197 (13.8)	248 (15.0)	96 (18.0)	18 (20.5)	**<0.001**
Antihypertensive Treatment *n* (%)	1414 (32.6)	162 (25.5)	447 (31.2)	564 (34.2)	202 (37.8)	39 (44.3)	**<0.001**
CVD conditions *n* (% ≥1)	496 (11.4)	281 (44.3)	642 (44.9)	821 (49.7)	301 (56.3)	49 (55.7)	**<0.001**

P vales are from ANOVA for normally distributed continuous variables, Kruskal-wallis for non normal and Chi² for categorical variables; SD=standard deviation; IQR=Intraquartile Range; MoCA=Montreal Cognitive Assessment; CVD=Cardiovascular Disease

Mean unadjusted SBP and DBP during orthostasis varied according to the category of subjective memory (Table 4.2). Those with poor subjective memory reached the lowest Nadir post-stand compared to those in higher categories.

Table 4.2: Orthostatic Blood Pressure by Subjective Memory *(unadjusted)*

***n*= 4340**	**Excellent**	**Very Good**	**Good**	**Fair**	**Poor**	***p***
N (%)	635 (14.6)	1431 (33.0)	1651 (38.0)	535 (12.3)	88 (2.0)	
	Systolic BP mean mmHg (SD)					
Supine	137.1 (20.9)	136.5 (21.9)	135.7 (22.7)	136 (22.9)	136 (22.3)	0.73
Nadir	98.6 (23.4)	97.4 (23.2)	96.8 (24.7)	95.3 (25.5)	93 (26.1)	0.080
10sec	110.3 (24)	108.7 (24)	107.9 (25.3)	106.9 (25.8)	104.9 (28.2)	0.092
20sec	134.6 (24.9)	132.6 (24.8)	131 (26.7)	128.8 (28.1)	128.8 (30)	0.001
30sec	137.2 (24.4)	135.6 (23.7)	134.3 (25.6)	132.3 (26.3)	133.5 (26.7)	0.007
	Diastolic BP mean mmHg (SD)					
Supine	74.5 (10.7)	73.5 (11)	72.8 (11.5)	72.9 (11.5)	73.4 (11.8)	0.015
Nadir	48.6 (13.3)	47.8 (13.4)	47.1 (13.8)	46.9 (14)	45.8 (14.3)	0.075
10sec	56 (13.6)	54.8 (13.8)	54.2 (14.1)	54 (14.1)	53.8 (15.1)	0.062
20sec	70.3 (14.1)	68.9 (13.9)	67.7 (14.6)	66.8 (15.2)	67.4 (15.3)	<0.001
30sec	74.1 (12.9)	72.7 (12.6)	71.6 (13.3)	70.8 (13.6)	71.7 (13.3)	<0.001

P vales are from ANOVA; 'BP'=blood pressure; 'Nadir'=lowest blood pressure recorded post-stand; 'mmHg'= millimetres of mercury

After minimal adjustment (Model 1) significant differences in SBP during orthostasis were evident across categories of subjective memory; predicted changes in SBP during orthostasis according to subjective memory are displayed in Figure 4.2.

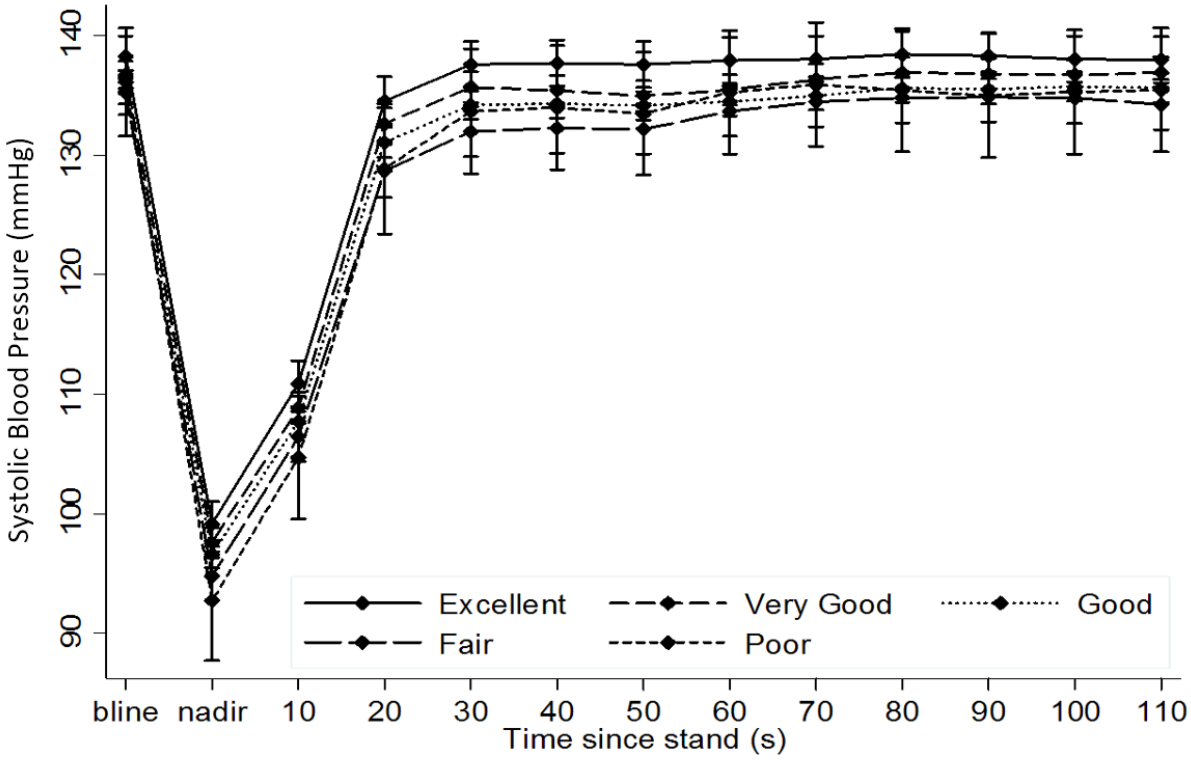


Figure 4.2: Systolic Orthostatic Blood Pressure by Subjective Memory
Systolic blood pressure from supine to standing across subjective memory categories adjusted for age, age squared and sex; 'bline'=baseline supine blood pressure; 'Nadir'=lowest blood pressure recorded post-stand; 's'=seconds; 'mmHg'= millimetre of mercury

Even after full adjustment for confounders (Model 2) those with poorer subjective memory had the lowest SBP Nadir: lowest adjusted mean SBP post-orthostasis in those with 'poor' subjective memory was 92.2mmHg (95%CI 87.1; 97.3) while in those with 'excellent' subjective memory it was 99.3mmHg (95%CI 97.4; 101.2); p=0.011. These differences tended to occur along a linear gradient and persisted throughout the first 30 seconds. Sensitivity analysis excluding those with poorer scores (<26) on the MoCA demonstrated a

similar linear pattern of orthostatic SBP responses across groups although the smaller sample size resulted in less certainty around the estimates (Table 4.3).

Table 4.3: Systolic Orthostatic Blood Pressure by Subjective Memory (adjusted)

n=4340	**Excellent**	**Very Good**	***p***	**Good**	***p***	**Fair**	***p***	**Poor**	***p***
Model 1									
Supine BP	***Ref.***	-1.53 (-3.57,0.51)	0.141	-2.93 (-4.93,-0.93)	0.004	-3.04 (-5.56,-0.52)	0.018	-2.16 (-7.02,2.70)	0.384
Nadir	***Ref.***	-1.57 (-3.82,0.67)	0.170	-2.53 (-4.74,-0.32)	0.025	-4.35 (-7.13,-1.57)	0.002	-6.43 (-11.79,-1.07)	0.019
10sec	***Ref.***	-2.03 (-4.34,0.28)	0.085	-3.13 (-5.41,-0.86)	0.007	-4.42 (-7.28,-1.55)	0.002	-6.18 (-11.70,-0.66)	0.028
20sec	***Ref.***	-1.92 (-4.36,0.51)	0.122	-3.47 (-5.87,-1.08)	0.005	-5.84 (-8.86,-2.83)	<0.001	-5.68 (-11.49,0.14)	0.056
30sec	***Ref.***	-1.90 (-4.23,0.43)	0.110	-3.39 (-5.68,-1.10)	0.004	-5.61 (-8.49,-2.73)	<0.001	-3.92 (-9.48,1.63)	0.166
Model 2									
Supine BP	***Ref.***	-1.59 (-3.63,0.45)	0.126	-3.29 (-5.32,-1.27)	0.001	-3.79 (-6.37,-1.21)	0.004	-3.55 (-8.54,1.44)	0.163
Nadir	***Ref.***	-1.65 (-3.90,0.60)	0.150	-2.76 (-4.99,-0.52)	0.016	-4.69 (-7.54,-1.85)	0.001	-7.12 (-12.63,-1.61	0.011
10sec	***Ref.***	-2.04 (-4.35,0.27)	0.084	-3.31 (-5.60,-1.01)	0.005	-4.75 (-7.67,-1.83)	0.001	-6.96 (-12.62,-1.30)	0.016
20sec	***Ref.***	-1.57 (-3.99,0.84)	0.201	-2.94 (-5.34,-0.54)	0.016	-4.98 (-8.04,-1.92)	0.001	-4.51 (-10.43,1.41)	0.136
30sec	***Ref.***	-1.61 (-3.93,0.70)	0.173	-2.96 (-5.27,-0.66)	0.012	-4.90 (-7.83,-1.97)	0.001	-2.89 (-8.57,2.79)	0.318
Sensitivity Analysis: Model 2 MoCA>=26 : n=2320/4340									
Supine BP	***Ref.***	-1.39 (-3.97,1.18)	0.290	-2.34(-4.95,0.27)	0.078	-3.98 (-7.51,-0.44)	0.027	-2.72 (-11.62,6.18)	0.554
Nadir	***Ref.***	-2.52 (-5.34,0.35)	0.086	-2.79 (-5.71,-0.13)	0.061	-5.12 (-9.07,-1.17)	0.011	-7.67 (-17.63,2.29)	0.131
10sec	***Ref.***	-3.03 (-5.98,-0.07)	0.045	-3.29 (-6.29,-0.29)	0.032	-4.72 (-8.78,-0.66)	0.023	-9.01 (-19.25,1.23)	0.085
20sec	***Ref.***	-1.96 (-5.04,1.12)	0.213	-2.41 (-5.53,0.72)	0.131	-3.70 (-7.94,0.53)	0.086	-4.94 (-15.61,5.74)	0.365
30sec	***Ref.***	-1.12 (-4.10,1.86)	0.461	-1.57 (-4.59,1.45)	0.309	-2.69 (-6.73-1.46)	0.207	-0.92 (-11.22,9.40)	0.862

Data are regression coefficients (95% Confidence Intervals) and associated p-values for differences between categories of subjective memory;
'Nadir'=lowest blood pressure recorded post-stand
Model 1 = age, age squared and sex
Model 2 = Model 1 + education level, BMI, depressive symptoms, objective cognitive deficits (MoCA), physical co-morbidities (chronic conditions and cardiovascular disease), medications (antidepressants and antihypertensive) and a history of smoking

Significant differences in DBP were evident during orthostasis both after minimal adjustment and after full adjustment for confounders (not shown). In line with the changes observed in SBP, Nadir DBP was lowest in those with poor subjective memory (-3.28mmHg; 95%CI -6.38; -0.18).

Investigation of SBP stabilisation after standing by adjustment for supine SBP in the models largely attenuated the differences across groups, however those with poor subjective memory had the lowest Nadir SBP (-4.33mmHg (95%CI -8.22; -0.45)) and had a greater SBP deficit at 10 seconds post-stand (-4.00 mmHg (95%CI -7.82; -0.17)) relative to those with excellent subjective memory. This association was modified by sex (interaction significant at the $p<0.1$ level) such that it remained only among men. The analysis was subsequently stratified by sex. After accounting for supine SBP, on average men with poor subjective memory had a Nadir SBP that was -6.14mmHg lower (95%CI -10.96; -1.31; $p=0.013$) than men with excellent subjective memory, and a prolonged time to SBP stabilisation at 10 seconds post-stand (-6.64 mmHg (95%CI -11.49; -1.79); $p=0.007$) (Figure 4.3 (a) and Figure 4.3(b)).

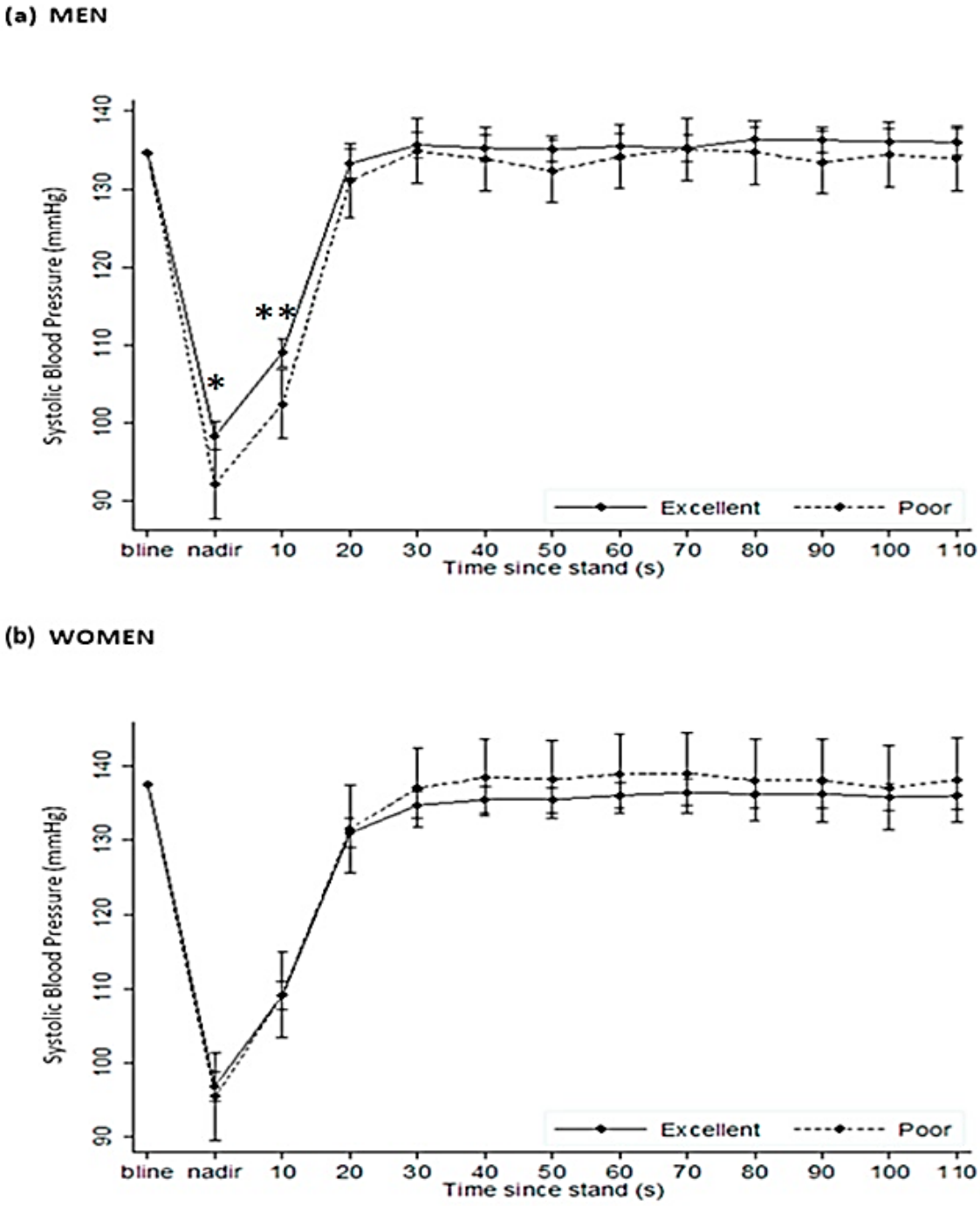


Figure 4.3: Systolic Orthostatic Blood Pressure Stabilisation by Subjective Memory stratified by Sex.

Systolic orthostatic blood pressure *stabilisation* after standing: 'excellent' subjective memory versus 'poor' subjective memory in (a) MEN and (b) WOMEN adjusted for age, age squared, education level, BMI, depressive symptoms, objective cognitive deficits, co-morbidities, medications, smoking and supine systolic blood pressure (Model 3); 'bline'=baseline supine blood pressure; 'Nadir'=lowest blood pressure recorded post-stand; 's'=seconds; 'mmHg'= millimetre of mercury

There were no differences in stabilisation of DBP among the categories of subjective memory after adjustment for baseline DBP. DBP stabilisation among the categories of subjective memory did not vary by sex.

Sensitivity Analysis

Model 2 (Supplementary Table 4.1) and Model 3 (Supplementary Table 4.2) were re-estimated excluding those with diabetes (*model a*), existing cardiovascular disease (*model b*), clinically significant depressive symptoms (*model c*), those on anti-depressant medications (*model d*), and finally excluding all of the above (*model e*). Any substantive conclusions regarding the pattern of associations remained unchanged.

4.5. Discussion

This study uses comprehensive data from a large community-dwelling population-based sample to demonstrate an association between lower orthostatic BP and poorer subjective memory. This relationship tended to occur in a linear 'dose-response' pattern and persisted after making adjustments for age, sex, education, BMI, cardiovascular/cerebrovascular conditions, smoking, medications, and importantly both depression and the MoCA, a clinically established objective measure of cognition sensitive to the presence of MCI – suggesting that neither depressive symptoms nor objective cognitive deficits alone explain this association.[352] In keeping with prior studies investigating the effects of orthostatic BP on outcomes in older adults, the associations were stronger with SBP but nevertheless accompanied by consistent patterns in DBP.[274]

This study provides support for the hypothesis that subtle cardiovascular autonomic dysfunction may be present in SMI and reflected in sub-clinical OH. Orthostatic BP is regulated by the ANS and accumulating evidence suggests that higher brain centres may be involved in cardiovascular autonomic regulation.[355] These regions may be among the first to be affected in dementia associated neurodegeneration and thus account for the relationships shown here.[218] SMI, in the absence of objective cognitive deficits, is proposed as an early stage of cognitive decline.[103] These findings were robust to adjustment for objective cognitive function and in sensitivity analysis including only those with the highest scores on the MoCA.

To my knowledge this is the first study to assess the relationship between SMI and orthostatic measures using continuous BP recordings at a population level. Elmståhl and

Widerström previously reported associations with symptoms of OI and SMI.[278] Orthostatic intolerance is classically attributed to cerebral hypoperfusion and continuous monitoring of orthostatic BP may detect subtle BP changes in those experiencing OI not detectable using traditional methods.[184] Sub-clinical orthostatic BP dysregulation may be related to cognitive decline via cerebral hypoperfusion.[356] The results suggest that the absolute lowest BP (or 'Nadir') reached post-stand may be important in determining the consequences for the cerebral circulation. We note that the predicted mean SBP reached post-stand in those with poor subjective memory was 92.2mmHg (95%CI 87.1; 97.3) relative to 99.3mmHg (95%CI 97.4;101.2) among those with excellent subjective memory. A SBP of <90mmHg is classically taken to represent critical hypotension; however this threshold may be higher in elders.[357] The differences in orthostatic BP we have demonstrated among the different categories of subjective memory are comparable to the BP lowering effect of antihypertensive monotherapy[358] and may reflect subtle autonomic dysfunction similar to that detected by continuous BP monitoring in early Parkinson's disease.[359]

Scuteri et al previously reported that hypotensive episodes (defined as at least one reading <100mmHg) during 24-hour ambulatory monitoring, which could plausibly have resulted from daytime orthostatic fluctuations – were more common in those with SMI.[116] The HUNT study, which sampled a population of 12,225 participants, aged 65 and over, found that relative to moderate sitting SBP levels, higher seated SBP was associated with better subjective memory - in line with these results suggesting that lower supine BP drives lower SBP following orthostatic stress.[114] Lower orthostatic BP, even at sub-clinical levels, may not be effectively compensated by auto-regulatory processes and this may result in inadequate hemodynamic responses to cognitive demands.[189] High metabolic requirements necessitate careful regulation of CBF; there is precise coupling of regional brain activity to

regional blood flow and this may contribute to the auto-regulation of cerebral perfusion.[192] In older adults, PET imaging in subjects with SMI demonstrated less efficient coupling of blood flow to regional brain activity.[344]

By adjusting for supine BP, stabilisation of BP to seated levels after standing was investigated. Time to stabilisation may better determine the consequences of orthostatic stress over and above absolute BP reached post stand.[274] This highlighted sex differences; men with poor subjective memory had a larger orthostatic SBP deficit and slower SBP stabilisation than men with excellent subjective memory - a pattern consistent with impaired cardiovascular autonomic homeostasis. Although sex differences in cognitive deficits remain poorly understood[121], a recent study has suggested that SMI may reflect objective cognition in men but affective state in women.[140] Women reported poorer subjective memory despite having better objective cognition; men however were more accurate in self-appraisal of cognitive abilities.[140] The HUNT study also described sex differences in their findings - in men, but not women, lower seated systolic BP was related to greater SMI relative to moderate seated systolic BP.[114] Interestingly, older men have previously been shown to have higher rates of OH-related hospitalizations and demonstrate poorer cerebral auto-regulation during standing than women.[185]

Limitations to this work include that it is a cross-sectional analysis so causation cannot be established. In keeping with many studies investigating SMI this study includes a single item measure of SMI. There remains a lack of consensus in the literature as to the best way to measure SMI[360]. Asking about decline in subjective memory may be a more reliable harbinger of dementia[361] and should be considered in future studies. Furthermore,

respondents who attended the health centre assessment tended to be younger, better educated and in better health. In mitigation, it could be argued that this will have the effect of biasing the estimates downwards. Finally we do not have access to corroborating measures of cerebral auto-regulation or neuroimaging in this cohort to further investigate hypotheses with regard to the underlying pathophysiology of these relationships.

SMI has known overlaps with psychiatric diagnoses.[102] Adjustment for measures of anxiety did not substantively alter the relationships shown here (results not shown). In those with established cardiovascular disease, poorer autonomic function has been linked to greater depressive symptoms.[362] While in sensitivity analysis findings remained robust to exclusion of those with indicators of clinical depression and cardiovascular disease, concomitant analysis of other markers of cardiovascular autonomic function e.g. HRV and BRS may have enriched understanding of autonomic function in those with SMI. Both HRV and BRS however require the additional analysis of electrocardiographic tracings which was beyond the scope of the current investigation.

No corrections for multiple comparisons were made thus the possibility of type 1 error must be acknowledged. Repeated comparisons were minimised however, by investigating the relationship with the 'Nadir' and by focusing analysis on the first 30 seconds. There is limited population data available on continuous orthostatic BP changes and as yet no definitive manner in which to approach this data[271], thus this analysis is somewhat exploratory and only consistent patterns across groups are interpreted.

While the oldest-old are those most at risk of developing dementia, the accompanying neuropathological changes may begin decades earlier.[35] The wide age range of this sample (50-91 years) encompasses those at risk for future dementia, however given that the mean age of the sample is 62 years, appropriate caution should be used in the extrapolation of these findings to older age groups – in particular to those aged 80+.

Despite such caveats these results point towards potentially modifiable contributors to SMI. SMI has been consistently associated with poorer quality of life thus efforts focused on intervention should represent both a clinical and public health priority.[102] Orthostatic BP dysregulation is treatable – often by employing simple conservative strategies including modification of culprit medications and ensuring adequate fluid intake.[363]

This study demonstrates that sub-clinical OH is associated with SMI; these results add to evidence linking orthostatic BP dysregulation to cognitive dysfunction and to research examining the organic underpinnings of SMI. Continuous BP monitoring may provide detailed insights into orthostatic BP patterns accompanying early autonomic dysfunction which is not detectable by standard methods. If these findings were to be replicated, subtle cardiovascular autonomic dysfunction as reflected in poorer BP response to orthostasis, may represent a modifiable risk marker for SMI in older adults.

Supplementary Table 4.1: Systolic Orthostatic Blood Pressure by Subjective Memory *(adjusted)*

	Excellent	Very Good	*p*	Good	*p*	Fair	*p*	Poor	*p*
	Model a								
	excluding participants with Diabetes n=4063/4340								
Supine BP	**Ref.**	-1.51 [-3.61,0.59]	0.158	-3.46 [-5.55,-1.38]	0.001	-3.48 [-6.15,-0.82]	0.010	-5.08 [-10.35,0.19]	0.059
Nadir	**Ref.**	-1.66 [-3.99,0.68]	0.164	-3.06 [-5.39,-0.74]	0.010	-4.50 [-7.46.-1.54]	0.003	-8.76 [-14.62,-2.90]	0.003
10sec	**Ref.**	-1.92 [-4.31,0.47]	0.116	-3.53 [-5.91,-1.15]	0.004	-4.50 [-7.54,-1.46]	0.004	-8.29 [-14.3,-2.28]	0.007
20sec	**Ref.**	-1.57 [-4.05,0.92]	0.216	-3.04 [-5.52,-0.57]	0.016	-4.52 [-7.68,-1.36]	0.005	-5.78 [-12.03-0.46]	0.070
30sec	**Ref.**	-1.53 [-3.92,0.86]	0.210	-2.91 [-5.29,-0.53]	0.017	-4.20 [-7.23,-1.16]	0.007	-3.97 [-9.98,2.04]	0.195
	Model b								
	excluding participants with existing CVD/cerebrovascular disease, n=3844/4340								
Supine BP	**Ref.**	-1.88 [-3.97, 0.21]	0.078	-3.59 [-5.67,-1.50]	0.001	-4.82 [-7.52,-2.12]	<0.001	-5.06 [-10.86,0.74]	0.087
Nadir	**Ref.**	-2.13 [-4.44,0.19]	0.071	-3.42 [-5.73,-1.11]	0.004	-5.34 [-8.33,-2.35]	<0.001	-9.72 [-16.14,-3.30]	0.003
10sec	**Ref.**	-2.39 [-4.78,-0.01]	0.049	-3.94 [-6.31,-1.56]	0.001	-5.18 [-8.25,-2.11]	<0.001	-9.98 [-16.58,-3.38]	0.003
20sec	**Ref.**	-2.04 [-4.51,0.44]	0.107	-3.74 [-6.21,-1.26]	0.003	-5.81 [9.01,-2.61]	<0.001	-7.52 [-14.4,-0.64]	0.032
30sec	**Ref.**	-2.03 [-4.42,0.37]	0.097	-3.61 [-6.00,-1.22]	0.003	-5.72 [-8.81,-2.62]	<0.001	-5.85 [-12.5,0.8]	0.085
	Model c								
	excluding participants with CESD>=16, n=3988/4340								
Supine BP	**Ref.**	-1.52 [3.58,0.55]	0.150	-3.20 [-5.26,-1.13]	0.002	-3.74 [-6.44,-1.05]	0.007	-2.22 [-7.91,3.47]	0.444
Nadir	**Ref.**	-1.52 [-3.81,0.76]	0.192	-2.83 [-5.11,-0.54]	0.015	-4.28 [-7.26,-1.29]	0.005	-5.96 [-12.25,0.34]	0.064
10sec	**Ref.**	-1.78 [-4.13,0.56]	0.136	-3.28 [-5.62,-0.93]	0.006	-4.22 [-7.27,-1.16]	0.007	-5.60 [-12.1,0.86]	0.089
20sec	**Ref.**	-1.38 [3.85,1.08]	0.271	-2.80 [-5.27,-0.34]	0.026	-4.78 [-8.00,-1.57]	0.004	-3.38 [-10.16,3.41]	0.330
30sec	**Ref.**	-1.40 [3.76-0.97]	0.247	-2.84 [-5.21,-0.48]	0.284	-4.89 [-7.97,-1.81]	0.018	-1.80 [-8.30,4.71]	0.588

	Model d								
	excluding participants on ADT, n=4086/4340								
Supine BP	**Ref.**	-1.46 [-3.53,0.61]	0.167	-3.08 [-5.14,-1.01]	0.004	-3.53 [-6.21,-0.85]	0.010	-0.24 [-5.78,5.30]	0.932
Nadir	**Ref.**	-1.14 [-3.43,1.16]	0.332	-2.23 [-4.51,0.06]	0.057	-3.74 [-6.71,-0.78]	0.013	-5.08 [-11.21,1.05]	0.104
10sec	**Ref.**	-1.44 [-3.79,0.92]	0.231	-2.75 [-5.10,-0.41]	0.022	-3.77 [-6.81,-0.73]	0.015	-4.59 [-10.9,2,1.7]	0.153
20sec	**Ref.**	-1.26 [-3.71,1.19]	0.314	-2.42 [-4.87,0.03]	0.052	-4.20 [-7.38,-1.03]	0.009	-1.72 [-8.27,4.83]	0.607
30sec	**Ref.**	-1.44 [-3.79,0.92]	0.232	-2.62 [-4.97,-0.27]	0.029	-4.67 [-7.72,-1.62]	0.003	-0.87 [-7.16,5.42]	0.786
	Model e								
	Excluding participants with CVD, Diabetes, ADT and CESD>=16: n=3230/4340								
Supine BP	**Ref.**	-1.75 [-3.95,0.45]	0.118	-3.64 [-5.85,-1.43]	0.001	-4.76 [-7.73,-1.79]	0.002	-2.80 [-10.46,4.86]	0.474
Nadir	**Ref.**	-1.57 [-4.03,0.89]	0.212	-3.52 [-6.00,-1.04]	0.005	-4.52 [-7.85,-1.18]	0.008	-8.41 [-17.00,0.19]	0.055
10sec	**Ref.**	-1.52 [-4.04,1.01]	0.240	-3.71 [-6.26,-1.17]	0.004	-4.09 [-7.51,0.67]	0.019	-7.68 [-16.0,1.14]	0.088
20sec	**Ref.**	-1.52 [-4.15,1.10]	0.255	-3.56 [-6.20,0.92]	0.008	-4.73 [-8.27,-1.18]	0.009	-5.12 [-14.26,4.03]	0.273
30sec	**Ref.**	-1.62 [-4.15,0.91]	0.210	-3.48 [-6.03,-0.93]	0.008	-4.96 [-8.38,-1.53]	0.005	-4.65 [-13.47,4.18]	0.302

Data are regression coefficients [95% Confidence Intervals] and associated p-values for differences between categories of subjective memory;
'Nadir'=lowest blood pressure recorded post-stand; CVD=cardiovascular disease; CES-D=Centre for Epidemiological Studies Depression Scale; ADT=Antidepressant treatment
Model a-e adjusted for (where not excluded as noted above) age, age squared and sex, education level, BMI, depressive symptoms, objective cognitive deficits (MoCA), physical co-morbidities (chronic conditions and cardiovascular disease), medications (antidepressants and antihypertensive) and a history of smoking

Supplementary Table 4.2: Systolic Orthostatic Blood Pressure Stabilisation by Subjective Memory stratified by Sex (*adjusted for supine Systolic BP*)

Model a
excluding participants with Diabetes

		Men (n=1831)		Women (n=2232)	
	Excellent	**Poor**	**p**	**Poor**	**p**
Supine SBP	**Ref.**	-	-	-	-
Nadir	**Ref.**	-7.33 (-12.58, -2.09)	0.006	-0.98 (-7.47,5.52)	0.768
10sec	**Ref.**	-7.63 (-12.90,-2.37)	0.005	0.98 (-5.30,7.27)	0.757

Model b
excluding participants with CVD/Cerebrovascular disease

		Men (n=1732)		Women(n=2112)	
	Excellent	**Poor**	**p**	**Poor**	**p**
Supine SBP	**Ref.**	-	-	-	-
Nadir	**Ref.**	-6.16 (-11.50,-0.83)	0.024	-3.70 (-11.,4.27)	0.363
10sec	**Ref.**	-6.84 (-12.25,-1.43)	0.013	-2.36 (-10.08,5.35)	0.548

Model c
excluding participants with CES-D >=16

		Men (n=1839)		Women (n=2095)	
	Excellent	**Poor**	**p**	**Poor**	**p**
Supine SBP	**Ref.**	-	-	-	-
Nadir	**Ref.**	-4.94 (-10.227,0.355)	0.067	-2.34 (-5.43,0.75)	0.137
10sec	**Ref.**	-4.81 (-10.11,0.49)	0.075	-1.13 (-8.69,6.43)	0.769

Model d
excluding participants with ADT

		Men (n=1924)		Women (n=2162)	
	Excellent	**Poor**	**p**	**Poor**	**p**
Supine SBP	**Ref.**	-	-	-	
Nadir	**Ref.**	-7.16 (-12.5,-1.79)	0.009	-1.73 (-8.61,5.15)	0.623
10sec	**Ref.**	-7.67 (-13.07,-2.27)	0.005	-0.04 (-6.69,6.61)	0.99

Model e
excluding participants with Diabetes, CVD, CES-D >=16, & ADT

		Men (n=1481)		Women (n=1749)	
	Excellent	**Poor**	**p**	**Poor**	**p**
Supine SBP	**Ref.**	-	-	-	-
Nadir	**Ref.**	-7.20 (-14.0,-0.35)	0.04	-2.54 (-14.21,9.14)	0.67
10sec	**Ref.**	-6.94 (-13.89,0.004)	0.05	-0.45 (-11.70,10.79)	0.937

Data are regression coefficients (95% Confidence Intervals) and associated p-values for differences between categories of subjective memory

'Nadir' =lowest blood pressure recorded post-stand, CVD=cardiovascular disease; CES-D=Centre for Epidemiological Studies Depression Scale; ADT=Antidepressant treatment

Models a- e further adjusted (where not excluded as noted above) for age, age squared and sex, education level, BMI, depressive symptoms, objective cognitive deficits (MoCA), physical co-morbidities (chronic conditions and cardiovascular disease), medications (antidepressants and antihypertensive), a history of smoking and supine SBP

5. STUDY II - Baroreflex Sensitivity, Depression, Anxiety and Anti-Depressant use in Older Adults

Study II investigates cardiac BRS as the independent variable of interest and affective symptoms as the outcome of interest. Prior population-based studies investigating BRS and affective symptoms have focused on depressive symptoms (despite known overlap between anxiety and depression) and suggest that associations may vary according to ADT. Here, associations between BRS and symptoms of depression *and* anxiety in older adults are investigated, additionally exploring potential sex differences and confounding effects of ADT.

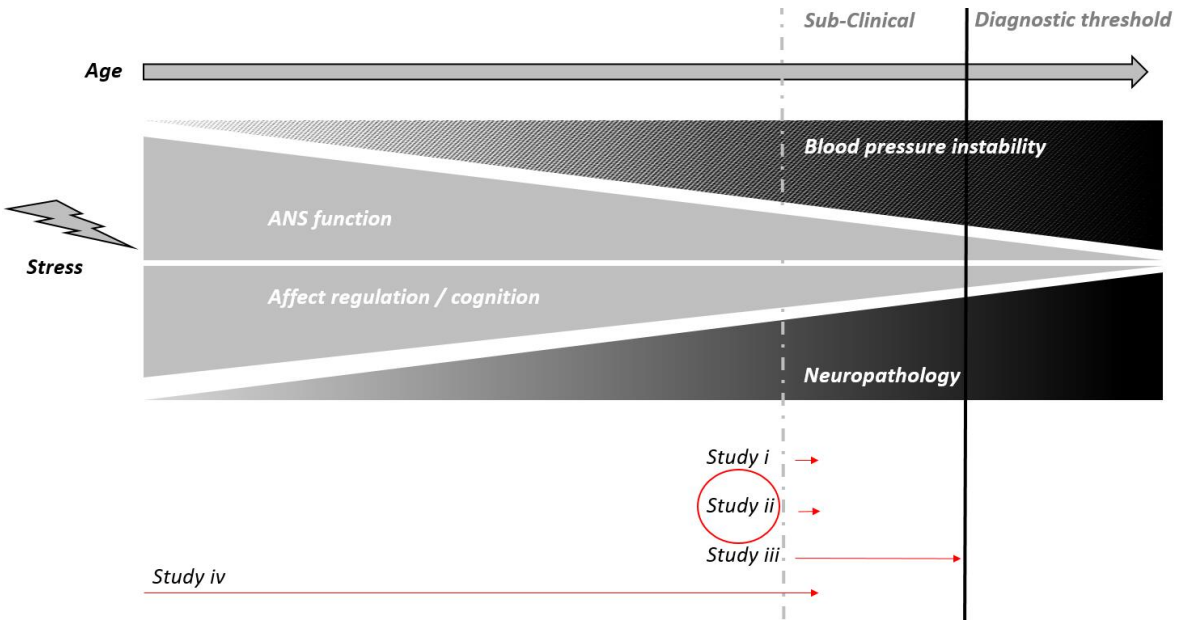


Figure 5.1: Thesis Figure: Study II
Study II investigates ***cross-sectional*** associations between Baroreflex Sensitivity, Depression, Anxiety and Anti-depressant use in Older Adults.

5.1. Abstract

Introduction: Baroreflex Sensitivity is a measure of cardiovascular autonomic function. This study investigates the hypothesis that lower BRS is associated with higher symptoms of anxiety and depression in older adults, and that these associations will differ according to sex and ADT status.

Methods: Data was from 3459 participants aged 50+ from the first wave (2009-2011) of the TILDA cohort study. Multivariate multiple regression was used to test associations between non-invasively measured BRS and symptoms of worry (assessed using the abbreviated Penn State Worry Questionnaire (PSWQ-A)), global anxiety (Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-A)) and depression (Center for Epidemiological Studies Depression Scale (CES-D)).

Results: Associations between BRS and symptoms of depression and anxiety were evident but varied according to sex and ADT status. For example, with respect to anxiety outcomes: for every one msec/mmHg increase in BRS in men there was on average a decrease of -0.06 (95% Confidence Interval -0.11;-0.02); p=0.01 and -0.03 (-0.06;-0.01); p=0.005 in scores on the PSWQ-A and HADS-A respectively. In contrast, in women on antidepressants, for every

one msec/mmHg increase in BRS there was an increase of 0.24 (0.03;0.44); p=0.02 and 0.12 (0.03;0.22); p=0.01 in scores on PSWQ-A and HADS-A.

Conclusions: This study reports complex, sex-specific associations between BRS, anxiety and depressive symptoms which may have implications for ADT in older adults.

5.2. Introduction

Impaired cardiovascular autonomic function may be associated with greater affective symptoms in older adults, however the relationship is understudied. The majority of investigations have focused on HRV[88,319,364–366], while few studies have investigated BRS. Baroreflex sensitivity reflects the ability of the cardiovascular ANS to respond to short term BP fluctuations[157] and lower BRS is associated with greater BP instability.[89] A change in systemic BP initiates the baroreflex via stretch sensitive mechanoreceptors located in the intima of the carotid artery and aorta causing, for example, an increase in HR and peripheral resistance in response to a drop in systemic BP.[157] A higher BRS indicates a closer relationship between BP and HR, while low BRS reflects the decoupling of this relationship, and is a known correlate of increased cardiovascular morbidity and mortality.[367]

Sex differences in the prevalence of both CVD[368] and affective disorders[69] are well described. Cardiovascular autonomic function, including BRS, may also differ according to sex.[369–371] Both anxiety and depression are more prevalent in women and this sex difference persists into later life.[58,372] Some studies suggest GAD is the most common affective disorder in later life and may precede the development of a depressive episode; symptoms of worry are the primary feature of GAD.[373,374] Recent studies investigating BRS and affect in older adults have focused solely on associations with depression – anxiety has not been investigated as an outcome of interest.[319–321] Moreover, results have been conflicting: two studies reported lower BRS in those with depressive symptoms[319,320], however a third found no association, instead reporting an association between lower BRS and ADT.[321]

Anti-depressants are commonly used to treat anxiety and depression in older adults but are more frequently prescribed to women.[375] ADT may adversely impact cardiovascular autonomic function.[376] Therefore any relationship between cardiovascular autonomic function and affective symptoms in older adults may be confounded by ADT.[376]

Here, associations between BRS and affective symptoms in older adults are examined.

Hypotheses under investigation:

1. BRS will be lower in older adults with higher levels of depressive and/or anxiety symptoms.

2. The relationship between BRS and symptoms of depression and/or anxiety will vary according to sex and concurrent ADT

5.3. Methods

Sample

This study is based on the analysis of cross-sectional data from the first wave of TILDA, conducted 2009-2011. This is a population-based, nationally representative study of community-dwelling adults aged 50 and over. The TILDA data collection process has been described in detail elsewhere.[349] Briefly, participants were assessed in their own home by means of a Computer Assisted Interview (CAPI) delivered by a trained interviewer. They were also invited to return a Self-Completion Questionnaire, which they completed unsupervised and which collected information on more sensitive topics. In total 8,175 participants aged 50 and older enrolled in the TILDA cohort of whom 6,636 returned the Self-Completion Questionnaire. Each participant was invited to attend a detailed physical health assessment in one of two university-affiliated centres and specially trained research nurses carried out 5035 individual 'health centre' assessments. Figure 5.2 outlines the sample included in the complete case analysis.

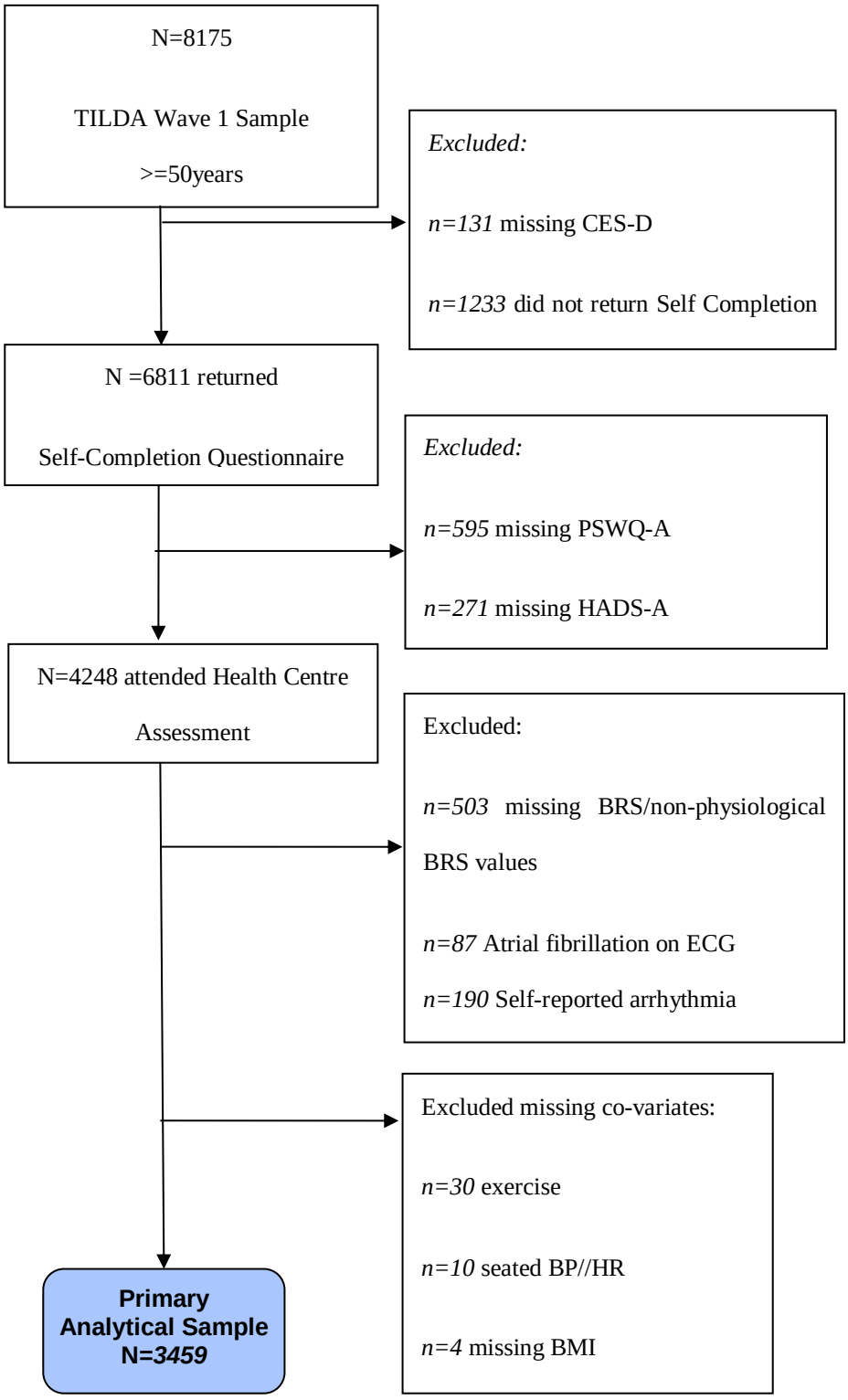


Figure 5.2: Study II: Flow Diagram

Ethics

Trinity College Dublin Health Research Ethics Committee granted Ethical Approval for the study. Each participant provided written informed consent prior to enrolment in the study. Those unable to give informed consent were excluded.

Primary Explanatory Variable:

Baroreflex Sensitivity

Baroreflex Sensitivity was derived using the non-invasive 'sequence' method.[313] Participants lay supine for ten minutes in a quiet, dimly lit room maintained at a steady ambient temperature. During this time BP was assessed non-invasively using a beat-to-beat plethysomnography device (Finometer® MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands, www.finapres.com) and HR was recorded using a three lead ECG tracing. An algorithm was applied to the extracted data and the rate of change of successive heart beats to a change in SBP of 10mmHg was calculated. A higher BRS thus corresponds to a more sensitive coupling of BP and HR.

All ECG tracings were screened and those with objective evidence of Atrial Fibrillation (n=87), a self-reported cardiac arrhythmia (n=190) and those without baroreflex readings (n=503) (including non-physiological readings) were excluded from this analysis.

Outcomes of Interest:

Anxiety Symptoms

Two questionnaires were used to investigate anxiety symptoms in later life - in order to measure both global anxiety symptoms and symptoms of worry.[98]

Global Anxiety

Symptoms of anxiety were recorded using the anxiety subscale of the HADS-A which is a self-report questionnaire, assessing the frequency of anxiety symptoms over the last week.[377] This scale is scored from 0-21 with higher scores reflecting greater symptoms of anxiety. A cut-point of ≥8 has been validated as potentially reflecting clinically relevant symptoms.[378]

Symptoms of Worry

Symptoms of worry were captured using the abbreviated version of the PSWQ-A which has been validated for use in older adults.[374,379] This is an 8 item questionnaire which assesses a person's tendency to worry and associated ability to control worry. Higher scores reflect greater levels of worry. A cut-point of 23 has previously been validated as reflecting potential case-level symptoms.[374]

Depressive Symptoms

Levels of depressive symptoms over the previous week were recorded using the CES-D.[380] Each question offers a four-point response scale with options ranging from, "Rarely or none of the time (less than 1 day)" to "All of the time (5-7 days)". This is a 20-item questionnaire, which produces a total score ranging from 0-60 and is validated for use in epidemiological populations. Higher scores indicate greater levels of depressive symptoms.[354] A cut-point of 16 has been shown to have a high sensitivity and specificity for clinically relevant case-level symptoms in older adults.[354]

Covariates

Age, sex and educational attainment were recorded. Smoking history was noted as current, past or never. BMI was calculated as kg/m2 from height and weight measurements.

Haemodynamic Variables

BP and HR were also measured in the seated position using an automated oscillometric device ('Omron'). SBP, DBP and resting HR were calculated as the average of two consecutive seated measures.

Medications

Medication use was determined by recording medication names from the medicine packaging in the participant's home and classified using the WHO ATC system (WHO, 2012).

Antidepressant use was identified where the first four digits of the World Health ATC code were "N06A" including SSRI's (N06AB) and SNRI (NO6AX).

Antihypertensive use was identified using the codes "C02*" (anti-adrenergic agents) "C03*" (diuretics), "C07*" (beta-blockers), "C08*" (calcium-channel blockers), "C09*" (angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers) and combinations of the above "(C02*)".

Cardiovascular conditions

Cardiovascular/ cerebrovascular conditions were recorded to include: angina, myocardial infarction, heart failure, stroke or Transient Ischaemic Attack, hypercholesterolemia, structural heart disease, angioplasty and coronary artery bypass graft. The total number of cardiovascular diseases was then summed and recoded as 0, 1, 2 or more conditions and added to models as a categorical variable.

Self-reported levels of physical activity were measured using the International Physical Activity Questionnaire - Short Form; validated cut-points were used to classify the population into three levels of physical activity: ‘Low’, ‘Moderate’ and ‘High’.[381]

Statistical Analysis

Appropriate descriptive statistics were employed to describe the population according to sex. Unadjusted associations between BRS and affective symptoms were examined using scatter plots and linear, quadratic and lowess fits. Simultaneous multivariate multiple regression analysis was employed to estimate the relationship between BRS as an independent variable across outcomes i.e. across CES-D, HADS-A and PSWQ-A scores. Multivariate multiple regression differs from simple linear regression in that several dependent variables are jointly regressed on the same independent variables.[382] The individual coefficients and standard errors produced are identical to those that would be produced by estimating each equation separately, however coefficients can be tested across equations thus allowing for tests of statistical significance to account for the co-variance of outcomes.[382]

An initial minimally adjusted model (Model 1) included age, sex and education as independent variables. Given potential non-linear effects, age was modelled as a piecewise linear function with knots at five year intervals. Model 2 additionally adjusted for BMI, height, smoking, CVD, co-morbidity, physical activity, seated SBP, seated DBP and HR. To assess the moderating influence of sex, an interaction term between BRS and sex was tested and, where significant, was retained in further modelling. In Model 3 the additional moderating influence of ADT on any sex-specific association between BRS and the dependent variables was assessed with the addition of a three way interaction term i.e. sex*BRS*ADT. Estimates from models were plotted to aid interpretation of interaction effects.

Sensitivity analysis

Given the skewed distribution of BRS, models were repeated using the natural log transformed variable. Further, to test associations between potentially more clinically relevant categorisations of both BRS and affective symptoms, outcomes were categorised according to 'case-level' cut-points, and BRS was categorised according to tertiles of the population distribution. Separate multivariable logistic regression analyses were run for each outcome (case-level symptoms: No=0, Yes=1) testing for interactions between sex and BRS (coded as a three-item categorical variable: lowest tertile; middle tertile; highest tertile - with the lowest tertile as the referent category). Where interactions were significant, subsequent analyses were stratified by sex. Models were repeated excluding those on ADT and subsequently those participants with a self-reported history of two or more cardiovascular conditions.

5.4. Results

The final analysis sample was 3459. 54.0% (n=1873) were women and the mean age was 61.1 years (*SD* 8.0) with no difference in mean age between men and women. Women had higher scores across all outcome measures and were more likely to be prescribed ADT (Table 5.1). Men had more cardiovascular conditions, were more likely to be current smokers and to have a higher BMI. Women had a higher HR but lower SBP and DBP.

Table 5.1: Characteristics of Sample

	Total Sample	**Men**	**Women**	
N	3459	1586 (45.85)	1873 (54.15)	p-value
Baroflex Sensitivity (msec/mmHg)*median IQR*	7.47 (6.19)	7.36 (6.19)	7.53 (6.09)	0.22
Affective Symptoms				
CES-D score, median IQR	3 (7)	3 (6)	4 (7)	<0.001
HADS-A score, median IQR	5 (4)	4 (5)	5 (5)	<0.001
PSWQ-A Score, median IQR	13 (11)	12 (8)	15 (12)	<0.001
Using Anti-Depressants *n %:*	192 (5.55)	59 (3.72)	133 (7.10)	<0.001
Demographics				
Age *years*, mean (SD)	61.11 (8.01)	61.19 (8.18)	61.04 (7.93)	0.57
Primary Education Only *n %*	648 (18.73)	341 (21.50)	307 (16.39)	<0.001
Cardiovascular				
Systolic Blood Pressure, mmHg, mean (SD)	134.61 (19.40)	139.03 (18.05)	130.87 (19.72)	<0.001
Diastolic Blood Pressure, mmHg, mean (SD)	82.60 (10.93)	84.08 (10.66)	81.34 (11.00)	<0.001
Heart Rate, bpm, mean (SD)	69.09 (11.11)	67.97 (11.38)	70.05 (10.77)	<0.001
>=2 cardiovascular conditions *n %*	257 (7.43)	143 (9.02)	114 (6.09)	0.001
>=2 comorbid diseases *n %*	446 (12.89)	137 (8.64)	309 (16.50)	<0.001
Using Antihypertensives *n %:*	1005 (29.05)	506 (31.90)	499 (26.64)	<0.001
Beta blockers *n %*	301 (8.70)	170 (10.72)	131 (6.99)	<0.001
Current Smoking *n %*	496 (14.34)	230 (14.50)	266 (14.20)	<0.001
BMI, kg/m^2, mean (SD)	28.49 (4.92)	29.16 (4.41)	27.93 (5.25)	<0.001
Exercise, *n % (inactive)*	1276 (36.89)	723 (45.59)	553 (29.52)	<0.001

SD=Standard Deviation; IQR=interquartile Range; bpm=beats per minute; mmHg=millimetres of mercury; BMI= Body mass Index; kg/m^2=kilogrammes/metre squared; msec=millisecond; BRS=Baroreflex Sensitivity; CES-D= The Center for Epidemiological Studies Depression Scale; PSWQ-A= Penn State Worry Questionnaire- Abbreviated; HADS-A= Hospital Anxiety and Depression Scale- Anxiety Subscale

Median BRS was 7.47 (IQR 6.19) and did not differ according to sex. The distribution of BRS was skewed. However, analyses using the natural log of BRS suggested similar associations and patterns across groups, therefore associations with the untransformed variable are reported for ease of interpretation.

Visual inspection of the unadjusted association between BRS and affective symptoms suggested a moderating effect of sex (Figure 5.3). In fully adjusted models there was no difference in the coefficient of BRS across outcomes, but there was an interaction with sex - the omnibus test of significance for the two way interaction (BRS*Sex) was significant across outcomes on simultaneous multivariate regression analysis (p=0.003) and was robust to adjustment for all covariates (Table 5.2).

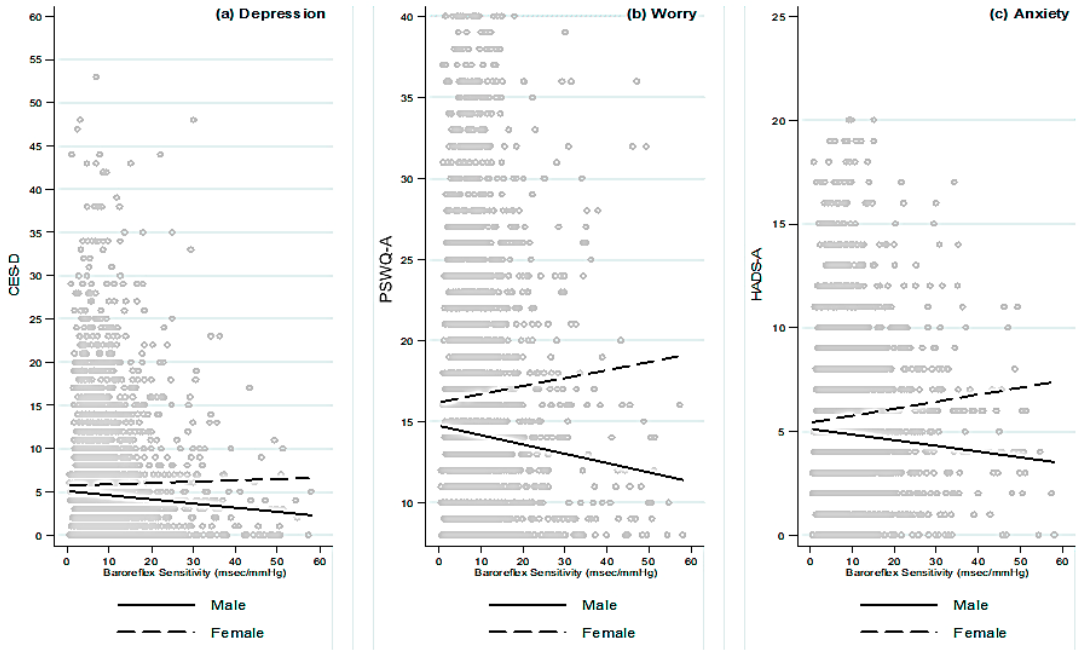


Figure 5.3: Association between Baroreflex Sensitivity and Affective Symptoms According to Sex (unadjusted)
CES-D= Center for Epidemiological Studies Depression Scale ; PSWQ-A= Penn State Worry Questionnaire- Abbreviated ; HADS-A= Hospital Anxiety and Depression Scale-Anxiety Subscale ; msec/mmHg=milliseconds/millimetre of mercury

Table 5.2: Multivariate Multiple Regression of the Association between Baroreflex sensitivity across Affective Outcomes according to sex and anti-depressant treatment

	Depression		Anxiety				
	CES-D		PSWQ-A		HADS-A		Omnibus p-value for Interaction
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	
Model 1							*BRS*Sex* = 0.008
Men	-0.05 (-0.10; -0.01)	*0.02*	-0.07 (-0.11;-0.02)	*0.008*	-0.03 (-0.06;-0.01)	*0.004*	
Women	0.01 (-0.04;0.06)	*0.64*	0.04 (-0.01;0.09)	*0.149*	0.02 (0.00;0.05)	*0.06*	
Model 2							*BRS*Sex = 0.003*
Men	-0.04 (-0.08;0.00)	*0.06*	-0.06 (-0.11;-0.02)	*0.009*	-0.03 (-0.06;-0.01)	*0.006*	
Women	0.03 (-0.01;0.08)	*0.15*	0.04 (-0.01;0.09)	*0.08*	0.04 (-0.01;0.09)	*0.08*	
Model 3							*BRS*Sex*ADT = 0.008*
No ADT							
Men	-0.03 (-0.08;0.01)	*0.13*	-0.06 (-0.11;- 0.02)	*0.01*	-0.03 (-0.06;-0.01)	*0.005*	
Women	0.01 (-0.03;0.06)	*0.53*	0.03 (-0.02;0.08)	*0.24*	0.02 (-0.00;0.05)	*0.09*	
ADT							
Men	-0.23 (-0.46;0.01)	*0.06*	-0.01 (-0.27;0.25)	*0.93*	-0.02 (-0.11;0.14)	*0.77*	
Women	0.34 (0.15;0.52)	*<0.001*	0.24 (0.03;0.44)	*0.02*	0.12 (0.03;0.22)	*0.01*	

Data are regression coefficients with 95% Confidence Intervals
Model 1 adjusted for age, sex, education
Model 2 Additionally adjusted for BMI, height, physical activity, Smoking status, Cardiovascular disease, co-morbidities, anti-hypertensives, antidepressants, systolic BP, diastolic BP, resting heart rate
BRS=Baroreflex Sensitivty; ADT=Antidepressant Medication; CES-D= The Center for Epidemiological Studies Depression Scale; PSWQ-A= Penn State Worry Questionnaire-Abbreviated; HADS-A= Hospital Anxiety and Depression Scale- Anxiety Subscale

There was an inverse association between BRS and affective symptoms in men, but a trend towards a positive association between BRS and affective symptoms in women (Table 5.2, Model 2; Figure 5.4). At low levels of BRS there was no difference in affective symptoms between sexes, however with increasing BRS the estimated difference between sexes in affective symptoms increased (Supplementary Figure 5.1).

There was a further moderating influence of ADT on the sex-specific relationship between BRS and outcomes such that the slope of the positive association between affective symptoms was steeper in women on ADT and the slope of the inverse relationship between BRS and depressive symptoms was more strongly negative in men on ADT (Table 5.2; Model 3; Figure 5.4; Supplementary Figure 5.2). The omnibus test of the three-way interaction (sex*BRS*ADT) i.e. the moderating effect of ADT on the sex-specific relationship between BRS and affective symptoms, was significant across outcomes ($p=0.008$) but was not significant in individual models with global anxiety nor worry as the outcome ($p>0.1$).

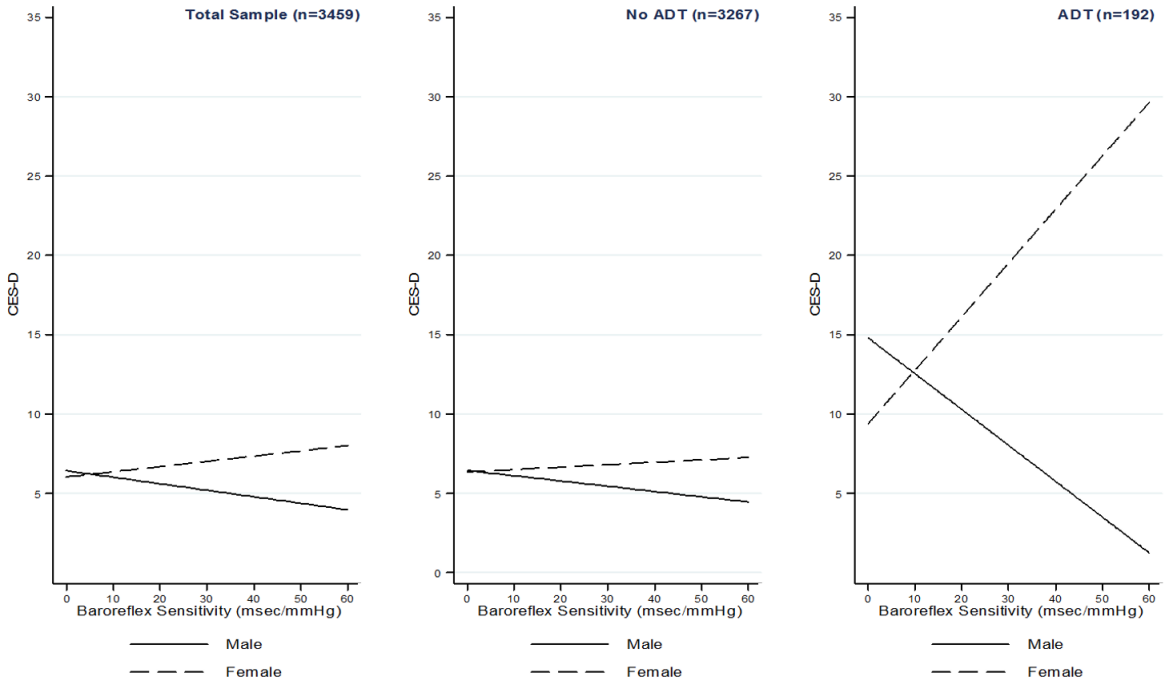


Figure 5.4: Association between Baroreflex Sensitivity and Depressive Symptoms According to Sex and Antidepressant Treatment (adjusted)
CES-D= Center for Epidemiological Studies Depression Scale (CES-D);
msec/mmHg=milliseconds/millimetre of mercury

Overall, there was evidence of a moderating relationship of ADT on the sex-specific relationship across outcomes. In men not on ADT there was a small negative association between BRS and symptoms of anxiety/worry: for every one msec/mmHg increase in BRS in men there was on average an estimated decrease of -0.06 (95% Confidence Interval -0.11;-0.02); *p*=0.01 in scores on the PSWQ-A and a decrease -0.03 (-0.06;-0.01); *p*=0.005 in scores on the HADS-A. There was an association of similar magnitude (-0.03(-0.08; 0.01) with symptoms of depression but this was non-significant (*p*=0.13). In contrast, in men on ADT, there was a strong negative association between BRS and symptoms of depression (-0.23 (-0.46; 0.01); *p*=0.06 but no similar increase in the magnitude of association with anxiety symptoms.

In women not on ADT, there were trends towards positive associations with affective symptoms which were small in magnitude and did not reach statistical significance. In women on ADT however, there were large positive associations between BRS and symptoms of anxiety and worry; for every one msec/mmHg increase in BRS there was a 0.24 (0.03; 0.44); *p*=0.02 increase in scores on PSWQ-A and a 0.12 (0.03; 0.22); *p*=0.01 increase in scores on HADS-A. Likewise in women on ADT there was a strong positive association between BRS and depressive symptoms: for every one msec/mmHg unit increase in BRS there was a 0.34(0.15; 0.52); *p*=0.001 increase in scores on the CES-D.

Sensitivity analyses

Similar results were seen in models using the maximal sample for each outcome. In fully adjusted logistic regression analyses, patterns of association between tertiles of BRS and case level affective symptoms were similar to the main analysis i.e. an inverse relationship in men and a positive relationship in women. Interactions between sex and BRS were significant in all models ($p<0.05$). Subsequent analyses stratified by sex demonstrated a linear 'dose-response' relationship - in men those in the highest tertile of BRS relative to the lowest had a decreased risk of case-level affective symptoms but the reverse association was seen in women i.e. risk of case-level affective symptoms increased across tertiles of BRS (Supplementary Table 5.1; Supplementary Figure 5.3). Results were similar when excluding participants on ADT and those with high levels of CVD (>=2 self-reported cardiovascular diseases).

5.5. Discussion

In this large population-based sample of older adults, the association between BRS and affective symptoms varied according to sex. In keeping with the primary hypothesis, BRS and affective symptoms were inversely related; however, this finding was restricted to men. In women, there was instead a trend towards a positive relationship between BRS and affective symptoms, an association which was stronger in women on ADT. Overall, effect sizes were small for those participants not on ADT and levels of significance varied, but patterns of sex differences were consistent across outcomes and persisted after accounting for a wide range of confounding factors including cardiovascular risk, BP, HR, smoking, BMI, physical activity, cardiovascular conditions and anti-hypertensive treatment.

To my knowledge this is the first population-based study to describe the association between BRS and measures of symptoms of depression *and* anxiety in older adults. This is important as both affective symptoms and cardiovascular risk differ in prevalence according to sex - including into later life.[58,132] Anxiety and depression are often co-morbid and both have been associated with increased vascular risk. Higher anxiety symptoms in those with a diagnosis of depression often reflect greater severity and may predict poorer treatment response.[383] Furthermore, in addition to a measure of global anxiety symptoms TILDA also specifically measured levels of worry – the primary feature of Generalised Anxiety Disorder (GAD) which, as previously noted, may be the most common affective disorder in later life and may precede the development of a depressive episode.[373,374]

In older men these findings are in keeping with prior small clinical studies in which lower BRS was associated with anxiety and depressive symptoms.[318,384] A case-control study based in a tertiary care setting also reported a relationship between lower BRS and greater depressive symptoms in patients in a secondary care psychiatric setting, however sex specific differences were not investigated and the authors acknowledged that the majority of patients were treated with ADT.[319] More recently, two large population-based studies have also investigated the cross-sectional relationships between BRS and depression, specifically in older adults – with conflicting results. As with the findings in men, Dauphinot et al reported an association between lower BRS and greater depressive symptoms in a large population-based sample of participants, all of whom were aged 65, which persisted in participants not on ADT[320]. In contrast, Empana et al found no association between BRS and depressive symptoms and reported no interaction according to sex. This difference may be due to their use of a volunteer sample recruited via occupational health screening, or the larger proportion (60%) of males included.[321] This investigation thus extends the literature by exploring anxiety as a related outcome and assessing associations across the full spectrum of affective symptoms in the population.

A positive association between BRS and affective symptoms in women was unexpected. Sex-specific relationships between cardiovascular autonomic function and affective symptoms however have previously been reported, and a positive relationship in women is in line with limited evidence from prior work. For example, in a small sample of middle aged women (N=41; mean age 43.73 (+/-)11.2) Verkuil et al. reported that those with higher levels of 'sadness' (one of the core symptoms of depression) had higher levels of parasympathetic activation as indexed by HRV measured over a 24hr period[369], which was

in line with earlier findings from the same group.[385] In a large group of Chinese older adults, Chen et al reported lower HRV only in men with depression and anxiety but not in women[370]. Thayer et al have thus suggested that while men may be predisposed to a 'fight or flight' response, women may be more likely to have a more adaptive 'tend and befriend' stress response (e.g. women may disclose their distress) which is reflected in greater parasympathetic tone.[369,385] Moreover, sex hormones may play a role. Oestrogen is a known neuroprotectant and may influence sex differences in cardiovascular ageing e.g. the average age of stroke is higher in women than men. [119,386] As TILDA is a relatively young cohort (mean age 61 years) the full extent of post-menopausal increased cardiac risk may not yet be evident – as the sample ages the association between BRS and affective symptoms in women may change.

The directions of associations are the same across all outcomes including in those participants not on ADT. The cardiovascular effects of ADT are controversial and some prior work on ADT and autonomic function in older adults has suggested that differences in autonomic function are attributable to ADT rather than psychopathology.[376] A recent meta-analysis suggests that differences in Heart Rate Variability persist however, even in non-medicated depressed patients.[387] In the current study it is not possible to conclude whether the statistical effect of ADT reflects the role of the medication or is instead a measure of disease severity i.e. those with more severe affective symptoms may be more likely to seek and be prescribed ADT. As with many observational studies investigating the effect of medication, confounding by indication may play a role. In sensitivity analyses excluding those participants on ADT, sex differences remain evident in associations with case-level symptoms – mirroring the associations seen in the main analysis – suggesting there may be

baseline sex-differences in the relationship between outcomes and BRS which are stronger in more severe symptom states. Alternatively, ADT may worsen BRS in men with higher levels of depression and improve BRS in women with depression and anxiety. The small number of participants on individual ADT, particularly when stratified by sex, precluded investigation of the effect of different classes of ADT. It is of note, however, that in this cohort there were more women on SSRI's than SNRI's. SNRI treatment has been associated with poorer BRS[321] but SSRI treatment may reduce sympathetic nervous activity[376] which may in turn have beneficial effects for BRS which primarily reflects parasympathetic tone. As men in this cohort have a higher prevalence of CVD it may be that this affects both BRS and risk of affective disorder, however neither adjustment for CVD in main analyses nor exclusion of those with high levels of CVD in sensitivity analyses altered overall associations. We note the small numbers overall on ADT and the cross-sectional nature of this investigation, therefore any interpretation of the effects of ADT should be treated with appropriate caution.

Limitations include a lack of information on lifetime anxiety or depressive disorder among participants. It is therefore uncertain if the reported differences relate to lifetime symptom burden or presentations unique to older age. Also we acknowledge that, in line with previous studies[321], this work does not account for peripheral vasomotor effects of the baroreflex. The large number of hypothesis tests conducted should also be considered as a limitation, although these tests were not independent as the outcomes are correlated with one another.[348] This is a cross-sectional analysis therefore interpretations with respect to causation are speculative. Future waves of TILDA data, in particular work incorporating neuroimaging, will help to unpick these complex processes. Additionally, loss of participants who did not

attend a health assessment and/or failed to return a SCQ may have introduced bias. In mitigation it could be argued that this would tend to lead to an underestimate of associations, as those with higher levels of affective symptoms and physical risk were less likely to complete the health assessment or self-completion questionnaire.

Strengths include that this investigation was conducted in a large population-based study in which we were able to examine a wide range of commonly occurring psychopathology with accurately measured co-variates including objective BP, HR and medications. Moreover, in keeping with moves towards understanding the causes of psychopathology across traditional diagnostic boundaries[388], the analyses acknowledged the overlap between symptoms of depression and anxiety in older adults by simultaneously modelling the three outcomes as dependent variables. In contrast to prior studies, we investigated affective symptoms as continuous outcomes hence acknowledging the importance of subthreshold symptoms for poorer outcomes in this demographic.[62] Similar patterns of sex differences were seen across the spectrum of anxiety and depressive symptoms, including in those in whom these were of case-level severity. These results thus support theories of shared aetiology of depression and anxiety in older adults.[70,389]

These results may have important implications with regard to the assessment and management of affective symptoms in older adults - particularly in the context of co-morbid cardiovascular disease. If these results were to be replicated it is possible that sex-specific treatment approaches may be required including monitoring of BRS during treatment or assessment of CVD risk prior to treatment.

Supplementary Material

Supplementary Table 5.1: Sex Stratified association between tertiles of Baroreflex Sensitivity and case-level symptoms of depression and anxiety.

	Depression				Anxiety							
	Case-Level Depressive Symptoms(CES-D)				Case-Level Worry (PSWQ-A)				Case-Level Global Anxiety (HADS-A)			
	men		women		men		women		men		women	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95%CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p -value	OR (95% CI)	p -value
Tertiles of BRS												
1 (lowest)	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
2	0.60 (0.35-1.03)	0.07	1.11 (0.73-1.68)	0.63	0.88 (0.59-1.30)	0.52	1.25 (0.93-1.69)	0.14	0.86 (0.62; 1.19)	0.37	1.13 (0.86-1.49)	0.40
3 (highest)	0.43 (0.23-0.82	0.01	1.36 (0.88-2.11)	0.17	0.67 (0.43-1.06)	0.09	1.51 (1.10-2.07)	0.01	0.55 (0.38; 0.80)	0.002	1.41 (1.05-1.89)	0.02
Excluding ADT[a]												
1 (lowest)	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
2	0.52 (0.29-0.94)	0.031	1.12 (0.71-1.79)	0.62	0.93 (0.62-1.40)	0.73	1.31 (0.95-1.80)	0.10	0.83 (0.60-1.16)	0.28	1.21 (0.91-1.62)	0.19
3 (highest)	0.42 (0.21-0.83)	0.012	1.49 (0.92-2.43)	0.11	0.62 (0.38-1.00)	0.05	1.53 (1.10-2.15)	0.01	0.53 (0.36-0.77)	0.001	1.42 (1.04-1.94)	0.03

Excluding CVD[b]												
1 (lowest)	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
2	0.61 (0.34-1.10)	0.10	1.13 (0.72-1.78)	0.60	0.83 (0.54-1.27)	0.38	1.29 (0.94-1.77)	0.11	0.83 (0.59-1.17)	0.28	1.16 (0.87-1.56)	0.31
3 (highest)	0.45 (0.23-0.90)	0.03	1.48 (0.92-2.39)	0.11	0.60 (0.37-0.98)	0.04	1.62 (1.16-2.27)	0.01	0.48 (0.32-0.72)	<0.001	1.47 (1.07-2.00)	0.02

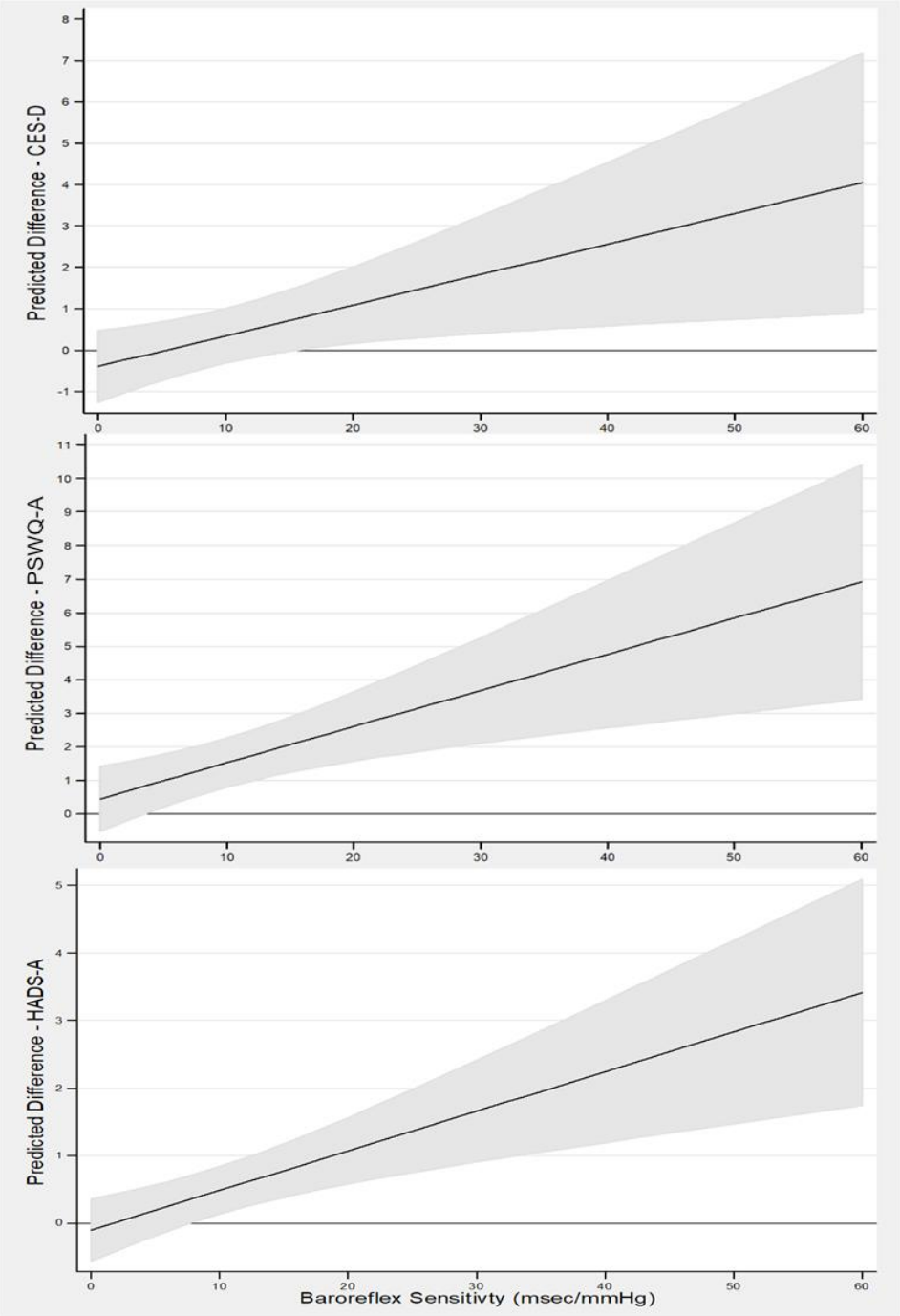
Data are Odds Ratios (OR) presented with 95% Confidence Intervals (95% CI)

Models additionally adjusted for age, sex, education, BMI, physical activity, Smoking status, Cardiovascular disease, co-morbidities, anti-hypertensives, antidepressants, systolic BP, diastolic BP, resting heart rate

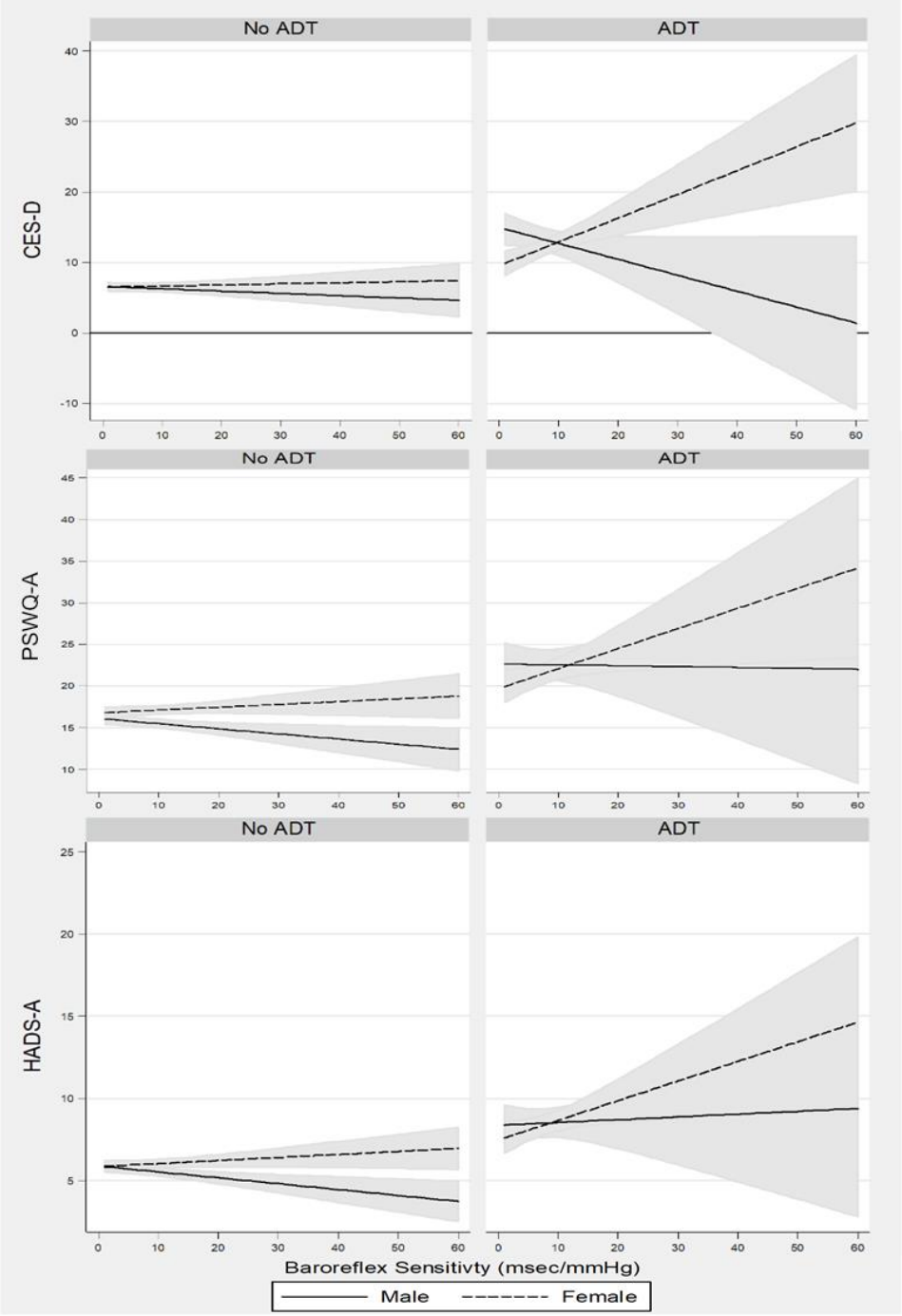
BRS=Baroreflex Sensitivty; ADT=Antidepressant Medication; CES-D= The Center for Epidemiological Studies Depression Scale; PSWQ-A= Penn State Worry Questionnaire-Abbreviated; HADS-A= Hospital Anxiety and Depression Scale- Anxiety Subscale; CVD=Cardiovascular Disease

[a]Excluding n=192 participants treated with antidepressant medication

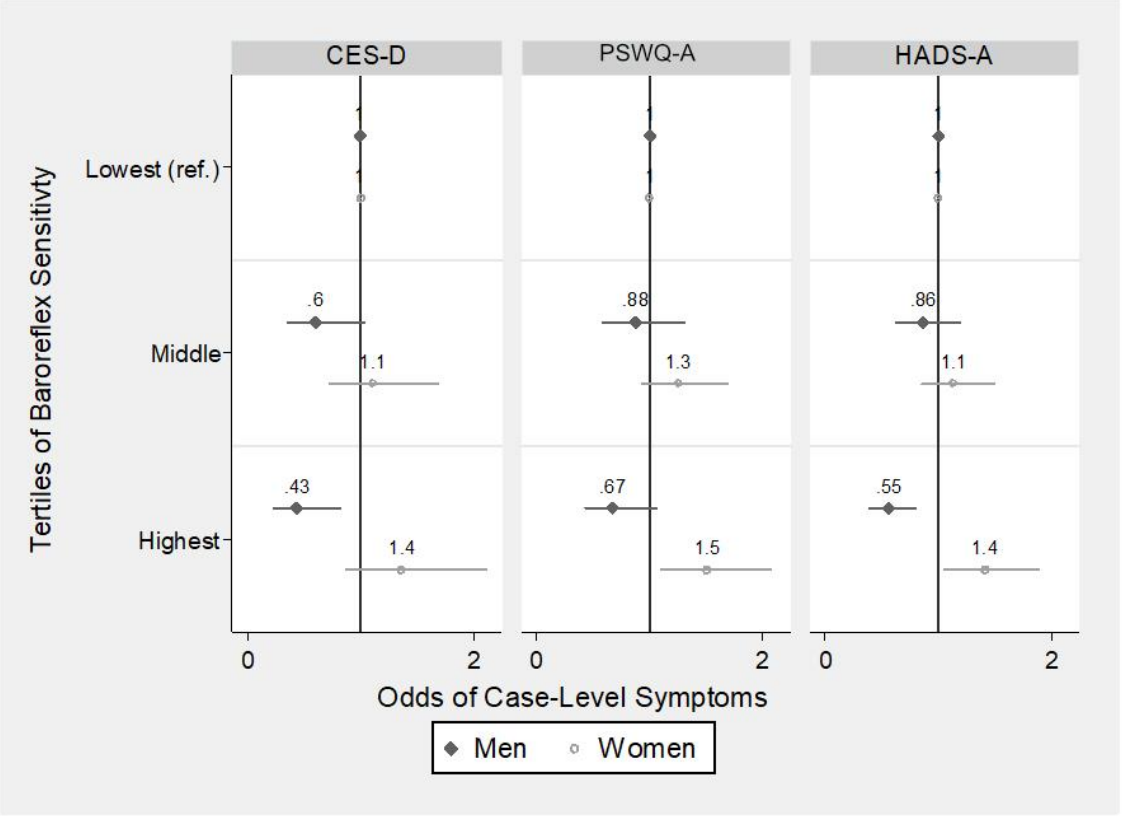
[b]Excluding n=372 participants with >=2self-reported cardiovascular disorders



Supplementary Figure 5.1: Average Marginal Effects of Sex on association between Baroreflex Sensitivity and Affective Symptoms.
CES-D= Center for Epidemiological Studies Depression Scale; PSWQ-A= Penn State Worry Questionnaire- Abbreviated; HADS-A= Hospital Anxiety and Depression Scale-Anxiety Subscale



Supplementary Figure 5.2: Association between Baroreflex Sensitivity and Affective Symptoms According to Sex and Antidepressant treatment (adjusted).
CES-D= The Center for Epidemiological Studies Depression Scale; PSWQ-A= Penn State Worry Questionnaire- Abbreviated; HADS-A= Hospital Anxiety and Depression Scale-Anxiety Subscale; msec/mmHg=milliseconds/millimetre of mercury



Supplementary Figure 5.3: Sex Stratified association between tertiles of Baroreflex Sensitivity and case-level symptoms of depression and anxiety.
Data are Odds Ratios (OR) presented with 95% Confidence Intervals (95% CI)
CES-D= The Center for Epidemiological Studies Depression Scale; PSWQ-A= Penn State Worry Questionnaire- Abbreviated; HADS-A= Hospital Anxiety and Depression Scale-Anxiety Subscale; msec/mmHg=milliseconds/millimetre of mercury

6. STUDY III - Cognitive Status, Grey Matter Atrophy and Lower Orthostatic Blood Pressure in Older Adults

Study III investigates orthostatic BP as the independent variable of interest and adjudicated CS as the outcome of interest. Study III aims to build on findings from Study I and II in TILDA which have demonstrated associations between lower orthostatic BP and lower BRS (even when sub-clinical) and poorer brain health in men aged 50+ (as denoted by greater SMI and greater affective symptoms). Study III uses data from the US-based longitudinal Health ABC cohort and 'The Healthy Brain Project' neuroimaging sub-study. Prior studies investigating longitudinal associations between orthostatic BP and CS have had various limitations including measurement of orthostatic BP at a single time point, a focus on consensus OH, and limited duration of follow-up; while the most comprehensive study to date did not investigate MCI nor address the potential mediating role of structural neuroimaging markers of brain health.

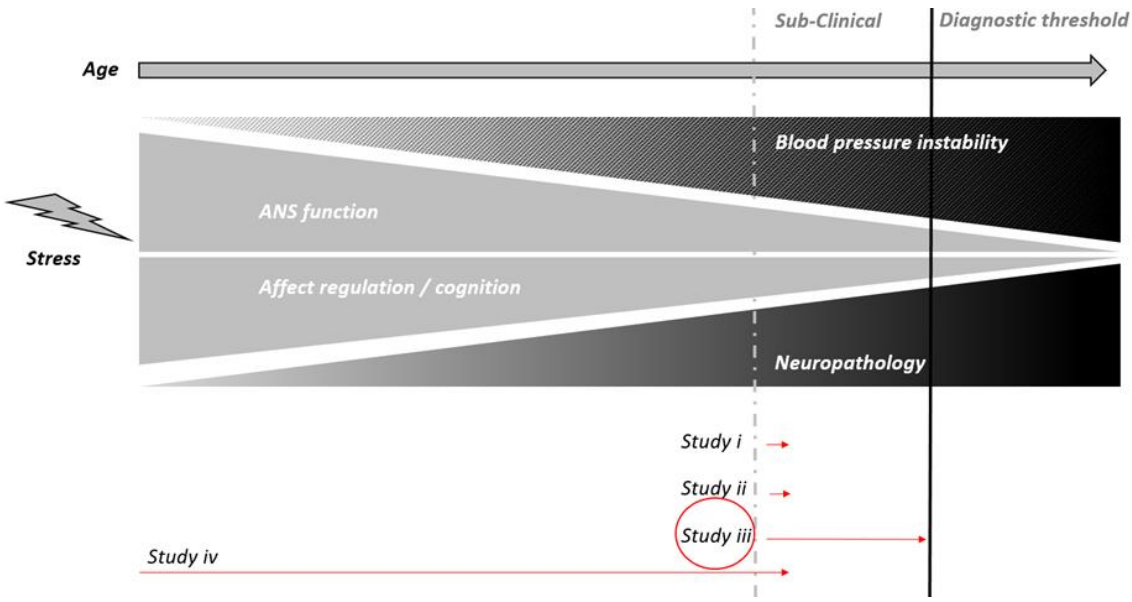


Figure 6.1: Thesis Figure: Study III
Study III investigates ***prospective associations*** between orthostatic blood pressure and Cognitive Status in Older Adults and explores the mediating effect of Grey Matter atrophy and White Matter Hyperintensities.

Cognitive Status, Grey Matter Atrophy and Lower Orthostatic Blood Pressure in Older Adults

6.1. Abstract

Introduction: Associations between orthostatic BP and CS have been described with conflicting results. This study investigates the hypothesis that long-term exposure to lower orthostatic BP is related to having worse CS later in life and that atrophy of regions involved in central regulation of autonomic function mediate these associations.

Methods: Three-to-four measures of orthostatic BP were obtained from 1997-2003 in a longitudinal cohort of ageing, and average systolic orthostatic BP response (ASOBPR) was computed as % change in systolic BP from sit-to-stand measured at one minute post stand. CS was determined in 2010-2012 by clinician-adjudication (n=240; age=87.1±2.6; 59% women; 37% black) with a subsample also undergoing concurrent structural neuroimaging (n=129). Grey matter volume (GMV) of regions related to autonomic function was measured. Multinomial regression was used to compare ASOBPR in those who were cognitively intact versus those with a diagnosis of MCI or Dementia, controlling for demographics, trajectories of seated BP, incident cardiovascular risk/events and medications measured from 1997 to 2012. Models were repeated in the subsample with neuroimaging, before and after adjustment for regional GM volume.

Results: There was an inverse association between ASOBPR and probability of Dementia diagnosis (9% lower probability for each % point higher ASOBPR: OR 0.91, 95%CI

0.85;0.98; p=0.01). Associations were similar in the subgroup with neuroimaging before and after adjustment for regional GM volume.

Conclusion: ASOBPR may be an early marker of risk of dementia in older adults living in the community.

6.2. Introduction

Lower orthostatic BP, the impaired stabilization of BP after standing, is common among older adults. Associations between lower orthostatic BP and poorer CS have been described with conflicting results. Lower orthostatic BP has been associated prospectively with poorer CS in four large epidemiological samples.[278,288,291,294] Lower orthostatic BP has also been associated with conversion to dementia in two clinical studies of patients with Parkinson's disease[390] and MCI.[280] Three other prospective population-based studies however found no longitudinal association.[281,292,293] Furthermore the associations described in the Atherosclerosis Risk in Communities study did not survive correction for demographic factors or conventional cardiovascular risk[294] and the most comprehensive cohort study to date did not investigate MCI.[288] The majority of prior studies have investigated screening tests of cognition rather than clinician-directed adjudicated diagnosis, and measured orthostatic BP at a single time point.[164,348,391] Moreover, measurement protocols and definitions of orthostatic BP investigated have varied across studies.[164,280,288,294]

This study aims to investigate the relationship between repeated measures of orthostatic BP and CS obtained 10 years later in a well-defined, prospectively-followed cohort of older adults. A secondary aim was to explore the mediating role of known MRI markers of brain health, WMH and GM atrophy. Examining the central nervous system pathways linking orthostatic BP to CS is important because accumulating evidence suggests that higher brain centres may be involved in cardiovascular autonomic regulation[355] and orthostatic BP levels.[220] Additionally it has been postulated that lower orthostatic BP may relate to CS via cerebral hypoperfusion[220] – to which watershed areas of the cortex may be particularly

vulnerable.[392] Investigations incorporating neuroimaging are limited, with variable directions and strengths of associations described. For example, lower orthostatic BP in patients has been associated with WMH in patients with dementia[289], however Soennysn et al[298] found no relationship between lower orthostatic BP and WMH in a clinical sample with 'mild dementia'. Most studies including neuroimaging are in clinical cohorts or small samples and have not examined regional cortical GM atrophy.[300,301,393]

Hypothesis

Long-term exposure to lower orthostatic BP is related to having worse CS in later life; this association will be mediated via smaller volume of brain regions involved in central regulation of autonomic function.

6.3. Methods

Study sample

Participants of this study were recruited from the Health Aging and Body Composition Study (ABC) at the Pittsburgh site. The Health ABC study began in 1997 in Memphis, TN and Pittsburgh, PA, USA with 3075 community-dwelling white and black older adults aged 70-79, recruited from a random sample of Medicare-eligible adults living within designated zip codes, with no difficulties performing activities of daily living, walking a quarter mile, or climbing 10 steps without rest, free of life-threatening cancers and who planned to remain within the study area for at least 3 years. Participants were invited to regular follow-up through to 2012. Of the 1527 participants enrolled in the study in 1997-98 at the Pittsburgh site, 819 were alive and were contacted in 2006-07 (year 10 of the parent Health ABC cohort) to participate in the Healthy Brain Project (HBP) a neuroimaging sub-study of cognition and mobility. Of the 314 enrolled in the HBP in 2006-07, 246 returned in 2010-12 for a cognitive assessment and follow-up MRI (63 had died before cognitive adjudication was completed, and 5 did not have complete data to allow determination of CS). 240 of these participants had complete data on orthostatic BP from 1997-2003 of whom a subset of 129 participants also were eligible for brain MRI in 2010-2012 and had complete data on MRI outcomes of interest. The study population used in this analysis is depicted in Figure 6.2.

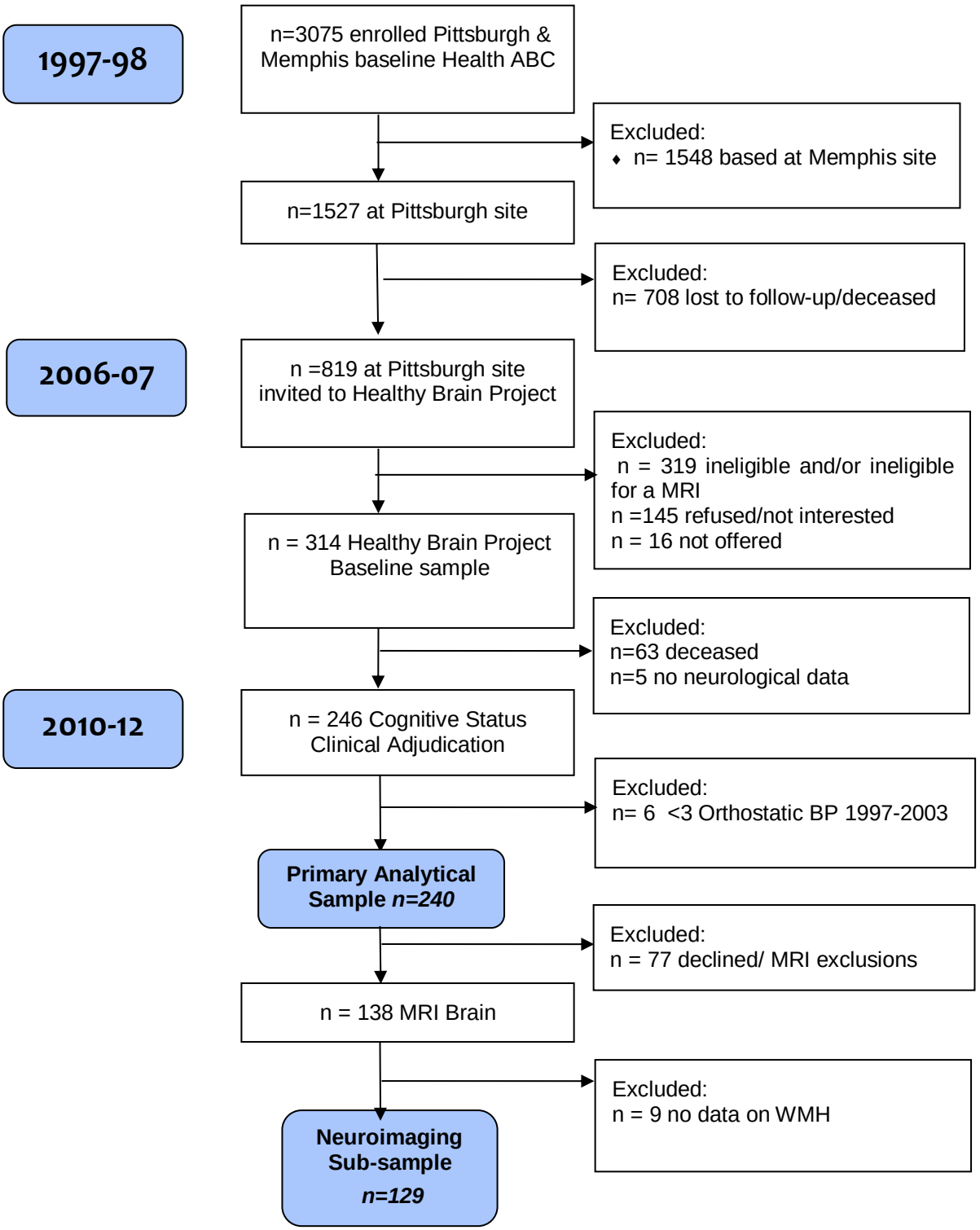


Figure 6.2: Study III Flow Diagram

Ethics

The study protocol was approved by the University of Pittsburgh Institutional Review Board. All participants provided written informed consent.

Magnetic Resonance Imaging

MRI scans were obtained at the MR Research Centre of the University of Pittsburgh with a 3Tesla Siemens TIM TRIO scanner equipped for echo-planer imaging. Acquisition and processing protocols have been published.[394] Brain tissue volumes (GM, white matter, cerebrospinal fluid) were quantified on skull-stripped T1-weighted images in native anatomical space. A FLAIR sequence was also acquired for WMH. Scans with incidental findings were excluded following review by a clinical radiologist.

Grey matter regions were identified using the Automated Anatomical Labelling atlas.[395] Regions of interest were chosen *a priori* based on a recently published meta-analysis which produced a map of brain areas involved in central autonomic regulation, these included: Dorsolateral Prefrontal Cortex, Precuneus, Lingual Gyrus, Cingulate Cortex, Insula, Thalamus, Amygdala, Hippocampus, Parahippocampus, Angular Gyrus, Suprmarginal Gyrus and Frontoinsular Cortex.[217] An index of Grey Matter Atrophy of total brain was calculated using the equation: 1- (total GMV/total intracranial volume). Total brain WMH volume was estimated by summing all voxels classified as WMH, which were then further normalized by total brain volume.[394]

Main Predictor Variable

Orthostatic Blood Pressure

The Health ABC study collected orthostatic BP in Years 1, 2, 4, 6 i.e. from 1997-1998 until 2002-2003. BP was measured in the seated position at the brachial artery using a mercury sphygmomanometer. Average seated SBP and DBP were derived as the means of two consecutive BP measures. Following a quiet rest period of at least five minutes, the participant was asked to stand and BP was recorded at heart level after one minute. Standardized protocols were followed for all BP measurements. Quality assurance and control protocols were regularly implemented for the centrally trained clinic staff. Testers were required to gain re-certification of competence in assessments annually.

Longitudinal Characterization of Orthostatic Blood Pressure

To be included in the analysis each participant had a minimum of three (from a maximum of four) annual observations of orthostatic BP. 174(72.5%) of participants had at least three measures with 66(27.5%) missing one orthostatic BP measure. In the neuroimaging subsample 98 participants (75.97%) had four measures and 31(24.03%) were missing one orthostatic BP measure from a maximum of four. Five participants who had only two measurements and one participant who had one measurement were excluded from this analysis (Figure 6.2).

Three derived measures of orthostatic BP were of interest:

I. Average Systolic Orthostatic BP response (ASOBPR): As per Hayakawa[280], Lagro[279], Feeney[238] and Romero-Ortuno[274], systolic orthostatic BP response was computed as (standing SBP/seated SBP)*100, thus yielding a continuous variable expressed in percentage points. Standing BP may be higher or lower than seated BP, thus participants with a systolic orthostatic BP response > 100% have a standing SBP that exceeds seated SBP. Systolic orthostatic BP response was computed as described above at each available time point for each individual and averaged across time points to obtain an index of prior exposure to systolic orthostatic BP response over time i.e. ASOBPR. Average diastolic orthostatic BP response was calculated in the same manner. Trajectories describing the slope between annual observations of systolic Orthostatic BP response were also computed by Dr. Robert Boudreau.

II. Consensus Orthostatic Hypotension(OH)[161]: Upon standing, if a drop in SBP of >=20mmHg and/or drop in DBP of >=10mmHg occurred this was denoted using a dichotomous variable where consensus OH was defined as present or absent. A binary variable (no/yes) was then coded to denote those participants who met consensus OH criteria (i.e. baseline or incident consensus OH) at any point over the available annual measures.

III. Absolute change in orthostatic BP: Orthostatic BP change was calculated for each year as ‘Delta SBP’ = seated SBP minus standing SBP; ‘Delta DBP’ = seated DBP

minus standing DBP. A positive Delta BP indicates that standing BP dropped lower than seated BP, whereas a negative Delta BP indicates that BP had risen above the seated measure when standing. Longitudinal average Delta SBP and Delta DBP were then calculated as the mean of available repeated annual observations.

Main Outcome of Interest:

Cognitive Status

According to a protocol previously validated in the Cardiovascular Health Study[396], CS was clinically adjudicated on Health ABC participants who were seen at the year 14 site visit in 2010-12, using all data from previous visits as well as cognitive assessments at the time of the MRI.[397] At the time of brain MRI an assessment of neurological function and extensive battery of cognitive tests was administered including: (1) pre-morbid intelligence: the American version of the National Reading test and Raven's Colored Progressive Matrices; (2) memory: California Verbal Learning Test, and Rey-Osterrieth figure; (3) language: Boston Naming Test and verbal fluency test; (4) visuo-perceptual and/or visuo-constructional: block design and copy of a geometric figure; and (5) executive function: Stroop test.[397] This neuropsychological battery and adjudication aimed to identify MCI and dementia; detailed normative data had previously been obtained through the Cardiovascular Health Study dementia study.[396,397] Adjudicated outcomes, which took educational attainment into account, included: cognitively normal (n=100), MCI (n=80), dementia (n=60), or no neurological data (n=5) with the prevalence of cognitive impairment reflecting national estimates of the prevalence of dementia in those over 80 years.[398]

Co-variates:

Demographics, Anthropometry and Health Behaviours

Age, sex and race were recorded at entry examination to the Health ABC study. Body Mass Index (kg/m^2) and smoking history ('pack-years') were also recorded at baseline. Average alcohol consumption throughout the study was based on participants annual report of alcoholic drinks consumed per week over the last 12 months and was summarized as: 0 = <=1 drink; 1 = >1-7 drinks per week; 2 = > 1 daily alcoholic drink. Participants were given examples of what constituted a 'standard drink' e.g. 12 ounces of beer (1 can), 5 ounces of wine (a full glass), as previously reported [399]. No information was collected on specific beverages.

Adjudicated Cardiometabolic Conditions

Stroke, coronary heart disease, diabetes and hypertension status were coded according to baseline prevalence and incidence during follow-up. This data was based on annually adjudicated health outcomes using a standardized protocol.

Longitudinal measures of seated BP

Seated BP was measured in years 1, 2, 4, 5, 6, 8 and yearly from year 10 - 15. Trajectories of SBP change were calculated using annualized slopes of the repeated measures of seated SBP together with the variability in SBP between visits by Dr. Robert Boudreau. Additionally, average seated SBP was calculated as the mean of SBP measurements from Year 1 (1997-1998) Health ABC until time of Cognitive Adjudication. No person was missing >=7 years of data for any seated SBP measurement.

Medications

A medication inventory was completed at each annual clinic visit (except year 4, 7 and 9) including antihypertensives and ADT. A variable was computed to report the percentage of annual visits a participant was on an antihypertensive or antidepressant i.e. ranging from 0% for participants who were not taking an antihypertensive medication at any visit, to 100% for a person who was recorded to have been taking the medication at every visit.

Statistical Analysis

Continuous orthostatic BP variables were normally distributed; oneway ANOVA was used to assess the unadjusted relationship between adjudicated CS groups (i.e. Normal vs. MCI; Normal vs. Dementia) and orthostatic BP. Multinomial regression models adjusted for age, sex and race were used to characterize the relationship between adjudicated CS (i.e. Normal vs. MCI; Normal vs. Dementia) and orthostatic BP. Other variables were added one at a time in separate blocks to this model and changes in the relationship between orthostatic BP and CS were examined: longitudinal average seated SBP; longitudinal trajectories of seated SBP; cardiometabolic conditions; health behaviours; antidepressants and antihypertensive medications. Parsimonious models included only variables that were significantly associated with CS in bivariate analysis.

The relationship between orthostatic BP and CS was also estimated in the subsample with concurrent neuroimaging adjusting for age, sex and race; the neuroimaging measures were then added to this model to explore potential mediation effects of brain structural characteristics on the relationship between orthostatic BP and CS. Parsimonious models included only neuroimaging variables that were significantly associated with CS in correlations adjusted for age, sex and race and total GM atrophy, corrected for multiple comparisons (given hypothesized lateralized relationships, Sidak correction for 14 comparisons was $p<0.00366$).

6.4. Results

A total of 100 participants were determined to have normal cognition, 80 MCI and 60 Dementia. The mean age of the sample at the time of MRI was 87 years (SD 2.9); there was a female preponderance (59% women) and 37% of the sample was black. Compared to those who remained cognitively normal, those who received a final diagnosis of MCI or Dementia were more likely to be black, to have had a stroke and there were significant differences in alcohol consumption between groups, although similar proportions of those with Dementia and normal CS consumed alcohol daily (Table 6.1). There were no significant age or sex differences between CS groups at baseline.

Table 6.1: Description of the sample by Cognitive Status

	Total Sample	**Normal**	**Mild Cognitive Impairment**	**Dementia**	***P***
	n=240	100	80	60	
Cumulative *Orthostatic* Blood Pressure Parameters[a]					
Average Systolic Orthostatic BP Response, %, mean (SD)	103.14 (4.86)	103.95 (4.96)	102.99 (4.95)	101.99 (4.37)	0.043
Consensus Orthostatic Hypotension, n (%)	25 (10.42)	11 (11.00)	8 (10.00)	6 (10.00)	0.969
Delta SBP, mmHg, mean (SD)	-4.00 (6.43)	-4.97 (6.61)	-3.70 (6.44)	-2.79 (5.94)	0.101
Slope of trajectory of Average Systolic Orthostatic BP Response, %, mean (SD)	-0.08 (2.09)	-0.24 (2.23)	-0.01 (1.91)	0.09 (2.10)	0.600
Seated SBP, mmHg, mean (SD)	135.63 (14.88)	132.82 (15.84)	136.66 (13.76)	138.96 (14.00)	0.030
Standing SBP, mmHg, mean (SD)	139.63 (15.93)	137.78 (16.69)	140.35 (13.93)	141.74 (17.00)	0.278
Cumulative *Seated* Systolic Blood Pressure Parameters[b]					
Average Seated SBP, mmHg, mean (SD)	134.00 (12.65)	131.54 (13.13)	135.18 (11.73)	136.50 (12.50)	0.032
Slope of trajectory of Seated SBP, mmHg, mean (SD)	-0.63 (0.80)	-0.58 (0.86)	0.62 (0.67)	-0.73 (0.85)	0.518
Demographics[c]					
Age, mean (SD)	72.30 (2.60)	72.47 (2.46)	72.55 (2.58)	73.27 (2.80)	0.142
Female n (%)	142 (59.17)	53 (53.00)	49 (61.25)	40 (66.67)	0.211
Black race n (%)	90 (37.50)	27 (27.00)	37 (46.25)	26 (43.33)	0.017
Medications[b]					
Antihypertensive Treatment, % visits, mean (SD)	61.91 (35.5)	59.5 (35.49)	69.90 (32.76)	55.28 (37.49)	0.036
Antidepressant Treatment, % visits, mean (SD)	8.09 (19.96)	8.58 (21.17)	6.77 (18.76)	9.03 (19.67)	0.601
Co-morbid disease[b]					
Cardiovascular disease n (%)	56 (23.33)	22 (22.00)	21 (26.25)	13 (21.67)	0.751
Stroke n (%)	14 (5.83)	0 (0.00)	10 (12.50)	4 (6.67)	0.002
Hypertension n (%)	203 (84.58)	78 (78.00)	72 (90.00)	53 (88.33)	0.056
Diabetes n (%)	58 (24.17)	25 (25.00)	15 (18.75)	18 (30.00)	0.296

Other risk factors					
Body Mass Index [c], kg/m2, mean (SD)	27.46 (4.49)	26.90 (4.65)	28.12 (4.23)	27.52 (4.49)	0.193
Smoking [c], pack year, mean (SD)	13.14 (24.85)	11.92 (22.26)	14.95 (27.29)	12.75 (25.79)	0.713
Weekly Alcohol Consumption[c], n (%)					
<1 drink per week	93 (38.75)	28 (28.00)	35 (43.75)	30 (50.00)	0.030
1-7 drinks per week	120 (50)	59 (59.00)	39 (48.75)	22 (36.67)	
Daily	27 (11.25)	13 (13)	6 (7.5)	8 (13.33)	

p values are from ANOVA for normally distributed continuous variables, Kruskal-Wallis for non-normal and χ^2 for categorical variables;

ASOBPR, Average Systolic Orthostatic BP Response; SD, standard deviation; %, Percentage; mmHg, millimeters of mercury; SBP, systolic blood pressure; DBP, diastolic blood pressure; Weekly Alcohol Consumption, 1–7 alcoholic drinks per week.

[a]Calculated from three-to-four annual observations 1997–2003 seated SBP to standing.
[b]From study entry to time of MRI (1997–98 until 2010–12).
[c]Recorded at study entry (1997–98).

In the group as a whole, ASBOPR was above 100% in 185 (77.1%) participants and below 100% in 55 (22.9%) participants. ASOBPR was significantly lower in those with Dementia (101.99 (SD 4.37)) or MCI (102.99 (SD 4.95)) as compared to those with normal CS (103.95 (SD 4.96)), in 2010-2012, p=0.04 for linear trend (Figure 6.3). Associations did not differ according to sex nor race. There were no significant differences between CS groups in consensus OH or in the slope of change of the trajectory of longitudinal orthostatic BP (p>0.1), nor were there differences between CS groups in Average Diastolic Orthostatic BP response or Delta DBP (p>0.1).

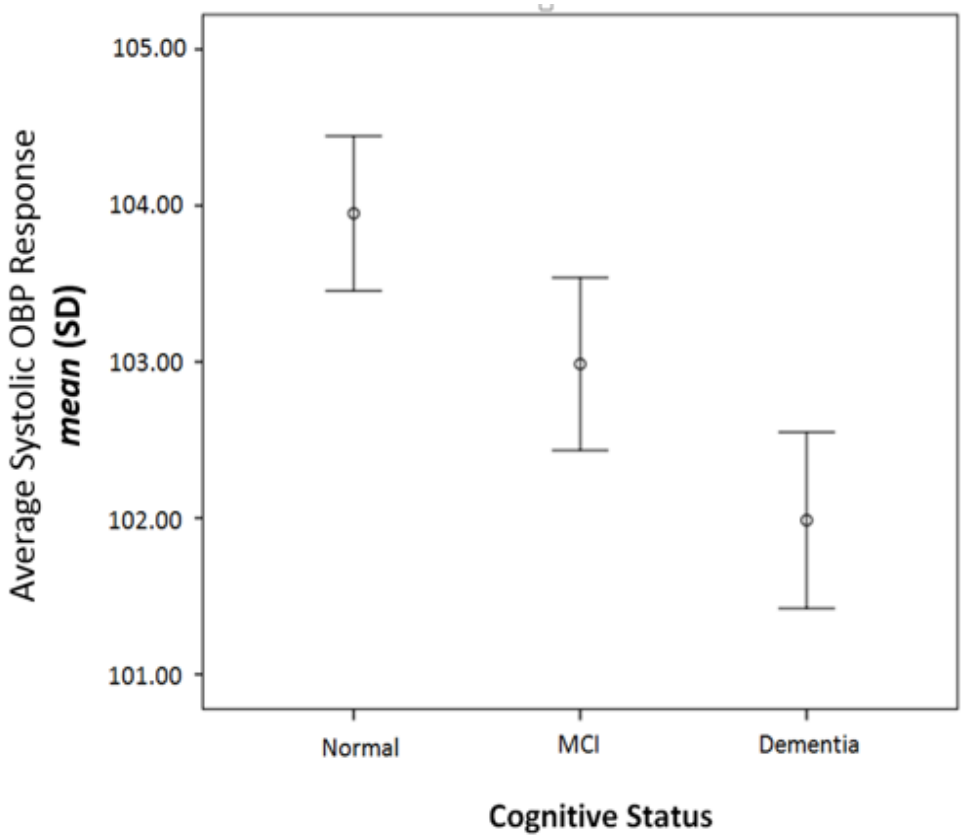


Figure 6.3: Average Systolic Orthostatic BP response and Cognitive Status
Unadjusted average systolic Orthostatic BP response (averaged across three to four repeated annual observations from 1997-1998 until 2002-2003 with higher values reflecting higher standing BP relative to seated BP) against later Cognitive Status (2010-2012). OBP=Orthostatic BP; MCI= Mild Cognitive Impairment; SD=Standard Deviation

In multinomial regression analysis adjusted for age, sex and race, ASOBPR was lower for those with Dementia as compared to those who had normal CS (Model 1). Each percentage point greater rise in ASOBPR was associated with a 9% reduced odds of a final Dementia diagnosis (Table 6.2). Additionally there was a trend towards a relationship between lower ASOBPR and MCI, although this did not reach statistical significance (p=0.12). Further adjustment for relevant co-variates did not meaningfully alter these relationships (Models 2, 3, 4, 5). Results were similar when adjusting for alcohol intake and stroke.

Table 6.2: Multivariate Multinomial Regression Results Comparing Average Systolic Orthostatic BP Response[a] across Diagnostic Categories of Cognitive Status[b] (n=240); coefficients of Average Systolic Orthostatic BP Response are reported as odds ratios (OR) and 95% confidence intervals (CI).

		Normal Cognition vs. Mild Cognitive Impairment		Normal Cognition vs. Dementia	
Model	**Variables in the model**	OR (95% CI)	*p*	OR (95% CI)	*p*
1	**Age, sex, race**	0.951 (0.891-1.014)	0.122	0.912 (0.849-0.980)	0.012
2	**Model 1 + Longitudinal seated SBP**	0.953 (0.893-1.017)	0.144	0.914 (0.850-0.983)	0.016
3	**Model 1 + Cardiometabolic conditions**	0.971 (0.907-1.039)	0.397	0.919 (0.855-0.988)	0.023
4	**Model 1 + Health Behaviours**	0.953 (0.892-1.017)	0.145	0.914 (0.848-0.984)	0.017
5	**Model 1 + Antidepressants & antihypertensives**	0.950 (0.891-1.014)	0.124	0.914 (0.850-0.983)	0.015

Data are Odd Ratios (95% Confidence Intervals) for differences between diagnostic categories of Cognitive Status.
Longitudinal seated SBP= average seated systolic blood pressure 1997-2012; Cardiometabolic conditions=Stroke, Coronary Heart Disease, Diabetes; Health behaviours= alcohol consumption, body mass index, physical activity, smoking history.
[a]Average Systolic Orthostatic BP Response : percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997-2003 with higher values reflecting higher standing SBP relative to seated SBP
[b]Cognitive Status i.e. Dementia, Mild Cognitive Impairment, Normal Cognition adjudicated 2010-2012

Of the 129 participants in the neuroimaging subsample, the mean age at time of MRI was 86 years (SD 2.7), 61.2% were female and 42.6% were black. After adjustment for age, sex, race and total atrophy index, lower ASOBPR was associated with lower GMV in subcortical regions spatially co-localized within the medial temporal lobe and lateralized to the right hemisphere (right hippocampus, right parahippocampus, and the right middle cingulate gyrus) in addition to the right dorsolateral prefrontal cortex and right lingual gyrus (Table 6.3). Using the most conservative adjustment for multiple comparisons ($p<0.00366$), associations remained significant with the right dorsolateral prefrontal cortex and right lingual gyrus. Associations with WMH were not significant.

Table 6.3: Relationship of Regional Grey Matter Volumes[a] with Average Systolic Orthostatic BP Response[b] (n = 129)

	Partial Correlation Co-efficient	*p*
Dorsolateral Prefrontal Cortex	**0.2823**	**0.0014**†**
Precuneus	0.1085	0.2283
Lingual Gyrus	**0.2751**	**0.0019**†**
Cingulate Cortex:		
Anterior	0.0919	0.3079
Middle	**0.2153**	**0.0159***
Posterior	0.1252	0.1642
Insula	0.1272	0.1575
Thalamus	-0.0123	0.8915
Amygdala	0.0491	0.5870
Hippocampus	**0.1815**	**0.0428***
Parahippocampus	**0.1804**	**0.0441***
Angular Gyrus	0.0749	0.4063
Suprmarginal Gyrus	-0.0282	0.7546
Frontoinsular Cortex	0.0616	0.4953

Data are Partial Correlation Coefficients adjusted for Age, Sex, Race & Atrophy Index.

**p<0.01 *p<0.05; † Survives Sidak Correction for multiple comparisons (14 comparisons; p<0.00366);
[a] MRI brain 2010-2012; Data shown are for Right Hemispheric Relationships; Left Sided Relationships were not significant.

[b] Average Systolic OBP Response : percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997-2003 with higher values reflecting higher standing SBP relative to seated SBP

In this subsample, the relationship between lower ASOBPR and dementia status remained significant after initial adjustment for age, sex and race and was similar in magnitude and in the same direction to the relationship in the larger sample (Table 6.4). The relationship between lower ASOBPR and dementia status was similar after adjustment for GMV. Table 6.4 shows results of the parsimonious models, adjusted for the regions of right dorsolateral prefrontal cortex or right lingual gyrus, associated with orthostatic BP after correction for multiple comparisons.

Table 6.4: Multivariate Multinomial Regression Results Comparing Diagnostic Categories of Cognitive Status[a].
Relationship with Average Systolic Orthostatic BP Response[b] adjusted for MRI[c] parameters (n=129); coefficients of Average Systolic Orthostatic BP Response are reported as odds ratios (OR) and 95% confidence intervals (CI).

		Normal Cognition vs. Mild Cognitive Impairment		Normal Cognition vs. Dementia	
Model	**Variables in the model**	OR (95% CI)	*p*	OR (95% CI)	*P*
1	**Age, sex, race**	0.940 (0.865-1.02)	0.143	0.863 (0.756-0.985)	0.029
2	**Model 1 + WMH**	0.940 (0.865-1.021)	0.144	0.861 (0.754-0.984)	0.028
3	**Model 1 + Atrophy Index**	0.944 (0.867-1.027)	0.179	0.869 (0.762-0.992)	0.038
4	**Model 1 + Atrophy Index & DLPFC GMV**	0.939 (0.858-1.028)	0.171	0.833 (0.723-0.958)	0.011
5	**Model 1 + Atrophy Index & Lingual Gyrus GMV**	0.930 (0.850-1.017)	0.110	0.852 (0.742-0.979)	0.023

Data are Odd Ratios (95% Confidence Intervals) for differences between diagnostic categories of Cognitive Status. WMH=White Matter Hyperintensities DLPFC=Dorsolateral Prefrontal Cortex; GMV= Grey Matter Volume; OBP=Orthostatic Blood Pressure

[a] Cognitive Status i.e. Dementia, Mild Cognitive Impairment, Normal Cognition adjudicated 2010-2012;

[b] Average Systolic Orthostatic BP Response : percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997-2003 with higher values reflecting higher standing SBP relative to seated SBP

[c] MRI brain 2010-2012

Sensitivity Analysis

Educational attainment was accounted for during cognitive adjudication, however given the importance of educational attainment to CS, models were re-estimated additionally adjusting for years of high school educational attainment (Supplementary Table 6.1). Given that the magnitude of orthostatic BP drop upon standing tends to correlate with a higher baseline BP, models investigating associations between ASOBPR and CS were re-estimated adjusting for seated SBP contemporaneous to the measures of standing SBP (Supplementary Table 6.2). The direction and size of the reported relationships remained unchanged. I also tested for a U-shaped relationship between orthostatic BP and CS, as reported by prior studies[291], however non-linear effects of ASOBPR (tested by addition of a quadratic ASOBPR term to regression models) were not significant.

Similar associations were evident between the absolute change in SBP ('Delta' SBP) and CS after adjustment for age, sex and race. These associations remained after adjustment for seated BP and other relevant co-variates (Supplementary Table 6.3).

Mean standing SBP was higher than mean seated SBP in all CS groups; accordingly ASOBPR in each group was above 100%. Given that our hypothesis related to exposure to lower orthostatic BP and its relationship with CS, I additionally created a binary variable which categorized participants into groups: those among whom systolic orthostatic BP response was >=100% (n=185 (77.1%)) and <100% (n=55 (22.9%)). Of participants with systolic orthostatic BP response <100%, 40/55 (72.7%) were classified as having either MCI

or Dementia versus 100/185 (54.1 %) of those with a response >100% (p=0.01) with similar patterns of association with CS evident, as with the continuous variable including after adjusting for age, sex and race (Supplementary Table 6.4).

Given the potential importance of co-medication on orthostatic BP I additionally computed variables to reflect the burden of prescription medication during the period of orthostatic BP collection i.e. 1997-2003. This included exposure to polypharmacy (defined as >=4 prescribed medications), medications used to treat prostate disorders (e.g. alpha blockers such as tamulosin), and use of anti-depressants and anti-hypertensives. There were no significant differences in ASOBPR between participants exposed versus not exposed to these medications 1997-2003 (Supplementary Table 6.5).

6.5. Discussion

This study reports associations between the average of repeated observations of systolic orthostatic BP and later CS in a community-dwelling, bi-racial cohort of the oldest-old, followed prospectively over 15 years. Specifically, a lower standing SBP relative to seated SBP averaged over six years from study entry (ASOBPR) increased odds of a dementia diagnosis at the end of the study period. Furthermore, lower ASOBPR was also related to lower GMV in brain regions known to be related to autonomic regulation and vulnerable to hypoperfusion injury. This study extends previous investigations of the relationship between orthostatic BP and CS with analysis of repeated measures of orthostatic BP, neuroimaging, clinical adjudication of CS and 15 years of prospective follow-up data in a well-defined cohort aged 69+ at time of first orthostatic BP assessment.

These findings are in line with a recent meta-analysis suggesting that lower orthostatic BP has independent prognostic value for end-organ disease.[345] The associations I report are independent of other cardio-metabolic risk factors, including longitudinal average seated SBP, seated SBP trajectories, and antihypertensive treatment. In this study, on average, standing BP was higher than mean seated BP (and therefore mean ASOBPR was >100%) which is in keeping with other study populations using a sit-to-stand orthostatic BP measurement protocol.[261,400] Furthermore, although the magnitude of orthostatic BP drop upon standing tends to correlate with a higher baseline BP, additional sensitivity analysis adjusting for average seated SBP contemporaneous to orthostatic BP measures did not substantively affect the associations reported here.

While other studies have suggested that higher orthostatic BP may also be associated with poorer CS[291,301], there was no evidence of a U-shaped relationship between ASOBPR and CS in this cohort. Kario et al. previously reported a cross-sectional U-shaped relationship between orthostatic BP, white matter changes and cognitive test scores.[299] More recently Curreri et al reported prospective associations between elevated orthostatic BP and lower cognitive scores 4 years later.[291] Discrepancies may reflect the longer duration of longitudinal follow-up in the current study, use of longitudinal orthostatic BP measurements, and investigation of a clinically adjudicated cognitive outcome rather than cognitive scores. However both lower and elevated orthostatic BP may reflect increased orthostatic BP variability – which has also been linked to poorer CS but which requires additional standing orthostatic BP measures to calculate.[288] Therefore the impact of elevated orthostatic BP may have been underestimated in the current study. Alternatively, as elevated orthostatic BP has also been hypothesized to reflect a pre-hypertension state[401] it may be less important in a cohort in whom dementia diagnosis was adjudicated aged 83+.

Prior studies of orthostatic BP and cognitive outcomes have focused on consensus OH.[164,293,348] This study additionally investigated the more recently proposed characteristic of ASOBPR based on emerging literature using continuous beat-to-beat orthostatic BP measurements[182,236] which has recently been shown to predict conversion from MCI to dementia in a clinical sample.[280] Population norms derived from continuous orthostatic BP measurement indicate that an initial systolic orthostatic BP drop immediately after standing is a universal finding among adults aged 50+.[184] With increasing age, time to stabilization of orthostatic BP to pre-stand levels and therefore the duration of exposure to lower BP is prolonged.[184] These findings, using more widely available and pragmatic standard clinical

measures, mirror those using more sophisticated techniques. Therefore one may speculate that lower ASOBPR in those participants with Dementia and MCI in this cohort may reflect larger initial orthostatic BP drops on standing and subsequent slower stabilization. This is further supported by sensitivity analyses categorizing ASOBPR indicating that the relationship with poorer CS was stronger in those with a systolic orthostatic BP response <100%. Thus ASOBPR may be a more sensitive indicator of hemodynamic homeostasis than the simple presence or absence of consensus OH, or absolute change in orthostatic BP, as it takes into account the conditional change from prestand SBP.

This study additionally hypothesized that the relationship between lower orthostatic BP and later CS may be mediated by lower GMV, possibly caused by central dementia-related neurodegeneration[218] cerebral hypoperfusion arising from lower peripheral orthostatic BP.[280] Lower ASOBPR was related to smaller GMV of the right hippocampus, right parahippocampus and right middle cingulate gyrus. Associations were strongest with regions of potential relevance to autonomic function including the right dorsolateral prefrontal cortex and the right lingual gyrus, and remained even after applying stringent conservative tests for significance due to multiple comparisons. Lateralized associations are in keeping with previously reported differential hemispheric vulnerability in the borderzone region of the right frontal cortex in AD[392] and dorsolateral prefrontal cortex involvement in sympathetic regulation.[217] In this cohort GMV did not however mediate the association between ASOBPR and CS, thus other pathways may exist to explain this association - for example endothelial dysfunction has been posited as a causal mechanism in both orthostatic BP dysregulation and dementia.[402,403]

This study found no relationship between ASOBPR and atrophy of the insula. The insula may be vulnerable to deep watershed ischemia and is involved in autonomic regulation.[218,404] The earliest dementia-related neuropathological changes may affect the insula[218], therefore neuroimaging concurrent to the measurement of orthostatic BP may have been better timed to demonstrate an association. There was no relationship between ASOBPR and WMH. This is in line with other studies using neuroimaging to investigate the relationship between orthostatic BP and dementia[298] but is perhaps surprising given relationships between orthostatic BP, stroke and cardiovascular disease.[345]

These findings must be interpreted in the context of several limitations. Importantly, although this study applied consensus OH criteria, participants underwent a seated-to-stand procedure rather than supine-to-stand and the measurement of orthostatic BP at 3 min is lacking. A larger orthostatic BP drop would be expected from the supine position and may account for a lack of association with traditional orthostatic BP indices and the low prevalence of consensus OH. Optimal timing of the standing BP measurement is contested however [405], and measurements of standing BP beyond one minute at each annual visit would have allowed investigation of within-person systolic orthostatic BP variability.[288] However a single measurement of standing orthostatic BP at one minute is a limitation common to other studies.[261,348] Future studies using more advanced measures will allow further investigation of the relationship between orthostatic BP drops occurring < 1 minute (e.g. Initial Orthostatic Hypotension - defined as drop of >=40mmHg occurring within 15seconds of standing associated with symptoms such as dizziness) and cognitive outcomes.

Loss to follow-up and differential participation of more robust older adults may have introduced bias; furthermore, neuroimaging was only available on a subset of those with cognitive adjudication. It is important to note however that the association between ASOBPR and CS was robust, remaining significant even when tested in the smaller subsample. This study cannot infer causality based on the determination of CS and MRI data at a single time point. Furthermore, orthostatic BP measures contemporaneous to MRI and cognitive adjudication were not available. Neuropathological changes associated with dementia however, likely begin decades prior to the onset of the clinical syndrome and are progressive[35], therefore it is plausible cortical atrophy at the time of MRI would be more advanced in those with earlier onset orthostatic BP dysregulation.

Further work is required to determine if a causal relationship exists between orthostatic BP and CS. If a causal relationship were to be established, interventions to improve ASOBPR may be important in preserving CS into late old age. Simple conservative strategies are the cornerstone of management of orthostatic BP dysregulation e.g. rationalization of medications, judicious use of antihypertensives and adequate fluid and salt intake. Examining ASOBPR response may help uncover future CS in the oldest-old. Lower ASOBPR may be on the causal pathway to poorer CS by reducing GMV of brain regions important in autonomic control. Strategies to control ASOBPR may impact future CS, possibly by reducing GM atrophy in these regions.

Supplementary Table 6.1: Multivariate Multinomial Regression Results Comparing Average Systolic Orthostatic BP Response[a] across Diagnostic Categories of Cognitive Status[b] (n=240); coefficients of Average Systolic Orthostatic BP Response are reported as odds ratios (OR) and 95% confidence intervals (CI) (additionally adjusting for years of education)

Model	Variables in the model	Normal Cognition vs. Mild Cognitive Impairment		Normal Cognition vs. Dementia	
		OR (95% CI)	*p*	OR (95% CI)	*p*
1	**Age, sex, race + education**	0.951 (0.892-1.014)	0.124	0.910 (0.847-0.979)	0.011
2	**Model 1 + Longitudinal seated SBP**	0.953 (0.893-1.017)	0.146	0.912 (0.848-0.981)	0.014
3	**Model 1 + Cardiometabolic conditions**	0.974 (0.910-1.043)	0.448	0.918 (0.854-0.988)	0.022
4	**Model 1 + Health Behaviours**	0.953 (0.893-1.017)	0.147	0.913 (0.846-0.984)	0.018
5	**Model 1 + Antidepressants & antihypertensives**	0.951 (0.891-1.014)	0.127	0.912 (0.848-0.981)	0.013

Data are Odd Ratios (95% Confidence Intervals) for differences between diagnostic categories of Cognitive Status.
OBP=Orthostatic Blood Pressure; Longitudinal seated SBP= average seated systolic blood pressure 1997-2012; Cardiometabolic conditions=Stroke, Coronary Heart Disease, Diabetes; Health behaviors= alcohol consumption, body mass index, physical activity, smoking history.

[a]Average Systolic Orthostatic BP Response : percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997-2003 with higher values reflecting higher standing SBP relative to seated SBP

[b]Cognitive Status i.e. Dementia, Mild Cognitive Impairment, Normal Cognition adjudicated 2010-2012

Supplementary Table 6.2: Multivariate Multinomial Regression Results Comparing Average Systolic Orthostatic BP Response[a] across Diagnostic Categories of Cognitive Status[b] (n=240); coefficients of Average Systolic Orthostatic BP Response are reported as odds ratios (OR) and 95% confidence intervals (CI); (additionally adjusting for seated SBPc at time of Orthostatic BP)

		Normal Cognition vs. Mild Cognitive Impairment		Normal Cognition vs. Dementia	
Model	**Variables in model**	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
1	**Age, sex, race, + seated SBP [c]**	0.955 (0.896-1.020)	0.170	0.919 (0.854-0.988)	0.023

SBP=Systolic Blood Pressure
Data are Odd Ratios (95% Confidence Intervals) for differences between diagnostic categories of Cognitive Status.

[a]Average Systolic Orthostatic BP Response : percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997-2003 with higher values reflecting higher standing SBP relative to seated SBP

[b]Cognitive Status i.e. Dementia, Mild Cognitive Impairment, Normal Cognition adjudicated 2010-2012

[c]Average Seated SBP, averaged across all (three to four) annual observations 1997-2003 where standing SBP was not missing

Supplementary Table 6.3. Multivariate Multinomial Regression Results Comparing Average 'Delta SBP'[a] across Diagnostic Categories of Cognitive Status[b] (n=240)

coefficients of Average 'Delta SBP' are reported as odds ratios (OR) and 95% confidence intervals (CI)

		Normal Cognition vs. Mild Cognitive Impairment		Normal Cognition vs. Dementia	
Model	**Co-variates**	OR (95% CI)	*p*	OR (95% CI)	*p*
1	**Age, sex, race**	1.040 (0.990-1.092)	0.114	1.061 (1.005- 1.119)	0.031
2	**Model 1 + seated SBP[c]**	1.038 (0.989-1.091)	0.127	1.059 (1.003-1.117)	0.040
3	**Model 1 + Longitudinal seated SBP**	1.042 (0.992-1.0943)	0.103	1.063 (1.007(1.224)	0.027
4	**Model 1 + Cardiometabolic conditions**	1.027 (0.976-1.081)	0.305	1.057 (1.001-1.116)	0.044
5	**Model 1 + Health Behaviors**	1.039 (0.989-1.091)	0.132	1.059 (1.002-1.120)	0.042
6	**Model 1 + Antidepressants & antihypertensives**	1.041 (0.991-1.094)	0.107	1.059 (1.003-1.118)	0.039

SBP=Systolic Blood Pressure

Data are Odd Ratios (95% Confidence Intervals) for differences between diagnostic categories of Cognitive Status.

[a]Average Delta SBP : seated SBP minus standing Systolic BP, averaged across all (three to four) annual observations 1997-2003 with higher values reflecting greater absolute drop in Systolic BP

[b]Cognitive Status i.e. Dementia, Mild Cognitive Impairment, Normal Cognition adjudicated 2010-2012

[c] Average Seated SBP contemporaneous to standing SBP measure, averaged across all (three to four) annual observations 1997-2003 where standing SBP was not missing

Supplementary Table 6.4: Multivariate Multinomial Regression Results Comparing 'Average Systolic Orthostatic BP Response'

(coded as a binary categorical variable <100% vs. >100%)[a] across Diagnostic Categories of Cognitive Status[b] (n=240); coefficients are reported as odds ratios (OR) and 95% confidence intervals (CI)

		Normal Cognition vs. Mild Cognitive Impairment		Normal Cognition vs. Dementia	
Model	**Co-variates**	OR (95% CI)	*p*	OR (95% CI)	*p*
1	**Age, sex, race**	2.64 (1.25-5.57)	0.011	2.12 (0.934-4.79)	0.072

Data are Odd Ratios (95% Confidence Intervals) for differences between diagnostic categories of Cognitive Status.

[a]Average Systolic Orthostatic BP Response coded as a binary categorical variable where 0= average systolic orthostatic BP response >100% and 1=Average Systolic Orthostatic BP Response <100% .

[c]Cognitive Status i.e. Dementia, Mild Cognitive Impairment, Normal Cognition adjudicated 2010-2012

Supplementary Table 6.5: Descriptive Statistics Comparing Average Systolic Orthostatic BP Response[a] according to medication[b] (n=240)

	Average Systolic BP Response		
Medication	No	Yes	*p*
Anti-Hypertensives	(n=81 (33.75%) 103.16 (4.71)	(n=159 (66.25%)) 103.13(4.95)	0.96
Anti-depressants	(n=225 (93.75%)) 103.06 (4.85)	(n=15 (6.24%)) 104.24(5.07)	0.36
'Anti-prostate'[c]	(n=215 (89.58%)) 103.10 (4.82)	(n=25 (10.42%)) 103.49(5.26)	0.71
Polypharmacy[c]	(n=116 (48.33) 103.02 (5.01)	(n=124 (51.66%)) 103.25 (4.73)	0.72

p-values are from independent t-tests

[a]Average Systolic Orthostatic BP Response : percent change in SBP from sitting to stand, averaged across all (three to four) annual observations 1997-2003 with higher values reflecting higher standing SBP relative to seated SBP

[b]Exposed vs Not exposed 1997-2003

[c]Medications used to treat prostate disorders

[d]4 or more prescribed medications

7. STUDY IV - Childhood Trauma and Lifetime Syncope Burden among Older Adults

Studies I-III have shown that greater BP instability may be associated with poorer brain health in older adults: greater SMI and affective symptoms in men, and poorer objective cognition and greater GM atrophy in a prospectively followed biracial cohort of the oldest old. Study IV recognizes the importance of the life course to the investigation of brain health – by acknowledging that cardiovascular autonomic function and brain health in older adults is underpinned by biological processes and environmental / behavioural exposures occurring earlier in life. VVS may be a lifelong tendency that first emerges in adolescence. Psychological stress is an important determinant of BP and may have lifelong consequences for ANS regulation; bidirectional associations between BP and affective symptoms have been descried across the life course. A small number of clinical studies have reported associations between childhood trauma (a severe psychological stressor) and syncope. **Study IV** investigates potential pathways from childhood trauma to recurrent syncope in later life.

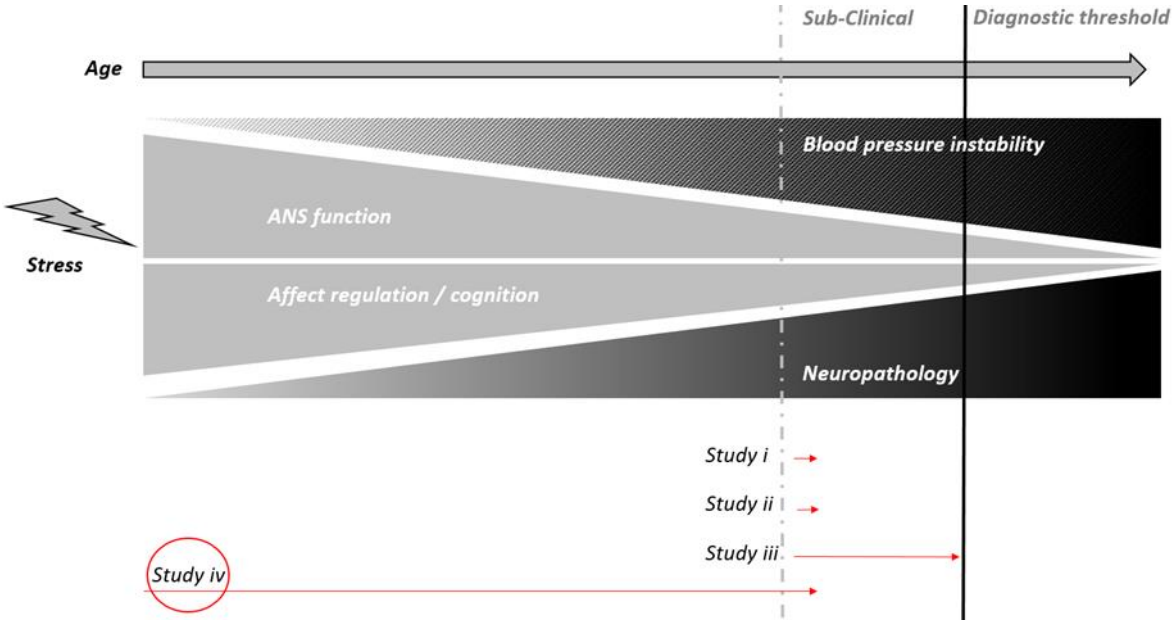


Figure 7.1: Thesis Figure: Study IV
Study IV investigates ***life course*** pathways linking stress and blood pressure instability.

Childhood Trauma and Lifetime Syncope Burden among Older Adults

7.1. Abstract

Introduction: Vasovagal syncope is governed by the ANS and often precipitated by highly salient emotional situations. This study investigates the hypothesis that a lifetime tendency toward VVS may be precipitated by exposure to childhood trauma.

Methods: This study uses data from the first wave of TILDA of adults aged 50+ (n=6497) who were asked to report lifetime syncope frequency and any history of childhood sexual or physical abuse. Mediation analysis was used to assess the relative importance of pathways via which childhood trauma could plausibly increase risk of later life recurrent syncope including via depression, mid-life cardiovascular disease and frequent syncope in youth.

Results: 18.2% reported a lifetime syncopal event: 4.0% frequent syncope in youth and 1.5% recurrent syncope in the last year. 10.9% reported childhood sexual or physical abuse, rising to 14.2% among those reporting any lifetime syncopal event, 21.0% with frequent syncope in youth and 20.2% with recurrent syncope in later life. In fully adjusted logistic regression models the report of childhood sexual or physical abuse was independently associated with frequent syncope in youth (OR 1.85 (95%CI% 1.27-2.71); p=0.001; OR 2.14 (1.48-3.10); p<0.001 respectively). A history of frequent syncope in youth and depression partially mediated the relationship between childhood sexual and physical abuse and recurrent syncope in later life, while mid-life cardiovascular disease was less important.

Conclusion: Childhood trauma may contribute to a lifelong vasovagal tendency. Early attention should be given to the potential precipitating and perpetuating psychosocial factors affecting recurrent syncope.

7.2. Introduction

Up to 40% of the population will experience at least one syncopal event during their lifetime, the majority of which will be attributable to the 'common faint', otherwise known as neurally mediated VVS.[406] In those with VVS, T-LOC results from cerebral hypoperfusion induced by reflex peripheral vasodilatation and/or bradycardia, although the exact mechanisms remain incompletely understood.[407] Clinical features include a typical prodrome of dizziness, unsteadiness and blurred vision, followed by brief self-limiting LOC and loss of postural tone, then complete and rapid recovery. Triggers are usually readily identifiable and may be physiological (e.g. prolonged orthostasis) and/or psychological (e.g. blood injury phobia).[408]

VVS affects all ages and may negatively impact quality of life, particularly if recurrent.[409] Childhood sexual and physical abuse are known to be associated with a broad range of poor health outcomes even into later life.[410] Although several small clinical studies have suggested higher rates of childhood maltreatment in those with syncope[253,254], a recent meta-analysis synthesizing the evidence to date on links between childhood sexual abuse and somatic outcomes specifically highlighted insufficient evidence relating to syncope.[255] Various pathways could plausibly link childhood trauma and syncope later in life including poor cardiovascular health in mid-life, poor mental health, and altered autonomic function.[253,255,411]

Clinical history is the key to diagnosis in VVS.[168] The pattern with which syncope occurs across a lifetime can be highly indicative of a VVS tendency – e.g. the experience of frequent syncope in youth.[242] VVS most commonly has its onset in the post-pubertal period with a female preponderance.[243] The incidence of childhood sexual and physical abuse also peak in this age group, and follows a similar sex distribution.[412] VVS is classically associated with readily identifiable triggers including highly salient emotional situations, hence 'trait faintness' has been suggested as an important stress-response in humans.[247] Across the life course syncope incidence has a bimodal distribution, with a second peak occurring after 65 years.[413] Those who have a history of VVS in youth are more likely to represent with events which are also attributable to VVS in later life.[243] These syncopal events, perhaps with an interlude lasting decades, are seen as a recurrence of the same underlying tendency and hence VVS has been likened to other chronic diseases which have a relapsing-remitting course.[414]

Syncope however may also herald a more malign diagnosis particularly in older adults in whom a cardiac cause must be considered.[415] Syncope may thus pose a diagnostic dilemma and often precipitates extensive high-cost, low-yield investigations; yet even in older adults, a definitive cause will remain elusive in up to 50%.[416] Childhood trauma has been associated with elevated mid-life cardiovascular risk[411], however a cardiac cause of syncope, particularly when examined at the population level, is less likely to account for frequent syncope in youth.[413]

VVS and psychiatric diagnoses commonly co-occur and may affect the course and recurrence of syncopal events.[244] Depression is more common in those with syncope[409], and an elevated risk of depression is a known sequela of exposure to childhood trauma.[235]

Among the psychiatric diagnoses regularly encountered in syncope clinic populations is 'psychogenic pseudosyncope'[254], believed to be akin to 'non-epileptic attacks' which in the neurology literature have been consistently linked to higher rates of childhood trauma.[417] Such dissociative events may account for up to 6% of referrals to specialist tertiary care syncope units[168] although this may be a significant underestimate. Seeking a history of psychological trauma remains an important element in the psychiatric evaluation of those presenting with such dissociative phenomena, however both the etiological and diagnostic relevance of such reports are debated.[418]

This study sought to explore associations between a history of childhood sexual and physical abuse and lifetime syncope burden in a large population-based sample of older adults aged 50+.

Hypotheses under investigation:

1. Given established links between childhood trauma and both mid-life cardiovascular disease and depression I hypothesize that childhood sexual and physical abuse will be related to recurrent syncope in later life via these mediators.

2. Similar to the effect seen in other chronic diseases, this study investigates the hypothesis that a life time tendency toward VVS or 'trait-faintness' may be precipitated by exposure to childhood trauma. I expect that those exposed to childhood sexual and physical abuse would report a greater lifetime burden of

syncopal events - particularly in a pattern suggestive of a tendency towards VVS e.g. those with a history of recurrent syncope in youth.

3. Given the recognition that a predisposition to VVS starts early and may persist for decades, I further anticipate that frequent syncope in youth would mediate any relationship between childhood trauma and recurrent syncope in later life, even after accounting for other plausible pathways linking syncope to childhood trauma, including cardiovascular disease and poorer mental health.

7.3. Methods

Sample

This analysis is based on data from the first wave of TILDA, conducted 2009-2011. This is a population-based, nationally representative study of community-dwelling adults aged 50 and over. The TILDA data collection process has been described in detail elsewhere.[349] Briefly, participants were assessed in their own home by means of a Computer Assisted Interview delivered by a trained interviewer. They were also invited to return a Self-Completion Questionnaire, which they completed unsupervised and which collected information on more sensitive topics. In total 8,175 participants aged 50 and older enrolled in the TILDA cohort of whom 6,636 returned the Self-Completion Questionnaire - which included questions on childhood sexual and physical abuse. Less than 2% (n=139) of those who returned the Self-Completion Questionnaire were missing on any of the variables of interest resulting in a final sample of 6,497 participants.

Ethics

Trinity College Research Ethics committee granted Ethical Approval for the study. Each participant provided written informed consent prior to enrolment in the study.

Outcome Variables

Assessment of Syncope Burden:

Three questions were used to record lifetime syncope burden:

1. Lifetime event: 'Have you ever had a blackout or fainted?' responses were coded as a binary categorical variable i.e. *never=0 / ever=1*.

2. Vasovagal tendency in youth: 'Were you a frequent fainter when you were younger?' with answers coded as a binary categorical variable i.e. *no=0 / yes=1*.

3. Recurrent late life syncope: 'Approximately how many times have you had a blackout or fainted in the last year?' a binary categorical variable was coded to indicate those participants with recurrent (>=2) reported syncopal episodes in the last twelve months i.e. recurrent syncope in the last year *no=0 / yes=1*.

Primary Predictor Variables:

Assessment of Childhood Trauma

As per the US population-based Health and Retirement Study[235], a history of childhood abuse was collected by four questions querying a history of sexual or physical abuse prior to the age of 18 by parents or others: 'Before you were 18 years old, were you ever sexually abused by either of your parents?', 'Before you were 18 years old were you ever sexually abused by anyone other than your parents?'; 'Before you were 18 years old, were you ever physically abused by either of your parents?', 'Before you were 18 years old were you ever

physically abused by anyone other than your parents?'. Responses to these questions were coded to produce two binary categorical variables: history of childhood sexual abuse *no=0 / yes=1;* history of childhood physical abuse *no=0 / yes=1.*

Co-variates

Age, sex and education were recorded, as was smoking history (current, past, never). Co-morbid somatic conditions were recorded as the number of self-reported doctor-diagnosed conditions including: asthma, lung disease, arthritis, osteoporosis, diabetes, peptic ulcer disease, cancer and hip fracture. These were summed to give a total number of age-related chronic physical co-morbidities. Further relevant cardiovascular/ cerebrovascular conditions were recorded to include: angina, myocardial infarction, heart failure, stroke, Transient Ischemic Attack, hypercholesterolemia, structural heart disease and arrhythmia. The total number of cardiovascular conditions was then summed and recoded as 0, 1, 2 or more, and was later added to regression models as a categorical variable.

The total number of prescribed medications was recorded in the participant's home and coded using the World Health Organizations Anatomical Therapeutic Chemical index.[419] Those participants who were taking 5 or more regular medications were defined as subject to 'polypharmacy'.

Levels of depressive symptoms over the previous week were recorded using the CES-D.[353] Each question offers a four-point response scale with options ranging from, "Rarely or none

of the time (less than 1 day)" to "All of the time (5-7 days)". This is a 20-item questionnaire, which produces a total score ranging from 0-60 and is validated for use in epidemiological populations. Higher scores indicate greater levels of depressive symptoms.[354]

Delayed word recall score was used as a measure of cognition.[420] In this test ten common words are presented orally which the participant is asked to remember, the number of words recalled after a short delay is recorded with higher scores indicating better recall.

Statistical Analysis

All statistical analysis was conducted using the statistical software package Stata v12. Appropriate descriptive statistics were employed to describe the population according to a history of lifetime syncope burden. Using multiple binary logistic regression I investigated associations of childhood sexual and physical abuse with syncope burden. Separate models were run with childhood sexual or physical abuse as the independent variable of interest and syncope burden (lifetime syncopal event *or* history of frequent syncope in youth *or* recurrent syncope in the last year) as the dependent variable. Co-variates including age, sex, education, cardiovascular disease, co-morbidity, smoking history, polypharmacy and current depressive symptoms were added to this model and changes in the relationship between childhood trauma and syncope burden were examined. Where late life recurrent syncope was the outcome of interest, these models were adjusted for frequent syncope in youth. Interactions between childhood sexual and physical abuse were tested, as were interactions between the trauma variables of interest and sex. Finally, formal mediation analysis was performed using the Stata macro 'binary_mediation'[421], in an attempt to better understand

the relative effects of hypothesized life-course factors in mediating the relationship between childhood trauma and recurrent late life syncope (see Figure 7.2 for conceptual pathway). I also calculated the proportion of the total mediating or "indirect" effect as a proportion of the total effect, and the proportion of each putative mediator's indirect effect as a proportion of the total indirect effect. This was followed by a bootstrapping procedure[422], clustered by household, to obtain standard errors for the indirect effects and their proportions along with 95% percentile confidence intervals.

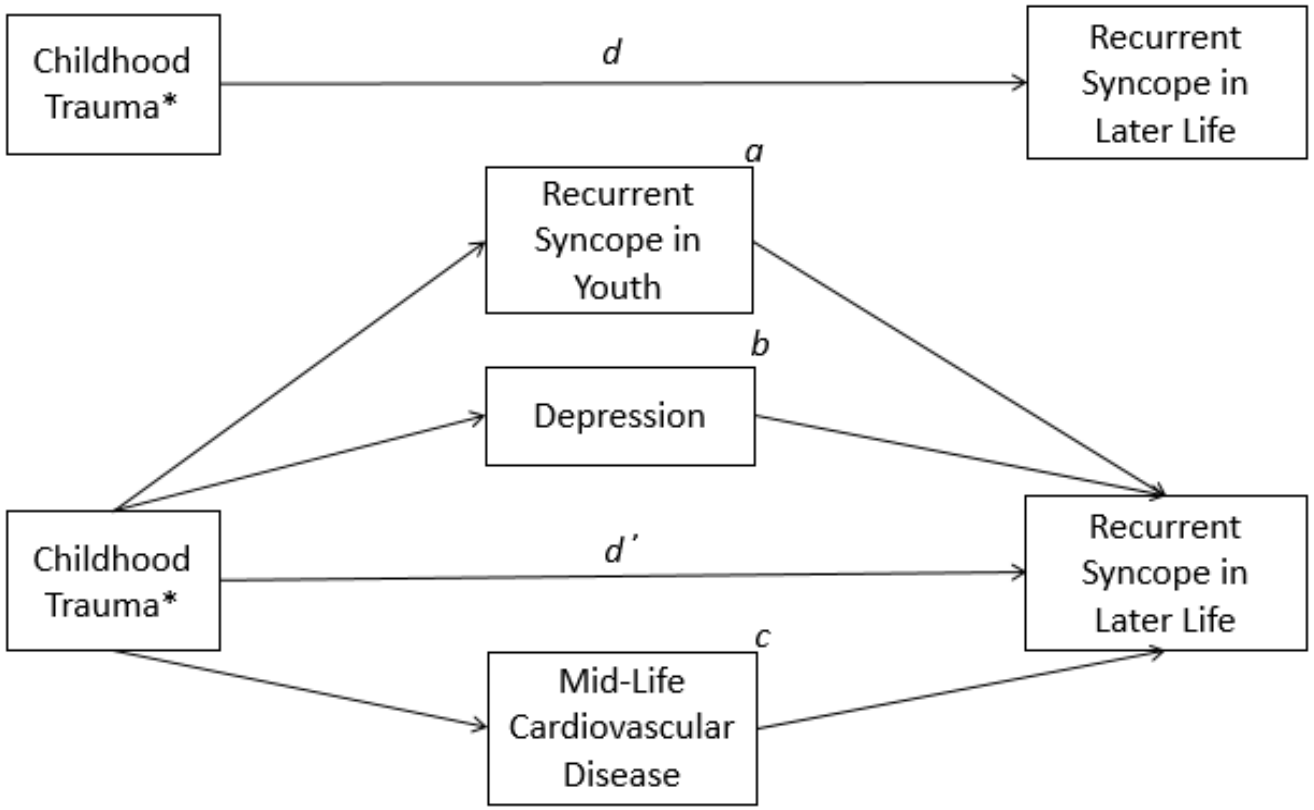


Figure 7.2: Conceptual pathways leading from childhood trauma to recurrent syncope in later life.
* A history of childhood sexual or physical abuse
Total effect $d = d' + a + b + c$; Total direct effect = d'; Total indirect effect = $a + b + c$

In sensitivity analysis I repeated all regression models, further adjusting for a history of self-reported ill-health in childhood and poverty in childhood, as potential alternative explanations for the associations reported. In addition, given that CES-D is a short-term assessment of depressive symptoms, I repeated all mediation analyses replacing CES-D in models with a lifetime self-reported doctor's diagnosis of a depressive disorder.

7.4. Results

Of the total analysis sample (*n*=6497), 18.2% (*n*=1,181) of the sample reported a lifetime history of syncope. Compared to participants with no lifetime history of syncope, participants who reported any episode also reported higher rates of physical health co-morbidities, including higher levels of cardiovascular disease and greater current depressive symptoms. Participants with any lifetime history of syncope did not differ on tests of cognitive function relative to those without a history of syncope (Table 7.1a).

Table 7.1a: Characteristics of Sample by Lifetime History of Syncopal Event[a]

	Total sample n=6497	**Never n=5316 (81.8 %)**	**Ever n=1181 (18.2 %)**	***p***
Demographics:				
Age(mean (SD))	63.39 (9.5)	63.48 (9.5)	62.96 (9.4)	0.042
Education n (% primary only)	1775 (27.0)	1454 (27.3)	304 (25.7)	<0.001
Gender n (% female)	3539 (54.6)	2825 (53.1)	714 (60.5)	<0.001
Childhood trauma:				
Any history of Abuse n (%)	706 (10.9)	538 (10.1)	168 (14.2)	<0.001
Childhood Sexual Abuse n (%)	440 (6.8)	329 (6.2)	111 (9.4)	<0.001
Childhood Physical Abuse n (%)	479 (7.4)	366 (6.9)	113 (9.6)	0.001
Affective Symptoms & Cognitive Health				
Depressive Symptoms[b], (median (IQR))	3 (7)	3 (6)	4 (8)	<0.001
Cognition[c] (mean (SD))	5.99 (2.3)	5.94 (2.3)	6.19 (2.3)	>0.99
Comorbidity & Cardiovascular Risk:				
CVD conditions n (% ≥2)	777 (12.0)	557 (10.5)	220 (18.6)	<0.001
Chronic conditions n (% ≥2)	1116 (17.2)	852 (16.0)	264 (22.4)	<0.001
Polypharmacy n (%)	1327 (20.4)	1019 (19.2)	308 (26.1)	<0.001
Current Smoker n (%)	1084 (16.7)	861 (16.2)	223 (18.9)	0.030

CVD=Cardiovascular conditions; Polypharmacy = five or more regular medications
IQR: Interquartile Range; SD: Standard Deviation
[a]Lifetime History of Syncopal Event i.e. Ever fainted *(no/yes)*
[b]Center for Epidemiological Studies Depression Scale score
[c]Delayed Word Recall score

4.0% (*n*=262) of the sample additionally reported a history of frequent syncope in youth, with 1.5% (*n*=94) of the sample having experienced recurrent syncope in the last year (Table 7.1b). Of those who reported frequent syncope in youth and those reporting recurrent syncope in the last twelve months, a majority were female (79.8%(*n*=209) and 62.8% respectively (*n*=59)).

Table 7.1b: Characteristics of Sample by Lifetime Syncope Burden[a]

	Ever **n=1,181 (18.2%)**	**Frequent in youth** **n=262 (4.0%)**	**Recurrent episodes in the last year** **n=94 (1.45%)**
Demographics:			
Age(mean (SD))	62.96 (9.4)	62.52 (8.8)	63.12 (9.9)
Sex n (% female)	304 (25.7)	209 (79.8)	59 (62.8)
Education n (% primary only)	714 (60.5)	66 (25.2)	30 (31.9)
Childhood trauma:			
Any history of Abuse n (%)	168 (14.2)	55 (21.0)	19 (20.2)
Childhood Sexual Abuse n (%)	111 (9.4)	36 (13.7)	12 (12.8)
Childhood Physical Abuse n (%)	113 (9.6)	39 (14.9)	17 (18.1)
Mental & Cognitive Health:			
Depressive Symptoms[b] (median (IQR))	4 (8)	4 (8)	5 (12)
Cognition[c] (mean (SD))	6.19(2.3)	6.43 (2.4)	5.95 (2.4)
Comorbidity & Cardiovascular Risk:			
CVD conditions n (% ≥2)	220 (18.6)	51 (19.5)	23 (24.5)
Chronic conditions n (% ≥2)	264 (22.4)	74 (28.2)	29 (30.9)
Polypharmacy n (%)	308 (26.1)	64 (34.8)	37 (39.4)
Current Smoker n (%)	223 (18.9)	51 (19.5)	23 (24.5)

IQR=Interquartile range; SD=Standard Deviation; Polypharmacy = five or more regular medications; CVD=Cardiovascular conditions.

[a]Lifetime Syncope Burden i.e. Ever fainted *(no/yes)*; Frequent fainting in youth *(no/yes);* Recurrent syncope in Later Life (>=2 events in the last 12 months: *no/yes)*

[b]Depressive Symptoms = Center for Epidemiological Studies Depression Scale score

[c]Cognition=Delayed Word Recall score

In multiple binary logistic regression analysis the relationship between childhood trauma and the report of any lifetime history of syncope was similar across those with a history of sexual abuse (OR 1.29 (95%CI% 1.03-1.63)) and those with a history of physical abuse (OR 1.22 (95%CI% 0.97-1.53)), although after full adjustment for all covariates there was no longer a statistically significant relationship with physical abuse (Table 7.2). Both childhood sexual and physical abuse were associated with a history of frequent syncope in youth. The associations were statistically significant and large even after adjustment for a history of later life syncope.

Table 7.2: Multivariate Binary Logistic Regression Analyses: Models showing associations of Lifetime Syncope Burden[a] with Childhood Trauma[b];

coefficients of Childhood Trauma are reported as odds ratios (OR) and 95% confidence intervals (CI).

	Lifetime Syncopal Event [c]		**Frequent Syncope in Youth[c]**		**Recurrent Syncope in Later Life[d]**	
	OR (95%CI)	**p**	**OR (95%CI)**	**p**	**OR (95%CI)**	**p**
Childhood sexual abuse	1.29 (1.03 – 1.63)	0.030	1.85 (1.27-2.71)	0.001	1.36 (0.71-2.62)	0.35
Childhood physical abuse	1.22 (0.97-1.53)	0.091	2.14 (1.48-3.10)	<0.001	1.91 (1.08-3.39)	0.026

[a]Lifetime Syncope Burden i.e. Ever fainted *(no/yes)*; Frequent fainting in youth *(no/yes);* Recurrent syncope in Later Life (>=2 events in the last 12 months: *no/yes)* with separate models for each outcome

[b]Childhood Trauma i.e. childhood sexual or childhood physical abuse *(no/yes)* with separate models for each exposure

[c]Model additionally adjusted for age, sex, education, smoking history, cardiovascular conditions, co-morbidity, polypharmacy, depression, delayed word recall

[d]Model additionally adjusted for age, sex, education, smoking history, cardiovascular conditions, co-morbidity, polypharmacy, depression, delayed word recall *& history of frequent syncope in youth*

A history of childhood physical abuse was independently associated with increased odds of recurrent syncope in the past twelve months (OR 1.91 (95%CI% 1.08-3.39)) – a relationship which was independent of adjustment for all covariates. Given the smaller number of cases reporting recurrent syncope in later life however, the standard errors of the estimates were larger (Table 7.2). The association between childhood sexual abuse and recurrent late life syncope was no longer significant after full adjustment; in addition, the effect size was smaller than that for the effect of childhood physical abuse.

Using mediation analysis to examine pathways linking childhood trauma to recurrent late life syncope revealed that the effect of both childhood sexual and physical abuse on later life recurrent syncope was partially mediated. Table 7.3 displays the proportions of the total effect (*d in Figure 7.2*) which was mediated (total indirect effect i.e. a + b + c *in Figure 7.2*). 0.42 (0.13-2.59) of the total effect of sexual abuse on recurrent syncope in later life was mediated by the combination of the hypothesized pathways, of which the proportion mediated via frequent syncope in youth was 0.60 (0.37-0.85) and via depressive symptoms was 0.34 (0.14-0.58). With regard to physical abuse, 0.30 (0.17-1.03) of the total effect was mediated: 0.57 (0.36-0.81) via frequent fainting in youth and 0.34 (0.11-0.53) via depression. 0.06 (-0.06-0.20) of the indirect effect from childhood sexual abuse to recurrent syncope in later life was mediated via established cardiovascular disease, while the equivalent proportion for childhood physical abuse was 0.10 (0.001-0.28), although these were estimated with less precision than the other pathways.

Table 7.3: Binary Mediation Analyses where Childhood Trauma[a] is the independent variable and Recurrent Syncope in Later Life[b] is the Outcome Variable with Frequent Syncope in Youth, Depressive Symptoms and Cardiovascular Disease as putative mediators.

Co-efficients are presented as proportions (ratios) with 95% Bias Corrected (BC) Confidence Intervals (CI)

	Childhood Sexual Abuse		Childhood Physical Abuse	
	Proportion	**Bootstrap 95% BC CI**	**Proportion**	**Bootstrap 95% BC CI**
Total Indirect effect [c]((a+b+c)/(a+b+c+d')=(a+b+c)/d)	0.42	(0.13-2.60)	0.30	(0.17-1.03)
Frequent syncope in Youth[d] [c]((a/(a+b+c))	0.60	(0.37- 0.85)	0.57	(0.36-0.81)
Depression[e] [c](b/(a+b+c))	0.34	(0.14-0.58)	0.33	(0.11-0.53)
Cardiovascular Conditions[f] [c](c/(a+b+c))	0.06	(-0.06-0.20)	0.10	(0.001-0.28)

[a]Childhood Trauma i.e. childhood sexual or childhood physical abuse (no/yes) with separate models estimated for each exposure

[b]Recurrent syncope in Later Life (>=2 events in the last 12 months: no/yes)

[c]Pathway effects calculated as proportions denoted as per conceptual pathways in Figure 7.2.

[d]Frequent fainting in youth (no/yes)

[e]Center for Epidemiological Studies Depression Scale score

[f]Two or more self-reported cardiovascular conditions

The predictive power of the logistic regression models was not improved when examining the additive and multiplicative effect on syncope risk of experiencing both sexual and physical abuse. Interaction terms between sex and either form of childhood maltreatment under investigation were not significant.

Sensitivity Analysis

After examination of models further adjusted for a history of self-reported ill-health or poverty in childhood, any substantive conclusions regarding the size and direction of associations remained unchanged. Similarly, mediation analysis using a self-reported diagnosis of a depressive disorder in place of the CES-D demonstrated a similar proportion of the indirect effects were mediated via mental health.

7.5. Discussion

In this large population-based cohort, exposure to childhood sexual abuse was independently associated with the report of any lifetime episode of syncope and also with the experience of frequent syncope in youth. Childhood physical abuse was related to reports of frequent syncope in youth and recurrent syncope in later life. These relationships persisted even after adjustment for a wide range of co-variates including demographics, depressive symptoms, physical co-morbidities and cardiovascular risk. In formal mediation analysis investigating pathways by which childhood trauma could plausibly affect later life recurrent syncope, frequent syncope in youth was shown to partially mediate the relationship - a pathway in keeping with childhood trauma contributing to a lifelong predisposition towards VVS[414] or 'trait faintness'.[247]

Several small clinical studies have suggested that childhood sexual and physical abuse may be clinically relevant in those presenting with syncope. A recent study based in a specialist tertiary-referral syncope clinic which described the semiology of psychogenic pseudosyncope (a dissociative disorder) reported that childhood sexual or physical abuse was present in 11.6 % of patients[254]; work from the same group has also recently reported that VVS and PPS co-occur [423], suggesting a potential common etiological pathway. Furthermore, an investigation of childhood syncope referrals in a pediatric unit suggested that psychosocial stressors, including maltreatment and familial discord, were common potential precipitants of recurrent unexplained syncopal events.[253]

VVS is arguably the most overt, and common, manifestation of autonomic malfunction thus these findings are in keeping with research suggesting a link between childhood sexual and physical abuse and altered autonomic equilibrium.[424,425] Of those who experience any lifetime syncope, the majority will have had an event attributable to VVS, similarly those with a history of frequent syncope in youth.[413] The exact mechanism underpinning VVS remains poorly understood but may result from paradoxical parasympathetic overdrive[414] in response to a sympathetic increase in heart rate. In face of threat, the recruitment of the parasympathetic division of the ANS may serve as a means of self-soothing, thus higher levels of parasympathetic tone may be adaptive.[247] Indeed 'trait faintness' has been likened to 'tonic immobility'[426] in mammals and may be an important omission from the commonly understood stress-response in humans.[247] However, although such defence mechanisms in animals may share a common evolutionary basis, T-LOC is unique to humans and thus potentially less adaptive.[173]

A stress response may be decoupled from the original acute stressor i.e. so that a stress response occurs despite no ongoing threat, as occurs in panic disorder[427] or post-traumatic stress disorder.[428] It is thus plausible that a VVS tendency may become habituated in youth in those exposed to childhood trauma, and persist throughout one's lifetime. VVS and psychological responses to childhood trauma may therefore have common neural substrates i.e. childhood trauma may lead to alterations in brain regions with relevance to both VVS and psychological responses. For example, relative to healthy controls, neuroimaging has identified differences in caudate GM volume both in those with recurrent VVS [172] and in those with a history of childhood sexual abuse.[429]

In support of the study hypothesis I also report evidence that there may be an indirect effect of childhood sexual and physical abuse on recurrent late life syncope mediated via depression. Depression has previously been related to syncope in older adults[329] and has repeatedly been shown to have a higher prevalence in those who experienced childhood sexual and physical abuse.[235] Prior studies have pointed to the high burden of psychiatric co-morbidity particularly among those with recurrent unexplained syncope.[244,430] Thus, in common with other studies investigating psychological correlates of syncope[244,409], these results demonstrate that mental health may be an important determinant of elevated syncope risk.

This study found less evidence of mediated relationships via mid-life cardiovascular disease, while there was an independent direct association between childhood physical abuse and late life recurrent syncope. Childhood abuse may increase even mid-life sub-clinical cardiovascular risk[411], therefore it is possible that a reliance on established cardiovascular diagnoses underestimated mediated effects via this pathway. In estimation of the direct effects however, this study did control for both cardiovascular behavioural risk markers (smoking) and conditions that increase cardiometabolic risk (diabetes) via which an effect of childhood trauma could also translate into increased syncope risk in later life. Among older adults presenting with syncope, a cardiac cause is more likely than in younger adults.[413] Even among elders however, the most common aetiology remains neurocardiogenic i.e. VVS or OH[431].

While in this sample childhood physical abuse remained independently associated with recurrent syncope in the last twelve months, childhood sexual abuse did not. The effect sizes

were similar in relation to the effect of childhood sexual and physical abuse across each of the syncope outcomes except in recurrent later life syncope. It is however important to note that the precision of the estimates for later life syncope were lower, in part determined by the lower rate of cases of later life syncope (<8% of lifetime and <36% of youth syncope). I did not find evidence of increased risk of syncope in those exposed to both childhood sexual and physical abuse nor of increased sex specific risk.

In this cohort, it was not possible to definitively delineate the type of syncope experienced, and thus the response may have captured heterogeneous causes of syncope, particularly with regard to those events which occurred within the last twelve months in older adults. It is accepted that the most important element in the diagnosis of VVS is clinical history.[168] The lifetime pattern of events, such as frequent events occurring in youth and recurring in later life, is strongly suggestive of an underlying tendency towards VVS.[243] Furthermore, although TILDA did not capture the age of participant's syncopal events in 'youth', it is reasonable to expect that these are in line with data (which was internationally consistent) suggesting that the peak of syncope onset in 'youth' is at 13 years.[243]

Both childhood sexual and physical abuse and syncope burden were self-reported. The lifetime prevalence of syncope in this cohort is lower than prior reports of up to 40%.[413] Kenny et al [170] suggest that differences in reported syncope prevalence may be explained by varying methods of syncope ascertainment e.g. the use of a single item question rather than detailed syncope interview or case adjudication, and the population under investigation. In the current study potential ambiguity in the terms 'faint' and 'frequent' in the questions on syncope history may have resulted in under-reporting. Given the nature of studies

investigating the outcomes of childhood sexual and physical abuse, the majority are based on self-reported retrospective data.[432] In this study, I was unable to investigate differences in outcomes based on the severity or duration of these stressors. I note however that the prevalence of childhood abuse in this population is in keeping with more detailed investigations in the Irish population, being consistent with the prevalence of the more severe forms of childhood abuse.[233]

This study uses retrospectively recalled data that was collected within a cross-sectional framework in an attempt to delineate life course pathways in older adults, therefore reverse causality cannot be ruled out. Given the temporal ordering of the events however, reverse causality is unlikely. Poor or inaccurate recall of trauma or syncopal events may be of further concern in an ageing cohort in whom a higher prevalence of syncope may be expected, however analysis controlled for a measure of cognitive function; moreover the mean age of this sample was ~63 years. Moreover, given the salient nature of events under investigation (i.e. childhood trauma and syncope) they are perhaps more likely to be recalled with accuracy than other retrospectively collected information. Additionally, sensitivity analyses adjusting for other childhood stressors such as childhood ill-health and poverty did not attenuate the associations described.

Further research is required to investigate the potential links between a history of childhood sexual and physical abuse and syncope, particularly in those who present with a history indicative of an underlying tendency towards VVS. Even decades after the initial exposure, those with a history of childhood sexual and physical abuse may be at greater risk for

recurrent syncope. Early attention should be given to the potential precipitating and perpetuating psychosocial factors affecting syncope.

8. CONCLUSIONS

8.1. Summary of Findings

It is increasingly understood that the ANS is of fundamental importance to optimal regulation of affect and cognitive function.[433] The current thesis reports novel links between BP instability (as underpinned by cardiovascular autonomic function) and brain health in older adults.

Evidence before Study I

Subjective Memory Impairment may be an early risk marker for dementia, potentially representing a preclinical phase when neurodegeneration remains amenable to intervention.[434] Orthostatic hypotension may also be on the pathway to dementia.[288] One prior study had reported a prospective association between OI, but not lower orthostatic BP, and SMI.[278] Orthostatic intolerance, but not orthostatic BP, had also been prospectively associated with white matter progression in the CHS.[304] In neither study however did the associations survive adjustment for confounders. Associations with OI but not with orthostatic BP may have been explained by use of standard orthostatic BP measurement not sensitive to early (i.e. <30seconds) post-stand orthostatic BP change. Study I thus focused on associations between BP instability (peripheral change in orthostatic BP assessed using beat-to-beat measurement) and SMI in older adults.

Contribution of Study I

Lower orthostatic BP as detected early post-stand (i.e. immediately after standing) - even when not meeting criteria for OH - was associated with greater SMI. This association was independent of objective cognition, co-morbidity, depressive symptoms and antihypertensive medication. After accounting for differences in supine BP, associations were stronger with systolic orthostatic BP and persisted only in men. Study I is, to my knowledge, the first report of associations between lower orthostatic BP, as measured using beat-to-beat BP technology, and SMI in a population-based study.

Evidence before Study II

Study II complemented the initial focus on orthostatic BP by investigating cardiac BRS as the independent variable of interest. The baroreflex is the fundamental autonomic reflex involved in regulating the BP response to standing.[435] Impaired BRS had previously been associated with orthostatic BP dysregulation[436], cognitive dysfunction[315], affective symptoms[320], reduced hippocampal perfusion[322] and lower microstructural integrity[310] in older adults. Notably, both SMI and affective symptoms may represent prodromal markers of neurocognitive disorders such as AD.[100,434] Prior studies investigating BRS and affective symptoms however, had focused solely on depressive symptoms[320], despite known overlap between anxiety and depression in later life. Study II thus investigated associations between BRS and symptoms of depression and anxiety in older adults additionally accounting for potential sex differences (as seen in Study I) and potential confounding by ADT.[366]

Contribution of Study II

This thesis reports evidence of an association between lower BRS and greater affective symptoms, however, similar to findings seen in the association between orthostatic BP and SMI, this association was seen only in men. The association between lower BRS and greater affective symptoms was stronger in those on ADT, but remained even in men not on any treatment. In general, associations were in the opposite direction in women. To my knowledge, this is the first study investigating associations between BRS and affective symptoms (i.e. investigating both anxiety and depression) in a population-based cohort of older adults.

Evidence before Study III

Findings from Study I and II in TILDA suggested that lower orthostatic BP and lower BRS (even at sub-clinical levels) may be associated with brain health in older men – as reflected in greater SMI and affective symptoms. To overcome the cross-sectional limitations of the TILDA data available at the time, this thesis thus extended investigation to the longitudinal Health ABC cohort. The Health ABC study had collected four measures of orthostatic BP over 6 years from study entry. After up to 15 years of follow-up, participants underwent MRI brain and CS adjudication as part of the 'The Healthy Brain Project' sub-study. Prior studies investigating longitudinal associations between orthostatic BP and CS had various limitations including measurement of orthostatic BP at a single time point, a focus on consensus OH, and a limited duration of follow-up (as reviewed in Table 3.1), while the

most comprehensive study from the Rotterdam cohort had not investigated MCI nor investigated the potential mediating role of structural brain change.[288]

Contribution of Study III

In line with findings from Study I and II, Study III reported associations between subclinical orthostatic BP change and poorer brain health (poorer CS and greater GM atrophy) 15 years later. This is, to my knowledge, the first investigation to report prospective associations between lower orthostatic BP and reduced regional GM volumes on MRI in a population-based sample. Associations between lower orthostatic BP and greater GM atrophy were seen in regions relevant to cognitive function, affect regulation and autonomic function – including the right hippocampus and dorsolateral prefrontal cortex. Contrary to Study I and II however, there were no differences in findings according to sex, nor were differences apparent according to race (although the sample size may have been underpowered to detect such differences). There was no evidence of associations between lower orthostatic BP and global WMH.

Evidence before Study IV

Studies I-III had shown that greater BP instability was associated with poorer brain health in older adults: poorer subjective cognition and greater affective symptoms in men, and with dementia, MCI and greater GM atrophy when assessed prospectively. The final investigation recognised the importance of the life course to the investigation of ageing outcomes. It acknowledged that cardiovascular autonomic function in older adults is underpinned by

biological processes and environmental/behavioural exposures occurring earlier in life. This may be particularly important in investigation of the ANS, given its role in the stress response. Vasovagal syncope is perhaps the most overt manifestation of autonomic dysfunction and BP instability – syncope has been associated with lower orthostatic BP and BRS[437], greater affective symptoms[338] and poorer cognition.[164] VVS is known to occur in response to stress – be that psychological (e.g. fear) or physiological (e.g. prolonged standing)[323] – and has been associated with psychiatric disorder.[244] Psychological stress is an important determinant of BP regulation, and exposure to stress in adolescence may have lifelong consequences for ANS regulation.[237] VVS may be a lifelong tendency or trait that most often first emerges in adolescence.[242] A number of small clinical studies had reported associations between exposure to childhood trauma and syncope.[254,438] We thus investigated potential pathways from childhood trauma to recurrent syncope in later life.

Contribution of Study IV

This thesis reports associations between childhood trauma (physical and sexual abuse) and recurrent syncope across the life course, and evidence of important life course mediators including mid-life depression. Childhood trauma is independently associated with frequent syncope in youth. Syncope in youth is on the pathway between childhood trauma and later life recurrent syncope. Exposure to childhood trauma may thus contribute to a lifelong vasovagal tendency and therefore potentially to lifelong associations with poorer brain health. There were no differences in the associations according to sex. Study IV adds to the literature linking stress, the ANS and BP regulation, bringing a novel life course perspective to associations with VVS.

Implications of all the available evidence

Taken together, Studies I-IV suggest that greater BP instability, even at subclinical levels, and as underpinned by the cardiovascular ANS, may be on the pathway to poorer brain health in later life. Furthermore, early exposure to stress may be a life course determinant of BP instability – thus further highlighting central regulation / integration of the ANS and peripheral BP responses.

Recognition of an important role for the cardiovascular ANS in regulation of affect and cognitive function in later life potentially provides new therapeutic opportunities. For example, the associations reported herein between BP instability and brain health are apparent at early, potentially preclinical stages of dementia – when effects on brain health may be more likely to be amenable to intervention. In Health ABC, lower orthostatic BP preceded dementia and MCI ascertainment by up to 15 years. Current recommendations for addressing the contributions of BP to brain health in later life focus on hypertension.[33] Results in this thesis suggest however that there are independent associations with BP instability, although associations may differ according to sex and medication status. Measurement of BP instability – even simple ascertainment of seated to standing BP – remains poorly adhered to in clinical practice.[439] This thesis thus underlines the importance of routine measurement of orthostatic vital signs in older adults.

Furthermore, we present a life course approach to reflex syncope; a vasovagal tendency – even among older adults – may have its roots in earlier life, potentially reflecting exposure to severe psychosocial stress. Clinically, this underlines the importance of a comprehensive psychosocial history in all patients presenting with syncope regardless of age[440], and provides further weight to evidence of potential central control of BP regulation.[232]

A major strength of the investigations in this thesis is that they were conducted on large population-based datasets and incorporate cross-sectional, longitudinal and life course analytical strategies. Both cohorts were well-characterised, allowing adjustment for other potential pathways. In particular, Study III is, to my knowledge, the first to have incorporated advanced structural MRI neuroimaging measures when investigating prospective associations between orthostatic BP and CS in a community-dwelling cohort free from dementia and functional limitations at baseline assessment.

Considering some of the Bradford Hill[441] criteria classically used to assess a causative association, this thesis demonstrates a temporal sequence of association between BP instability and cognition across the spectrum of cognitive impairment in older adults, ranging from potential preclinical symptoms (i.e. SMI) in TILDA, to prodromal dementia (i.e. MCI) and dementia in Health ABC. Furthermore, there is consistency of findings across these two populations. A biological gradient is seen in associations between BP instability and cognition in both Health ABC and TILDA. This thesis has additionally outlined biologically plausible mechanisms linking BP instability and poorer brain health, including BP instability as a peripheral consequence of accumulating neuropathology and/or cerebrovascular change as a consequence of cerebral hypoperfusion.

8.2. Limitations

Bias in an epidemiological setting has been defined by Holmes as, 'any systematic error which leads to an inaccurate estimate of the association between an exposure and an outcome'.[442] Limitations to the individual investigations in this thesis are discussed in detail in the chapter relating to each study. Here however, potential sources of bias of greatest relevance across the studies are reviewed: selection bias, information bias and confounding.

According to Holmes, selection bias occurs**,** 'when participants of the study differ from the target population that the investigators are trying to study.'[442] This is of particular relevance to population-based cohorts.

Two of the most common causes of participant-loss in population-based cohort studies are in evidence in this thesis: the TILDA-based studies were vulnerable to initial non-response, while, given the long running nature of the Health ABC study, Study III was vulnerable to attrition bias or bias due to participant drop-out between waves. As noted by Matthews, 'Any hypothesis in longitudinal studies may be affected by attrition and poor response rates.'[443]

Wave 1 of TILDA had a response rate (62%) in line with other large population-based cohorts[444], however, relative to the 2006 Irish census and 2011 Quarterly National Household Survey, the TILDA sample had a lower proportion of participants from socioeconomically disadvantaged backgrounds and from the oldest age groups.[445] Further, there was differential non-response between the different components of the study i.e.

between the CAPI, the SCQ and the Health Assessment, which was likely a function of the varying data-collection methods employed. There was a lower response to the SCQ among disadvantaged participants and those who had reported higher levels of depressive symptoms on the CES-D in the CAPI.[445] Similarly, with respect to the in-clinic health assessment, socioeconomic disadvantage was associated with lower rates of participation, as was increasing distance from the health assessment centre.[445] A TILDA pilot study had demonstrated the risk of systematic underrepresentation of older participants and those with greater levels of co-morbidity in the larger cohort, therefore participants were offered a shortened home health assessment.[262] Measurement of beat-to-beat orthostatic BP and BRS (which were of primary interest to this thesis) however was not feasible outside of the formalised health-centre setting.

In TILDA, to account for differing participation rates in the sample versus the target sample (i.e. the Irish population aged 50+), survey weights were derived. Survey weights can be used to give greater weight in analysis to those in the study sample who have features similar to those with missing data e.g. to those from a lower socioeconomic position (SEP).[445] After careful consideration these weights were not used in this thesis, a decision which reflects ongoing debate with regard to the necessity of a 'representative' sample, particularly when investigating 'biological' associations.[446,447] This issue has been brought to the fore by low response rates to the UK biobank survey.[448] While population representativeness may be necessary to make correct inferences about society, it has been argued this is not necessarily true with respect to causal inferences in biological associations, where accuracy of the data collection (information bias) and controlling for confounders is perhaps of paramount importance.[446]

The baseline Health ABC sample was derived from randomly selected participants within designated 'zip-codes'. In US-based research however, the use of zip-codes in participant selection has been criticised, in particular with regard to recruiting participants representative of varying socioeconomic circumstances given that indices of neighbourhood deprivation are likely to vary widely.[449] However, underrepresentation of the oldest old and African Americans in research[450], and the tendency for greater survival of women to older ages, were prospectively addressed by Health ABC. All participants were aged 70+ at study entry and followed over 15 years, and black participants and men were oversampled. Moreover, with regard to this thesis, the inclusion of the Health ABC cohort helps to address the relatively young mean age (~60 years) and lack of ethnic diversity in the TILDA sample.

Due to its long running nature, drop out due to death, loss to follow-up, or voluntary withdrawal is a potential source of bias in Health ABC – limitations common to all population-based longitudinal cohorts.[451] Indeed drop out due to death is unavoidable in any long running study of the oldest old, however the frequent follow-up assessments as occurred in Health ABC (every two years) may have helped to mitigate the potential impact of reverse causality e.g. terminal decline.[452] Biannual assessments over 15 years however, may have represented a high participant-burden and individuals may have both left and re-entered the study.[452] A 2005 systematic review of the causes of drop-out in long running longitudinal studies of older adults concluded that, other than death, older age and cognitive impairment were the two most likely cause of attrition.[451] Oversampling of those most likely to be lost to follow-up (as in the oversampling of men and black participants in the health ABC study) may thus have reduced bias in estimates of these groups in Study III.[450]

Perhaps the biggest limitation to Study III is that the Healthy Brain Project included only a small sub-sample of the original cohort of Health ABC in whom CS adjudication +/- MRI neuroimaging were available. Survival bias is thus an important caveat i.e. that healthier participants may have been more likely to survive to the end of the study and partake in in-depth assessments including MRI. However, as one of the overarching themes of this thesis was the identification of early points of association between the ANS and brain health, examination of healthier participants is in keeping with this aim and may rather have been expected to bias estimates towards the null.

Information Bias

Exposures

- *Measurement of Orthostatic Blood Pressure*

Adequate training, standardised protocols and monitoring of potential sources of variation – e.g. between sites of data collection – are of particular importance to the internal validity of research conducted in large observational cohorts.[453] In both TILDA and Health ABC, measurement of orthostatic BP was conducted according to standardised protocols. For example in TILDA, orthostatic BP measurement was conducted in a temperature controlled room and peripheral finger measurement of BP using the sphygmomanometer was calibrated to brachial BP.[454,455] Three phases of BP processing were then conducted by TILDA bioengineers to exclude participants with excessive BP artefacts.[184]

It is known that time of day, season and food consumption may each affect BP, however in neither cohort were participants asked to refrain from their usual medication, food or caffeine consumption.[454] In a TILDA pilot study however, Fan[454] demonstrated that although time since food consumption was associated with lower supine SBP, the impact on orthostatic BP was limited – as those with more recent food consumption also had lower SBP throughout the stand.[454] Recent data on the repeatability of continuous orthostatic BP measurements however, suggest they show only low to moderate reliability even within a 4–12-week period.[455] To overcome cross-sectional limitations of the TILDA data available at the time however, this thesis additionally investigated associations between orthostatic BP and brain health in Health ABC. Similar associations were seen using standard measurements of orthostatic BP - which had the advantage of up to four repeated annual measures over six years.

TILDA is the first population-based large scale study to incorporate beat-to-beat orthostatic BP measures and, at the time of the investigations presented here, longitudinal data was not available.[184] Therefore optimal clinical cut-points with respect to associations with important outcomes (e.g. falls, cognitive outcomes) were not (and have yet to be) agreed.[271] Moreover, the application of cut-points, even categorisation of data into quantiles, has long been argued against in epidemiological research, given the loss of information and possible introduction of bias.[456] In line with this, and given our aim to focus on subclinical parameters, this thesis focused on orthostatic BP (and BRS) as continuous phenomena.

Perhaps the most important limitation to the measurement of orthostatic BP is in the Health ABC cohort where a seated-to-stand rather than supine-to-stand BP protocol was utilised.

Moreover, HR response to stand was not measured. Notably the seat-to-stand procedure has been used to induce changes in CBF when assessed using TCD and may be more generalizable to everyday clinical use.[457] Lastly, investigation of delayed orthostatic BP change was not possible in TILDA or Health ABC, as measures of orthostatic BP beyond two minutes were not available in either cohort. A more recent study however has suggested that in line with the findings of this thesis early orthostatic BP changes (1 min or less) are key in predicting poor outcomes.[458]

- *Baroreflex Sensitivity*

In TILDA, BRS was measured using a non-invasive method of assessment – the sequence method – which has the advantage of being applicable at scale. However, the sequence method does not permit assessment of the entire range of function of the baroreflex, which has been demonstrated to exist along a sigmoidal curve with saturation occurring at either end.[311] Moreover, as noted by Barnes the sequence method assesses only the cardiac component of BRS and not necessarily the peripheral sympathetic efferent response, which in turn may change with age and according to sex.[27] Future studies should seek to clarify if sex differences in MSNA may also be implicated in associations between BRS and affective symptoms.

- *Syncope*

Syncope in youth, and within the last year, were both retrospectively reported by participants and are thus subject to recall bias. Based on prior work in clinical settings, those reporting both a history of recurrent syncope in youth and later in life were considered to have evidence of a lifelong vasovagal tendency.[242] In the specialist clinical setting confirmation of vasovagal tendency may require HUT, which is beyond the scope of a large scale population-based cohort. Notably however, both the ESC[168] and the AHA guidelines suggest that VVS[323] can be diagnosed on history alone. Use of a diagnostic risk score (such as brief screening scores validated in clinical settings[459]) to categorise participants in TILDA according to likelihood of cardiac aetiology versus benign aetiology, may have improved accuracy of ascertainment. However investigation of self-reported syncopal events is in line with prior studies.[170,413] With respect to reporting a lifetime frequency of syncope occurrence, participants may have been some decades past the index event, in particular given that VVS is most common in teenage years. Notably however, accounting for a marker of current cognitive ability in the study analysis did not attenuate associations.

- *Childhood adversity*

Study IV additionally relied on retrospective reporting of traumatic events in childhood by participants – namely a history of childhood sexual and physical abuse – and recall bias may again have been of concern. The majority of studies exploring adult life health sequelae of childhood exposure to trauma also use retrospectively reported data. In an examination of the consistency of reporting of traumatic events in the Kaiser Permanente Adverse

Childhood Events ('ACE') cohort, where the mean age (~64years) was similar to the average age of the TILDA cohort, there was moderate to good consistency in reporting of events across waves.[432] However, consistent reporting is not equivalent to accurate reporting, with other studies suggesting both under and over reporting of childhood traumatic events.[460,461]

Prospective studies investigating the adult sequelae of childhood abuse pose difficulties of representativeness (by its very nature childhood abuse is an exposure that is hidden), hence its prevalence may be significantly underestimated in prospective studies of those who have come to the attention of services in childhood.[461] Moreover, the experience of those who have had intervention in childhood is likely to differ systematically from those who report abuse in adult life. While details relating to duration, frequency and severity may be less well remembered, the presence or absence of a history of abuse has been proposed as the most reliable information[462] – as is used in Study IV. McCrory and colleagues also note that within the Irish context the prevalence of severe abuse in contemporaneous Irish-based surveys is similar to the overall prevalence of childhood trauma reported in the TILDA cohort.[235] Finally, a frequently raised concern is the impact of concurrent affective symptoms on reporting of past traumatic events. However, while some studies suggest this may increase retrospective reporting, others have suggested current affective symptoms have no effect.[463] Future studies using information from prospective studies to supplement those using retrospective reporting may be required to better determine the associations with syncope and childhood trauma across the life course.[460]

Outcomes

- *Subjective Memory Impairment*

In line with the HRS this thesis used a single item in the assessment of SMI. At present, SMI is tested in multiple ways across studies, with reviews highlighting many sources of variation and limitations.[101] For example, findings may differ depending on the population investigated e.g. participants attending memory clinics likely differ from those in population-based studies. Moreover there is often little overlap between the assessment scales used in studies, the time period over which impairment or change in subjective function is assessed, or even what is meant by 'normal cognitive testing'.[101] The terminology to define the concept of SMI is also debated; a working group has been established to provide consensus on definitions and research criteria used to define 'subjective cognitive decline', with a focus on improving the consistency of terminology across studies.[101] Despite these limitations, the report of SMI remains one of the few ways in which the earliest stages of dementia may be both readily and inexpensively identified. Subsequent waves of TILDA have additionally asked participants about *change* in SMI – this should be incorporated into future studies to confirm associations with BP instability.

- *Cognitive screening tests vs adjudicated outcomes*

In common with many large-scale population-based studies, objective global cognitive function in TILDA was assessed via use of short cognitive screening tests administered in person including the MMSE and MoCA.[352,464] Both the MMSE and MoCA have been subject to Cochrane Reviews as to their use in community-dwelling populations as screening

tools for dementia. The evidence was deemed insufficient to recommend a cut-point for dementia diagnosis on MoCA.[465] It was suggested that scores on the MMSE may contribute to a dementia diagnosis however it was recommended that it should not be used in isolation in a community based setting.[466] The MoCA was used in sensitivity analyses in Study I however as it may have superior sensitivity to Vascular Cognitive Impairment relative to the MMSE, although in turn it may overestimate cognitive impairment in those with lower educational attainment.[467,468]

Case ascertainment of dementia in population-based studies may involve a screening process e.g. administration of a cognitive screening tool, followed by more detailed examination of those screened positively by a clinical examination / consensus group.[469] For example, in the US-based HRS, use of detailed cognitive testing on a representative subsample was used to estimate CS in participants in the larger sample and subsequently the US population.[470] Alternatively, case ascertainment may involve diagnosis via medical record linkage.[469] In the Healthy Brain Study, a smaller number of participants, the availability of linked medical records, neuroimaging and proxy information allowed adjudication of CS. By contrast, this was not feasible in the TILDA cohort at the time of this investigation. While differing methods of cognitive assessment between the TILDA cohort and Health ABC could be viewed as a limitation in this thesis, findings were consistent across studies i.e. a linear, graded association between subclinical orthostatic BP change and cognition (both subjective and objective CS).

- *Affective symptoms vs standardised clinical interviews*

In common with the majority of epidemiological studies, screening instruments were used in TILDA to assess affective symptoms e.g. the CES-D is used in the HRS family of studies as well as LASA, the CHS and Health ABC. Medical record linkage was not available in TILDA, although it can be used as an adjunct, or as an alternative to, affective symptom assessment within a cohort. Structured diagnostic interviews (e.g. Diagnostic Interview Schedule[471] and Composite International Diagnostic Interview[472]) provide higher specificity in identifying clinical psychiatric disorder but have the disadvantage of being more time consuming (and thus costly) to administer and must be delivered by trained clinical or lay interviewers. Structured diagnostic interviews are more commonly used in investigations where there is a greater emphasis on categorical psychiatric outcomes e.g. the Epidemiological Catchment Area[471] studies and National Comorbidity Surveys[69,473] in the US, and LASA[474] in Europe. However, the investigation of affective symptoms rather than disorder is in keeping with the continuum approach favoured throughout this thesis. The findings in Study II investigating affective symptoms as continuous outcomes add weight to the view that within the population affective symptoms occur across a spectrum of severity.[62]

Investigation of affective symptoms, and symptom overlap, as in Study II is also in line with the National Institute of Mental Health Research Domain Criteria (RDoC) which have advocated for a move away from categorical diagnoses in research.[65] Perhaps similarly to the revised criteria for AD, where a continuum approach is emphasised, the RDoC seeks to promote investigation of psychiatric symptoms across traditional diagnostic boundaries and

across diagnostic categories e.g. cognitive dysfunction as a trans-diagnostic feature of psychiatric disorder.[65]

- *Neuroimaging*

One of the central limitations to Study III investigating neuroimaging outcomes pertains to the small sample size limiting the power to investigate potential sex and ethnic differences in associations. Further, the timing of neuroimaging concurrent with dementia adjudication only, rather than also contemporaneous to the orthostatic BP measures, limits inferences with respect to the direction of associations.

Region of interest analysis was used to select the GM regions investigated rather than a 'data-driven' voxel-wise analysis.[475] Data driven analysis may be less subject to predetermined hypotheses with respect to the function of brain regions and investigator bias.[475] In addition, the systematic review from which GM regions of interest were chosen was primarily based on functional studies[217] – structure may not equate to function. Furthermore, studies included in meta-analysis were based on small samples of functional neuroimaging most likely among young adults[217], such findings may not translate to older adults in whom imaging was performed in the 9th decade. Finally, more advanced parameters of white matter integrity such as microstructural integrity of white matter tracts as provided by Diffusion Tensor Imaging[14] may have helped to better elucidate associations with BP instability, particularly at early stages of disease.

At the time of the investigations in TILDA no neuroimaging was available, thus many of the hypothesised mediating factors between BP instability and brain health as discussed in Section 1.2 (i.e. cerebral hypoperfusion, impaired cerebral autoregulation, brain structural and functional change, border zone ischaemia and amyloid deposition), could not be investigated. Future studies should include more detailed measures of brain structure and function such as those which have been collected in TILDA Wave 3. Studies investigating change in neuroimaging may be important e.g. in the CHS study OI was associated with WMH *progression* but did not survive adjustment.[304]

Potential Confounders

'.. the main road to general statements on nature is through studies that control skilfully for confounding variables and thereby advance our understanding of causal mechanisms.' (Rothman, 2013) [446]

- *Socioeconomic position*

'It is the same cause that wears out our bodies and our clothes'. Bertolt Brecht[476]

Socioeconomic position is a known determinant of health outcomes.[476] Prior studies in TILDA have suggested that there may be an SEP gradient in autonomic function, and there are well described associations between SEP and cognition and affect in later life.[477,478] In both TILDA and Health ABC education level was used throughout to adjust for SEP. In the US, black race may additionally reflect a greater level of socioeconomic disadvantage and disparity in access to health services[479], therefore in Study IV both education and race were adjusted for in all analyses. Moreover, educational attainment was also considered during CS adjudication. Other indicators of SEP include income, occupation and health insurance cover. All participants in the Health ABC were recruited from Medicare lists within selected zip-codes and were eligible for 'Medicare' or free care in light of their age.[480]

Use of other indictors of SEP in TILDA had limitations. For example, missing data was high on questions relating to income[477], perhaps due to the reluctance of the participants to disclose sensitive information. Moreover, other commonly used indicators of SEP – such as occupation – may be less easily applied within the Irish context, as the income and socioeconomic status associated with an occupation such as farming in Ireland will be dependent on the associated acreage and location.[481] Childhood SEP may be an important indicator of childhood disadvantage and life course outcomes in Study IV, however once again fathers' occupation poses a similar difficulty as ~25% of the TILDA sample reported that they were from a farming background.[481] In the TILDA-based studies there may be residual confounding given that adjustment was made only for a single measure of SEP. Overall however, less advantaged participants were less likely to participate in the health assessment and the loss of less advantaged participants from analyses, among whom health status may also have been poorer, may have biased the associations reported herein towards the null.

- *Medications*

In the investigations presented in this thesis one of the most important potential confounding variables is medication use. Accordingly, medication use was adjusted for in all analyses. Ascertainment of medication use in TILDA participants was conducted during the CAPI interviews when participants were interviewed in their own homes and interviewers reviewed the packaging of all the medications which the participants reported they were taking on a regular basis.[60] This allowed the interviewers to accurately record the medication names which were then assigned the appropriate WHO ATC codes. In TILDA however,

Richardson et al[482] have validated the information collected during CAPI assessments against pharmacy records. The study concluded that there was 'good' or even 'very good' agreement for the majority of medication classes – including antidepressant medications and antihypertensives. Of particular importance to the conclusions of this thesis, neither sex, cognition nor affective symptoms affected agreement between the CAPI and pharmacy records.[482] Notably however, only those participants who were in receipt of free medication via government insurance ('a medical card') were included in the validation study. Overall agreement between the self-reporting and pharmacy records in TILDA with respect to cardiovascular medications was similar to that reported in the Rotterdam study. This is important as one of the most comprehensive investigations into the association between orthostatic BP and CS was based in the Rotterdam cohort.[288] Notably however, neither the duration of treatment, timing of administration, nor dosage were recorded. Similarly in Health ABC, participants were asked to bring medications taken in the past 2 weeks with them to their clinic assessment and these were recorded and coded according to the Iowa Drug Information System.[483] To account for potential change in medication burden between waves, these were coded as time-varying variables to account for variation in treatment across waves in Study III.

- *Co-morbid disease*

The associations herein may also have been subject to confounding by co-morbid disease. While these were adjusted for in all analyses e.g. for hypertension and diabetes, the accuracy with which these were ascertained potentially differed between cohorts. In TILDA, all co-morbidities were based on self-reported 'doctor diagnosed disease' i.e. participants were

asked to report diseases or disorders of which they had previously received a diagnosis from a doctor.[60] In the Health ABC study, some co-morbid disorders were centrally adjudicated i.e. a self-reported diagnosis or hospitalisation for a disorder was confirmed by health records, discharge summaries and medications and agreed on by a centrally validated protocol.[484] Due to the lack of medical record linkage this was not possible in the TILDA cohort. Despite differing levels of objective verification of reports of co-morbidity, similar findings were identified in both cohorts.

- *Analytic strategies*

The primary limitation to the investigations based in TILDA is the cross-sectional nature of the data, thus limiting interpretation of causality in associations. In Study III (Health ABC / Healthy Brain Project), causality cannot be inferred simply by the temporal ordering of the assessments i.e. that orthostatic BP was measured prior to CS and neuroimaging. Similarly, in Study IV this thesis applied a life course framework within a cross-sectional study; even here, temporal ordering (i.e. an event in youth cannot be caused by an event in later life) does not prove causality.

Causal inference is however classically limited in epidemiological analyses, thus modern epidemiological techniques such as Mendelian Randomisation (MR) may prove useful in future analyses seeking to identify causality.[442] MR is an instrumental variable approach based on genetic associations and as such has been referred to as 'nature's randomised controlled trials'.[442] An instrumental variable is one related to the outcome only through the exposure. Increasingly, genetic associations are emerging for ANS: including VVS[242],

orthostatic BP[485] and HRV[486]; thus MR may be a method which could potentially be utilised in future studies investigating associations between BP instability and brain health.

In Study I and III, conditional change in orthostatic BP was investigated i.e. change in orthostatic BP dependent on the baseline measure. Classically this may pose a statistical challenge whereby investigating absolute 'change' versus the relative change (i.e. taking into account the baseline measure) may result in varying associations (Lord's paradox).[487] It is of note however that in both Study I and III associations were in the same direction and of a similar magnitude (although statistical significance varied) when investigating absolute change or conditional change. In both studies, conditional change indices were reported in primary analyses given known associations between hypertension and the degree of BP change on standing.

In Study I, the associations between orthostatic BP and SMI were investigated using separate linear regressions, although as noted in the investigation only overall patterns and consistent associations across time-points were interpreted. An analytic method such as multilevel modelling may have more appropriately accounted for the non-independent nature of the measures across time points.

8.3. Future Directions

Clarifying the role of anti-hypertensives in determining associations between blood pressure instability and brain health in older adults

- *The Systolic Blood Pressure Intervention Trial*

Observational studies have consistently suggested that lower and decreasing BP in later life is associated with poor outcomes – including greater mortality.[488] As reviewed, much of the work suggesting that BP instability in later life may be associated with poor brain health, in addition to the findings of this thesis, is observational.[288] Such observational evidence is therefore challenged by the SPRINT Randomised Control Trial, published during the work of this thesis, which has demonstrated a positive effect of intensive BP lowering in older adults.[489]

- *What was the SPRINT trial?*

The US-based multi-centre randomised controlled trial investigated the impact of standard versus intensive treatment of SBP in 9261 participants at increased cardiovascular risk (i.e. ≥15% Framingham risk score) but free from diabetes with an SBP of >= 130mmHg.[489] The primary outcome was a composite of fatal and non-fatal major cardiovascular events (i.e. myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes). Exclusion criteria for entry onto the study included dementia, nursing home residents, eGFR <20ml/min, heart failure (ejection fraction <35%), a history of stroke, diabetes or 'non-adherence' risk. The intensive treatment target SBP was

120mmHg versus the standard treatment target of 140mmHg. The trial was stopped prematurely after a median of 3.26 years due to significant reductions in the primary outcome and the risk of all cause-mortality in those treated to the intensive SBP target relative to those treated to 140 mmHg.[489]

- *Older Adults and SPRINT*

Despite the exclusion criteria (which clearly meant that many patients within the day-to-day remit of a clinician working with older adults were not included) the SPRINT trial did include 2636 (28%) participants aged 75+.[490] Efforts were also made by the investigators to establish baseline frailty status using the deficit accumulation model (Rockwood's Frailty Index (FI)) and gait speed.[489,491] Approximately one third of participants aged 75+ would have been considered *'frail'* according to the FI or using a gait speed < 0.8 m/s. The benefits of treatment to <120mmHg extended to those in the older group – irrespective of frailty status.[489,491] In the older group those treated to the intensive target had a 34% lower risk of the primary outcome (*Number Needed To Treat (NNT)= 27*) and a 33% lower risk (*NNT=41*) of all-cause mortality.[490]

- *Blood Pressure Instability in SPRINT*

Importantly however, among those aged 75+ rates of syncope and hypotension were more common in the intensive treatment group at rates of 3.0% and 2.4% respectively versus 2.4% and 1.4% in the standard target group; with similar rates described in the larger trial.[490] There were no differences between groups in rates of injurious falls. At study entry orthostatic BP was measured using a seated-to-stand protocol with SBP measured upon standing at one minute; *standing SBP <110mmHg was an exclusion criteria – which notably included 9.4%*

of those older adults screened for eligibility.[400] Additionally, orthostatic BP was measured throughout trial follow-up (median of 3.4 years) at visits 1, 6 and 12 months and thereafter at yearly intervals.[489] Rates of OH were similar in both groups at study end in those aged 75+, but overall were significantly lower in the intensively treated group.[492]

- *TILDA vs SPRINT*

A recent investigation compared the TILDA population with the SPRINT population in terms of adverse outcomes i.e. injurious falls and syncope.[493] The authors identified 407 participants in the TILDA cohort who at baseline assessment were >=75 years and would have met criteria for entry to the SPRINT trial.[493] After a similar duration of follow-up to the SPRINT trial, during which the TILDA participants were undergoing standard community-based hypertension treatment, rates of injurious falls and syncope were ~5 times higher than those recorded in the SPRINT trial i.e. 111 (27.3%) reported an injurious fall and 54 (13.3%) reported syncope in TILDA; in SPRINT the respective numbers were 73/1319 (5.5%) and 32/1319 (2.4%). The TILDA group suggests that these findings raise concerns with respect to intensive BP lowering among older adults – in particular with respect to the external validity of SPRINT and thus its application to a real world setting.[493] It is of note however that in TILDA these outcomes were self-reported, whereas in SPRINT injurious falls were recorded via ED attendance – suggesting that only the most serious events were captured in the SPRINT data.[494]

- *SPRINT & Cognition – 'SPRINT MIND Sub-Study'*

A planned sub-study of the SPRINT RCT is ongoing; this incorporates neuroimaging (including PET amyloid imaging) and detailed neuropsychological testing with the aim to

clarify the effect of systolic BP lowering on cognitive outcomes in older adults.[52] In common with TILDA, the MoCA was used to assess global cognitive function in SPRINT, and the median score among older adults was similar to the population mean for those aged 75+ in TILDA, with less than tertiary level education.[495,496]

Prior work has suggested that the beneficial effects of antihypertensive treatment on cognitive function may be restricted to particular classes e.g. beta-blockers, calcium channel blockers and ACE-inhibitors.[52] As the SPRINT study is open-label, it may be underpowered to adequately assess anti-hypertensive class effects on brain health. Measures of affective symptoms have been included in the SPRINT trial, however results with a focus on 'quality of life' measurement (which included a screener for affective symptoms) suggested no difference between groups.[497]

As noted by Supiano[495] and Lipsitz[498], clinicians have historically been cautious with respect to lowering BP in the older adults with hypertension – in particular among frail older patients. Concerns have commonly included the risk of adverse consequences including OH and falls – potentially as a result of cerebral hypoperfusion.[498] Indeed in the setting of OH, antihypertensive treatment may be withdrawn.[492] Lipsitz has previously noted a small literature (now bolstered by the SPRINT trial) which suggests that treatment of hypertension may, perhaps counterintuitively, reduce OH and improve cerebral autoregulation and CBF.[498] For example, in a 2005 clinical study Lipsitz and colleagues followed three groups of patients aged 65+ years: 19 patients were normotensive, 18 were patients with treated hypertension (SBP<140mmHg) and 14 were patients with poorly controlled BP (i.e. SBP>160 mmHg).[499] At baseline, blood flow velocity in the middle cerebral artery and

distensibility of the carotid artery were measured; these measures were repeated after 6 months of treatment to a BP target <140 mmHg in the uncontrolled group only – the other patients groups were observed. At repeat, in those now treated to <140mmHg, there were improvements in CBF and carotid artery distensibility – an effect not seen in the groups who were simply observed.[499] These findings underscore the importance of future studies to better phenotype BP behaviour which may help clinicians understand how to better tailor antihypertensive treatment for older adults; thereby incorporating the heterogeneity of ageing into personalised treatment approaches.

If BP instability is a consequence of hypertension, then treating hypertension may help to reduce its prevalence. For example, if BP is under central control, treating hypertension may limit further damage to central vascular control centres of the brain. Any beneficial effects of lower BP targets on BP instability may however depend on the degree of BP instability (e.g. asymptomatic OH vs recurrent syncope) which may in turn vary according to the cumulative duration of exposure to hypertension and co-morbidity. Despite standing hypotension representing an exclusion criteria at study entry, higher rates of syncope and hypotension were nevertheless seen in the intensive target group.[489] It is possible that those who experienced increased syncope and hypotension may have had greater baseline impairments in BP homeostasis (potentially reflected in lower BRS) – thus more work is required to prospectively identify those patients in whom intensive BP treatment may also benefit BP instability. As reviewed in Chapter 1, *mid-life* hypertension is a risk marker for later-life brain health, thus treatment in mid-life (or earlier) with anti-hypertensives / lifestyle interventions may be required to prevent deleterious effects of prolonged exposure to hypertension.[52] Managing mid-life hypertension, and *life course* vascular risk, may additionally reduce any late-life tendency towards BP instability.

Clarifying the role of Anti-depressant Medication in associations between Blood Pressure Instability and Brain Health in Older Adults

Observational evidence has suggested that there are both benefits and potential risks for brain health associated with ADT in older adults.[500] Further work is required to delineate the impact of ADT on cardio-vagal BRS/BP instability and on brain health in older adults, and whether effects differ by sex. Notably, the Sertraline Against Depression and Heart Disease ('SADHART') trial found that SSRI's are safe and effective in the treatment of major depression in patients with coronary heart disease – there was no change in R-R variability on 24-hour recording.[501] An analysis of the Three City Study suggested that the highest risk of mortality was among older depressed men on ADT, however the authors concluded that it was depression, rather than ADT, which was driving the association with mortality.[502] Such findings are therefore in line with the associations described between BRS, ADT and affective symptoms herein.

Nonetheless, concern has been expressed regarding the increasing prescription of ADT among older adults – in particular for subthreshold affective symptoms.[86] Therefore increasing the availability, and evidence base, for psychosocial interventions in older adults with subthreshold symptoms (importantly considering both depression and anxiety) may help to mitigate concerns regarding autonomic side effects of ADT. For example, the ENhancing Recovery in Coronary Heart Disease (ENRICHD) trial showed that cognitive-behavioural therapy was effective for treating depression in patients with coronary heart disease – however similarly to the results seen with sertraline, there was no impact on cardiovascular morbidity or mortality.[503]

Overall, further work is required to clarify if autonomic dysfunction is associated with affective symptoms in older adults, and the direction of causality across the life course. Carney has suggested that there may be different sub-types of depression in which autonomic function / cardiovascular function is affected[504] – this thesis further suggests that there may be differences according to sex in older adults. It is possible that effective treatment of affective symptoms – be that pharmacological or psychological - across the life course may be important in maintaining brain health into later life.

Longitudinal follow-up and Neuroimaging in the TILDA sample

Longitudinal follow-up of the TILDA cohort will help to clarify if the sex differences identified in associations between BP instability and brain health herein persist; notably these differences were seen only in Study I and II - both of which were cross-sectional. Sex-differences were not seen in Study III and IV in which longitudinal / life-course perspectives were investigated. However, if these results were to be replicated it is possible that sex-specific treatment approaches to maintain brain health into later life may be required.

Since the completion and publication of the findings in Study III, increasing numbers of cohort studies have reported links between orthostatic BP and later dementia / cognitive imapriment.[505–507] Although at the time of writing, the investigation herein remains the only population-based study to incorporate neuroimaging into the prospective investigation of associations between orthostatic BP and CS in older adults, and only one other study based in a middle aged sample has incorporated repeated measures of orthostatic BP.[507]

Longitudinal follow-up of the TILDA sample, which has since incorporated both structural and functional neuroimaging (including advanced measures of cortical microstructure and CBF) will help to clarify the role of BP instability in determining brain health in older adults. Future studies additionally incorporating amyloid imaging will also be useful in assessing the relationship between BP instability and amyloid neuropathology – although studies with repeat measures over time will be required to better understand any bidirectional associations.

Study III is one of the first studies to apply insights from continuous measures of orthostatic BP to standard clinical assessment. At present, use of continuous orthostatic BP measures remains confined to research and specialist settings. To increase applicability of the findings herein, greater consensus is required with respect to the interpretation of continuous orthostatic BP measures – and how any prognostic insights may usefully be applied to traditional measures.

'Big Data' & 'Disruptive technologies'

According to Rajtmajer, 'The human brain has ~80 billion neurons each with between 100 and 1000 synaptic connections, making the task of modelling brain functioning the ultimate big data problem'.[475] Data science has been described, 'as the extraction of knowledge from high-volume datasets by use of computing science and statistics'.[508]

Continuous measurement of orthostatic BP generates large quantities of data – which in this thesis were summarised into 10-second bins in line with prior studies in TILDA.[184] In future, studies which utilize the beat-to-beat nature of this data may help to better delineate and individualise associations with brain health outcomes. Investigators should seek to integrate 'multimodal' MRI data (i.e. parameters from different imaging sequences) to assess associations between BP instability and brain health. Imaging may be more informative if investigated concurrently – so called 'data fusion'.[475] Techniques to synthesise the 'big data' available both in continuous autonomic measurements (orthostatic BP, BRS, HRV) and MRI neuroimaging in TILDA, in particular when incorporating repeat time points, may pose a computational challenge, yet provide opportunities to better understand the fine-grained, and potentially individual / sub-group-specific, associations between BP instability and brain health.

This thesis has focused on BP instability as a marker of loss of adaptation to quotidian stressors e.g. standing; but also as a potential reflection of cortical adaptions to stress e.g. VVS secondary to trauma exposure potentially mediated by altered BRS. Such loss of adaptive variability is characteristic of impaired autonomic function[148] – and perhaps

characterises ageing itself. Indeed according to Lopez-Otin[509], 'Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death.' Interestingly, Gorelick[221] has most recently described a state of optimal brain health as the 'capacity to function adaptively in the environment' with intact, measurable, 'competencies across the domains of "thinking, moving, and feeling"'. Researchers should aim to capitalise on the detailed haemodynamic measures and brain imaging captured in cohorts such as TILDA, to intricately track how physiological systems change and interact, in ageing and across the life course. In a 1992 paper, Lipsitz[510] described ageing as a '*process of complexity loss'* across physiological systems and suggested that loss of complexity in haemodynamic indices is mirrored, for example, by changes in higher cortical function. Lipsitz further highlighted the potential of the application of advanced data analysis (e.g. chaos theory, fractal dynamics) to track physiological measures as they change with age. Over twenty five years later, increasing technological capability e.g. mobile physiological and behavioural data capture, multimodal MRI, machine learning techniques, may now allow us better harness this data to track changes in complexity at the individual level. Tracking trajectories of change may permit better understanding of how peripheral haemodynamics drive changes in central processes with age – or vice versa – and may allow identification of the earliest points of loss of adaptability allowing quantification of individual risk for poor outcomes, thus highlighting the very earliest points of potential intervention.

Understanding how autonomic function underpins optimal cognitive and affective regulation in older adults, and indeed how this process tracks from earlier in life, may ultimately help to better identify the type and timing of appropriate intervention. Thus allowing older adults

to maintain better brain health, and thus, crucially, independence and better quality of life – for longer.

9. BIBLIOGRAPHY

1. Coca A, Sierra C. Beyond Subjective Cognitive Failures in Patients With Hypertension? *Hypertension*. 2014;64(3):455-456. doi:10.1161/HYPERTENSIONAHA.114.03730

2. Petersen RB, Lissemore FM, Appleby B, et al. From Neurodegeneration to Brain Health: An Integrated Approach. *J Alzheimers Dis JAD*. 2015;46(1):271-283. doi:10.3233/JAD-150043

3. Sacco RL. Evolution from Stroke Risk Factors to Brain Health Determinants. *Cerebrovasc Dis Basel Switz*. 2015;40(3-4):102-113. doi:10.1159/000437285

4. Gardener H, Wright CB, Rundek T, Sacco RL. Brain health and shared risk factors for dementia and stroke. *Nat Rev Neurol*. 2015;11(11):651-657. doi:10.1038/nrneurol.2015.195

5. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838. doi:10.1016/S1474-4422(13)70124-8

6. Ritchie SJ, Tucker-Drob EM, Cox SR, et al. Risk and protective factors for structural brain ageing in the eighth decade of life. *Brain Struct Funct*. 2017;222(8):3477-3490. doi:10.1007/s00429-017-1414-2

7. Ritchie SJ, Dickie DA, Cox SR, et al. Brain volumetric changes and cognitive ageing during the eighth decade of life. *Hum Brain Mapp*. 2015;36(12):4910-4925. doi:10.1002/hbm.22959

8. Vernooij MW, de Groot M, Bos D. Population imaging in neuroepidemiology. *Handb Clin Neurol*. 2016;138:69-90. doi:10.1016/B978-0-12-802973-2.00005-7

9. Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol*. 2015;11(3):157-165. doi:10.1038/nrneurol.2015.10

10. Gudmundsson P, Olesen PJ, Simoni M, et al. White matter lesions and temporal lobe atrophy related to incidence of both dementia and major depression in 70-year-olds followed over 10 years. *Eur J Neurol*. 2015;22(5):781-788, e49-50. doi:10.1111/ene.12651

11. Chao LL, DeCarli C, Kriger S, et al. Associations between White Matter Hyperintensities and β Amyloid on Integrity of Projection, Association, and Limbic Fiber Tracts Measured with Diffusion Tensor MRI. *PLOS ONE*. 2013;8(6):e65175. doi:10.1371/journal.pone.0065175

12. Scott JA, Braskie MN, Tosun D, et al. Cerebral amyloid is associated with greater white-matter hyperintensity accrual in cognitively normal older adults. *Neurobiol Aging*. 2016;48:48-52. doi:10.1016/j.neurobiolaging.2016.08.014

13. Oh H, Villeneuve S, Madison C, Vogel J, Jagust W. Association of gray matter atrophy with age, beta-amyloid, white matter hyperintensity and cognition in normal aging. *Alzheimers Dement J Alzheimers Assoc*. 2013;9(4):P701-P702. doi:10.1016/j.jalz.2013.04.387

14. Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *J Am Heart Assoc*. 2015;4(6):001140. doi:10.1161/JAHA.114.001140

15. Fanning JP, Wesley AJ, Wong AA, Fraser JF. Emerging Spectra of Silent Brain Infarction. *Stroke*. January 2014:STROKEAHA.114.005919. doi:10.1161/STROKEAHA.114.005919

16. Longstreth WT, Manolio TA, Arnold A, et al. Clinical Correlates of White Matter Findings on Cranial Magnetic Resonance Imaging of 3301 Elderly People The Cardiovascular Health Study. *Stroke*. 1996;27(8):1274-1282. doi:10.1161/01.STR.27.8.1274

17. Fatemi F, Kantarci K, Graff-Radford J, et al. Sex differences in cerebrovascular pathologies on FLAIR in cognitively unimpaired elderly. *Neurology*. January 2018. doi:10.1212/WNL.0000000000004913

18. Jorgensen DR, Shaaban CE, Wiley CA, Gianaros PJ, Mettenburg J, Rosano C. A population neuroscience approach to the study of cerebral small vessel disease in mid- and late-life: an Invited Review. *Am J Physiol Heart Circ Physiol*. February 2018. doi:10.1152/ajpheart.00535.2017

19. Tudorascu DL, Karim HT, Maronge JM, et al. Reproducibility and Bias in Healthy Brain Segmentation: Comparison of Two Popular Neuroimaging Platforms. *Front Neurosci*. 2016;10:503. doi:10.3389/fnins.2016.00503

20. Lockhart SN, DeCarli C. Structural imaging measures of brain aging. *Neuropsychol Rev*. 2014;24(3):271-289. doi:10.1007/s11065-014-9268-3

21. DeCarli C, Massaro J, Harvey D, et al. Measures of brain morphology and infarction in the framingham heart study: establishing what is normal. *Neurobiol Aging*. 2005;26(4):491-510. doi:10.1016/j.neurobiolaging.2004.05.004

22. Jack CR, Wiste HJ, Weigand SD, et al. Age, Sex, and APOE ε4 Effects on Memory, Brain Structure, and β-Amyloid Across the Adult Life Span. *JAMA Neurol*. 2015;72(5):511-519. doi:10.1001/jamaneurol.2014.4821

23. Hajjar I, Quach L, Yang F, et al. Hypertension, White Matter Hyperintensities, and Concurrent Impairments in Mobility, Cognition, and MoodClinical Perspective: The Cardiovascular Health Study. *Circulation*. 2011;123(8):858-865. doi:10.1161/CIRCULATIONAHA.110.978114

24. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *The Lancet*. 2016;388(10060):2665-2712. doi:10.1016/S0140-6736(16)31134-5

25. Wills AK, Lawlor DA, Matthews FE, et al. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. *PLoS Med*. 2011;8(6):e1000440. doi:10.1371/journal.pmed.1000440

26. Hardy R, Lawlor DA, Kuh D. A life course approach to cardiovascular aging. *Future Cardiol*. 2015;11(1):101-113. doi:10.2217/fca.14.67

27. Barnes JN, Matzek LJ, Charkoudian N, Joyner MJ, Curry TB, Hart EC. Association of cardiac baroreflex sensitivity with blood pressure transients: influence of sex and menopausal status. *Front Physiol*. 2012;3:187. doi:10.3389/fphys.2012.00187

28. Pinto E. Blood pressure and ageing. *Postgrad Med J*. 2007;83(976):109-114. doi:10.1136/pgmj.2006.048371

29. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. *Nat Rev Cardiol*. 2010;7(12):686–698.

30. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4(8):487–499.

31. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia—A double edged sword. *Ageing Res Rev*. 2009;8(2):61-70. doi:10.1016/j.arr.2008.11.001

32. McAleese KE, Alafuzoff I, Charidimou A, et al. Post-mortem assessment in vascular dementia: advances and aspirations. *BMC Med*. 2016;14(1). doi:10.1186/s12916-016-0676-5

33. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;42(9):2672-2713. doi:10.1161/STR.0b013e3182299496

34. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005

35. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *N Engl J Med*. 2012;367(9):795-804. doi:10.1056/NEJMoa1202753

36. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord*. 2014;28(3):206-218. doi:10.1097/WAD.0000000000000034

37. Sharp SI, Aarsland D, Day S, Sønnesyn H, Alzheimer's Society Vascular Dementia Systematic Review Group, Ballard C. Hypertension is a potential risk factor for vascular dementia: systematic review. *Int J Geriatr Psychiatry*. 2011;26(7):661-669. doi:10.1002/gps.2572

38. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The Association Between Blood Pressure and Incident Alzheimer Disease: A Systematic

Review and Meta-analysis. *Epidemiology*. 2011;22(5):646-659. doi:10.1097/EDE.0b013e31822708b5

39. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging*. 2000;21(1):49-55.

40. Gelber RP, Launer LJ, White LR. The Honolulu-Asia Aging Study: Epidemiologic and Neuropathologic Research on Cognitive Impairment. *Curr Alzheimer Res*. 2012;9(6):664-672.

41. Petrovitch H, White LR, Izmirilian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. *Neurobiol Aging*. 2000;21(1):57-62.

42. Korf ESC, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. *Hypertens Dallas Tex 1979*. 2004;44(1):29-34. doi:10.1161/01.HYP.0000132475.32317.bb

43. Gottesman RF, Schneider ALC, Albert M, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol*. 2014;71(10):1218-1227. doi:10.1001/jamaneurol.2014.1646

44. Gottesman RF, Schneider ALC, Zhou Y, et al. Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. *JAMA*. 2017;317(14):1443-1450. doi:10.1001/jama.2017.3090

45. Power MC, Schneider ALC, Wruck L, et al. Life-course blood pressure in relation to brain volumes. *Alzheimers Dement J Alzheimers Assoc*. 2016;12(8):890-899. doi:10.1016/j.jalz.2016.03.012

46. Power MC, Tingle JV, Reid RI, et al. Midlife and Late-Life Vascular Risk Factors and White Matter Microstructural Integrity: The Atherosclerosis Risk in Communities Neurocognitive Study. *J Am Heart Assoc*. 2017;6(5). doi:10.1161/JAHA.117.005608

47. Muller M, Sigurdsson S, Kjartansson O, et al. Joint effect of mid- and late-life blood pressure on the brain: the AGES-Reykjavik study. *Neurology*. 2014;82(24):2187-2195. doi:10.1212/WNL.0000000000000517

48. Skoog I. Highs and lows of blood pressure: a cause of Alzheimer's disease? *Lancet Neurol*. 2003;2(6):334.

49. Guo Z, Fratiglioni L, Winblad B, Viitanen M. Blood pressure and performance on the Mini-Mental State Examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project. *Am J Epidemiol*. 1997;145(12):1106-1113.

50. Corrada MM, Hayden KM, Paganini-Hill A, et al. Age of onset of hypertension and risk of dementia in the oldest-old: The 90+ Study. *Alzheimers Dement J Alzheimers Assoc*. 2017;13(2):103-110. doi:10.1016/j.jalz.2016.09.007

51. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2009. doi:10.1002/14651858.CD004034.pub3

52. Walker KA, Power MC, Gottesman RF. Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review. *Curr Hypertens Rep*. 2017;19(3):24. doi:10.1007/s11906-017-0724-3

53. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7(8):683–689.

54. Hajjar I, Rodgers K. Do angiotensin receptor blockers prevent Alzheimer's disease?: *Curr Opin Cardiol*. 2013;28(4):417-425. doi:10.1097/HCO.0b013e3283620745

55. Watfa G, Rossignol P, Kearney-Schwartz A, et al. Use of calcium channel blockers is associated with better cognitive performance in older hypertensive patients with subjective memory complaints. *J Hypertens*. 2010;28(12):2485-2493. doi:10.1097/HJH.0b013e32833e4108

56. Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: Methodological issues and a review of the literature. *J Affect Disord*. 2008;109(3):233-250. doi:10.1016/j.jad.2007.11.008

57. Grayson L, Thomas A. A systematic review comparing clinical features in early age at onset and late age at onset late-life depression. *J Affect Disord*. 2013;150(2):161-170. doi:10.1016/j.jad.2013.03.021

58. Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML. High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2010;67(5):489-496. doi:10.1001/archgenpsychiatry.2010.35

59. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. *J Gerontol A Biol Sci Med Sci*. 2017;72(3):343-352. doi:10.1093/gerona/glw241

60. Barrett A, Savva G, Timonen V, Kenny RA. Fifty plus in Ireland 2011. *First Results Ir Longitud Study Ageing TILDA Dublin Ir Longitud Study Ageing*. 2011.

61. Sutin AR, Terracciano A, Milaneschi Y, An Y, Ferrucci L, Zonderman AB. The trajectory of depressive symptoms across the adult life span. *JAMA Psychiatry*. 2013;70(8):803-811. doi:10.1001/jamapsychiatry.2013.193

62. Meeks TW, Vahia IV, Lavretsky H, Kulkarni G, Jeste DV. A tune in "a minor" can "b major": A review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *J Affect Disord*. 2011;129(1-3):126-142. doi:10.1016/j.jad.2010.09.015

63. Penninx BWJH, Geerlings SW, Deeg DJH, van Eijk JTM, van Tilburg W, Beekman ATF. Minor and Major Depression and the Risk of Death in Older Persons. *Arch Gen Psychiatry*. 1999;56(10):889. doi:10.1001/archpsyc.56.10.889

64. Hybels CF, Blazer DG, Pieper CF. Toward a Threshold for Subthreshold DepressionAn Analysis of Correlates of Depression by Severity of Symptoms Using Data From an Elderly Community Sample. *The Gerontologist*. 2001;41(3):357-365. doi:10.1093/geront/41.3.357

65. Cuthbert BN, Insel TR. Toward new approaches to psychotic disorders: the NIMH Research Domain Criteria project. *Schizophr Bull*. 2010;36(6):1061-1062. doi:10.1093/schbul/sbq108

66. Gale CR, Sayer AA, Cooper C, et al. Factors associated with symptoms of anxiety and depression in five cohorts of community-based older people: the HALCyon (Healthy Ageing across the Life Course) Programme. *Psychol Med*. 2011;41(10):2057-2073. doi:10.1017/S0033291711000195

67. Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. *Psychiatr Clin North Am*. 2002;25(4):685-698.

68. Andreescu C, Tudorascu D, Sheu LK, et al. Brain structural changes in late-life generalized anxiety disorder. *Psychiatry Res*. 2017;268:15-21. doi:10.1016/j.pscychresns.2017.08.004

69. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602.

70. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. "Vascular depression" hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915-922.

71. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report – a critical update. *BMC Med*. 2016;14(1). doi:10.1186/s12916-016-0720-5

72. Valkanova V, Ebmeier KP. Vascular risk factors and depression in later life: a systematic review and meta-analysis. *Biol Psychiatry*. 2013;73(5):406-413. doi:10.1016/j.biopsych.2012.10.028

73. Mast BT, Miles T, Penninx BW, et al. Vascular Disease and Future Risk of Depressive Symptomatology in Older Adults: Findings from the Health, Aging, and Body Composition Study. *Biol Psychiatry*. 2008;64(4):320-326. doi:10.1016/j.biopsych.2008.01.025

74. Mehta KM, Simonsick EM, Penninx BW, et al. Prevalence and Correlates of Anxiety Symptoms in Well-Functioning Older Adults: Findings from the Health Aging and Body Composition Study. *J Am Geriatr Soc*. 2003;51(4):499–504.

75. Maatouk I, Herzog W, Böhlen F, et al. Association of hypertension with depression and generalized anxiety symptoms in a large population-based sample of older adults. *J Hypertens*. 2016;34(9):1711-1720. doi:10.1097/HJH.0000000000001006

76. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963-974. doi:10.1038/mp.2013.20

77. Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. *J Neurol Neurosurg Psychiatry*. 2008;79(6):619-624. doi:10.1136/jnnp.2007.124651

78. Allan CL, Sexton CE, Filippini N, et al. Sub-threshold depressive symptoms and brain structure: A magnetic resonance imaging study within the Whitehall II cohort. *J Affect Disord*. 2016;204:219-225. doi:10.1016/j.jad.2016.06.049

79. Sexton CE, Mackay CE, Ebmeier KP. A Systematic Review and Meta-Analysis of Magnetic Resonance Imaging Studies in Late-Life Depression. *Am J Geriatr Psychiatry*. 2013;21(2):184-195. doi:10.1016/j.jagp.2012.10.019

80. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22(7):613-626. doi:10.1002/gps.1723

81. Batelaan NM, Seldenrijk A, Bot M, van Balkom AJLM, Penninx BWJH. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. *Br J Psychiatry J Ment Sci*. 2016;208(3):223-231. doi:10.1192/bjp.bp.114.156554

82. Nabi H, Chastang J-F, Lefèvre T, et al. Trajectories of Depressive Episodes and Hypertension Over 24 Years: The Whitehall II Prospective Cohort Study. *Hypertension*. 2011;57(4):710-716. doi:10.1161/HYPERTENSIONAHA.110.164061

83. Hildrum B, Romild U, Holmen J. Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway. *BMC Public Health*. 2011;11(1):601.

84. Briggs R, Kenny RA, Kennelly SP. Systematic Review: The Association between Late Life Depression and Hypotension. *J Am Med Dir Assoc*. 2016;17(12):1076-1088. doi:10.1016/j.jamda.2016.06.027

85. Briggs R, Kenny RA, Kennelly SP. Does baseline hypotension predict incident depression in a cohort of community-dwelling older people? Data from The Irish Longitudinal Study on Ageing (TILDA). *Age Ageing*. 2017;46(4):648-653. doi:10.1093/ageing/afx033

86. Mojtabai R. Diagnosing depression in older adults in primary care. *N Engl J Med*. 2014;370(13):1180-1182. doi:10.1056/NEJMp1311047

87. Licht CMM, de Geus EJC, Seldenrijk A, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. *Hypertens Dallas Tex 1979*. 2009;53(4):631-638. doi:10.1161/HYPERTENSIONAHA.108.126698

88. Noordam R, van den Berg ME, Niemeijer MN, et al. Antidepressants and heart-rate variability in older adults: a population-based study. *Psychol Med*. 2016;46(6):1239-1247. doi:10.1017/S0033291715002779

89. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet Lond Engl*. 2010;375(9718):938-948. doi:10.1016/S0140-6736(10)60309-1

90. Nagai M, Hoshide S, Dote K, Kario K. Visit-to-visit blood pressure variability and dementia. *Geriatr Gerontol Int*. 2015;15 Suppl 1:26-33. doi:10.1111/ggi.12660

91. Alpérovitch A, Blachier M, Soumaré A, et al. Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. *Alzheimers Dement J Alzheimers Assoc*. 2014;10(5 Suppl):S330-337. doi:10.1016/j.jalz.2013.05.1777

92. Tully PJ, Tzourio C. Psychiatric correlates of blood pressure variability in the elderly: The Three City cohort study. *Physiol Behav*. 2017;168:91-97. doi:10.1016/j.physbeh.2016.10.024

93. Kayano H, Koba S, Matsui T, et al. Impact of depression on masked hypertension and variability in home blood pressure in treated hypertensive patients. *Hypertens Res Off J Jpn Soc Hypertens*. 2015;38(11):751-757. doi:10.1038/hr.2015.75

94. Kabutoya T, Kario K. Depression in hypertension and blood pressure variability over shorter time periods. *Hypertens Res Off J Jpn Soc Hypertens*. 2015;38(11):713-715. doi:10.1038/hr.2015.92

95. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry J Ment Sci*. 2013;202(5):329-335. doi:10.1192/bjp.bp.112.118307

96. Gulpers B, Ramakers I, Hamel R, Köhler S, Oude Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry*. 2016;24(10):823-842. doi:10.1016/j.jagp.2016.05.015

97. Bijanki KR, Stillman AN, Arndt S, et al. White matter fractional anisotropy is inversely related to anxious symptoms in older adults with atherosclerosis: FA inversely related to anxiety in atherosclerosis. *Int J Geriatr Psychiatry*. 2013;28(10):1069-1076. doi:10.1002/gps.3930

98. Karim H, Tudorascu DL, Aizenstein H, Walker S, Good R, Andreescu C. Emotion Reactivity and Cerebrovascular Burden in Late-Life GAD: A Neuroimaging Study. *Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry*. 2016;24(11):1040-1050. doi:10.1016/j.jagp.2016.07.015

99. Pietrzak RH, Scott JC, Neumeister A, et al. Anxiety symptoms, cerebral amyloid burden and memory decline in healthy older adults without dementia: 3-year prospective cohort study. *Br J Psychiatry J Ment Sci*. 2014;204:400-401. doi:10.1192/bjp.bp.113.134239

100. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. *JAMA Psychiatry*. 2017;74(7):712-718. doi:10.1001/jamapsychiatry.2017.0660

101. Rabin LA, Smart CM, Crane PK, et al. Subjective Cognitive Decline in Older Adults: An Overview of Self-Report Measures Used Across 19 International Research Studies. *J Alzheimers Dis JAD*. 2015;48(0 1):S63-S86. doi:10.3233/JAD-150154

102. Stewart R. Subjective cognitive impairment: *Curr Opin Psychiatry*. 2012;25(6):445-450. doi:10.1097/YCO.0b013e3283586fd8

103. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement*. doi:10.1016/j.jalz.2014.01.001

104. Knopman DS. Subjective cognitive impairment Fickle but fateful. *Neurology*. 2012;79(13):1308-1309. doi:10.1212/WNL.0b013e31826c1bd1

105. Paradise MB, Glozier NS, Naismith SL, Davenport TA, Hickie IB. Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: a cross-sectional study. *BMC Psychiatry*. 2011;11:108. doi:10.1186/1471-244X-11-108

106. Stewart R. Cerebral white matter lesions and subjective cognitive dysfunction: the Rotterdam Scan Study. *Neurology*. 2001;57(11):2149.

107. Peter J, Scheef L, Abdulkadir A, et al. Gray matter atrophy pattern in elderly with subjective memory impairment. *Alzheimers Dement J Alzheimers Assoc*. 2014;10(1):99-108. doi:10.1016/j.jalz.2013.05.1764

108. Snitz BE, Weissfeld LA, Cohen AD, et al. Subjective Cognitive Complaints, Personality and Brain Amyloid-beta in Cognitively Normal Older Adults. *Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry*. 2015;23(9):985-993. doi:10.1016/j.jagp.2015.01.008

109. Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr Scand*. 2014;130(6):439-451. doi:10.1111/acps.12336

110. Iliffe S, Pealing L. Subjective Memory Problems. *BMJ*. 2010;340(mar19 1):c1425-c1425. doi:10.1136/bmj.c1425

111. Breteler MMB, van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology*. 1994;44(7):1246-1252.

112. Uiterwijk R, Huijts M, Staals J, et al. Subjective Cognitive Failures in Patients With Hypertension Are Related to Cognitive Performance and Cerebral MicrobleedsNovelty and Significance. *Hypertension*. 2014;64(3):653-657. doi:10.1161/HYPERTENSIONAHA.114.03621

113. van Norden AGW, van Uden IWM, de Laat KF, et al. Cerebral microbleeds are related to subjective cognitive failures: the RUN DMC study. *Neurobiol Aging*. 2013;34(9):2225-2230. doi:10.1016/j.neurobiolaging.2013.03.021

114. Langballe EM, Tambs K, Saltvedt I, Midthjell K, Holmen J. The association between vascular factors and subjective memory impairment in older people: The HUNT Study, Norway. *Nor Epidemiol*. 2012;22(2). http://www.ntnu.no/ojs/index.php/norepid/article/view/1568. Accessed July 19, 2014.

115. Holmen J, Langballe EM, Midthjell K, et al. Gender differences in subjective memory impairment in a general population: the HUNT study, Norway. *BMC Psychol*. 2013;1(1):19.

116. Scuteri A, Tesauro M, Guglini L, Lauro D, Fini M, Di Daniele N. Aortic stiffness and hypotension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss. *Int J Cardiol*. 2013;169(5):371-377. doi:10.1016/j.ijcard.2013.09.009

117. Sajjad A, Mirza SS, Portegies MLP, et al. Subjective Memory Complaints and the Risk of. *Stroke*. 2015;46(1):170-175. doi:10.1161/STROKEAHA.114.006616

118. Mazure CM, Swendsen J. Sex differences in Alzheimer's disease and other dementias. *Lancet Neurol*. 2016;15(5):451-452. doi:10.1016/S1474-4422(16)00067-3

119. Gibson CL. Cerebral ischemic stroke: is gender important? *J Cereb Blood Flow Metab*. 2013;33(9):1355-1361. doi:10.1038/jcbfm.2013.102

120. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol*. 2007;6(12):1106-1114. doi:10.1016/S1474-4422(07)70291-0

121. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol*. 2014;6:37-48. doi:10.2147/CLEP.S37929

122. Ruigrok ANV, Salimi-Khorshidi G, Lai M-C, et al. A meta-analysis of sex differences in human brain structure. *Neurosci Biobehav Rev*. 2014;39:34-50. doi:10.1016/j.neubiorev.2013.12.004

123. Richards M, Barnett JH, Xu MK, et al. Lifetime affect and midlife cognitive function: prospective birth cohort study. *Br J Psychiatry*. 2014;204(3):194-199. doi:10.1192/bjp.bp.113.128942

124. Weber MT, Rubin LH, Maki PM. Cognition in perimenopause: the effect of transition stage. *Menopause N Y N*. 2013;20(5):511-517. doi:10.1097/gme.0b013e31827655e5

125. Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: a systematic review and meta-analysis. *J Steroid Biochem Mol Biol*. 2014;142:90-98. doi:10.1016/j.jsbmb.2013.06.001

126. Miller VM, Garovic VD, Kantarci K, et al. Sex-specific risk of cardiovascular disease and cognitive decline: pregnancy and menopause. *Biol Sex Differ*. 2013;4(1):6.

127. Hoekzema E, Barba-Müller E, Pozzobon C, et al. Pregnancy leads to long-lasting changes in human brain structure. *Nat Neurosci*. 2017;20(2):287-296. doi:10.1038/nn.4458

128. Mielke MM, Milic NM, Weissgerber TL, et al. Impaired Cognition and Brain Atrophy Decades After Hypertensive Pregnancy Disorders. *Circ Cardiovasc Qual Outcomes*. 2016;9(2 Suppl 1):S70-76. doi:10.1161/CIRCOUTCOMES.115.002461

129. Fields JA, Garovic VD, Mielke MM, et al. Preeclampsia and cognitive impairment later in life. *Am J Obstet Gynecol*. 2017;217(1):74.e1-74.e11. doi:10.1016/j.ajog.2017.03.008

130. Postma IR, Bouma A, de Groot JC, Aukes AM, Aarnoudse JG, Zeeman GG. Cerebral white matter lesions, subjective cognitive failures, and objective neurocognitive functioning: A follow-up study in women after hypertensive disorders of pregnancy. *J Clin Exp Neuropsychol*. 2016;38(5):585-598. doi:10.1080/13803395.2016.1143453

131. Vaccarino V, Badimon L, Corti R, et al. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology. *Cardiovasc Res*. 2011;90(1):9-17. doi:10.1093/cvr/cvq394

132. Vaccarino V, Badimon L, Corti R, et al. Presentation, management, and outcomes of ischaemic heart disease in women. *Nat Rev Cardiol*. 2013;10(9):508-518. doi:10.1038/nrcardio.2013.93

133. Hart EC, Joyner MJ, Wallin BG, Charkoudian N. Sex, ageing and resting blood pressure: gaining insights from the integrated balance of neural and haemodynamic factors. *J Physiol*. 2012;590(9):2069-2079. doi:10.1113/jphysiol.2011.224642

134. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen treatment, and cognitive aging: clinical evidence for a window of opportunity. *Brain Res*. 2011;1379:188-198. doi:10.1016/j.brainres.2010.10.031

135. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008;7(10):915-926. doi:10.1016/S1474-4422(08)70193-5

136. Gilsanz P, Mayeda ER, Glymour MM, et al. Female sex, early-onset hypertension, and risk of dementia. *Neurology*. 2017;89(18):1886-1893. doi:10.1212/WNL.0000000000004602

137. Davis D, Bendayan R, Muniz Terrera G, Hardy R, Richards M, Kuh D. Decline in Search Speed and Verbal Memory Over 26 Years of Midlife in a British Birth Cohort. *Neuroepidemiology*. 2017;49(3-4):121-128. doi:10.1159/000481136

138. Laws KR, Irvine K, Gale TM. Sex differences in cognitive impairment in Alzheimer's disease. *World J Psychiatry*. 2016;6(1):54-65. doi:10.5498/wjp.v6.i1.54

139. Sundermann EE, Biegon A, Rubin LH, Lipton RB, Landau S, Maki PM. Does the Female Advantage in Verbal Memory Contribute to Underestimating Alzheimer's Disease Pathology in Women versus Men? *J Alzheimers Dis*. 2017;56(3):947-957. doi:10.3233/JAD-160716

140. Tomita T, Sugawara N, Kaneda A, et al. Sex-specific effects of subjective memory complaints with respect to cognitive impairment or depressive symptoms. *Psychiatry Clin Neurosci*. 2014;68(3):176-181.

141. Sundermann EE, Edmonds EC, Delano-Wood L, et al. Sex Influences the Accuracy of Subjective Memory Complaint Reporting in Older Adults. *J Alzheimers Dis JAD*. 2018;61(3):1163-1178. doi:10.3233/JAD-170425

142. Roberts RO, Geda YE, Knopman DS, et al. The incidence of MCI differs by subtype and is higher in men: The Mayo Clinic Study of Aging. *Neurology*. 2012;78(5):342-351. doi:10.1212/WNL.0b013e3182452862

143. Geda YE. Mild Cognitive Impairment in Older Adults. *Curr Psychiatry Rep*. 2012;14(4):320-327. doi:10.1007/s11920-012-0291-x

144. Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM. Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Dement Transl Res Clin Interv*. 2015;1(2):103-110. doi:10.1016/j.trci.2015.07.001

145. Snyder HM, Asthana S, Bain L, et al. Sex biology contributions to vulnerability to Alzheimer's disease: A think tank convened by the Women's Alzheimer's Research Initiative. *Alzheimers Dement J Alzheimers Assoc*. 2016;12(11):1186-1196. doi:10.1016/j.jalz.2016.08.004

146. Guyenet PG. The sympathetic control of blood pressure. *Nat Rev Neurosci*. 2006;7(5):335-346. doi:10.1038/nrn1902

147. Thomas GD. Neural control of the circulation. *Adv Physiol Educ*. 2011;35(1):28-32. doi:10.1152/advan.00114.2010

148. Captur G, Karperien AL, Hughes AD, Francis DP, Moon JC. The fractal heart - embracing mathematics in the cardiology clinic. *Nat Rev Cardiol*. 2017;14(1):56-64. doi:10.1038/nrcardio.2016.161

149. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol*. 2007;74(2):224-242. doi:10.1016/j.biopsycho.2005.11.013

150. Hall JE, Granger JP, do Carmo JM, et al. Hypertension: physiology and pathophysiology. *Compr Physiol*. 2012;2(4):2393-2442. doi:10.1002/cphy.c110058

151. Meel-van den Abeelen ASS, Lagro J, Gommer ED, Reulen JPH, Claassen JAHR. Baroreflex function is reduced in Alzheimer's disease: a candidate biomarker? *Neurobiol Aging*. 2013;34(4):1170-1176. doi:10.1016/j.neurobiolaging.2012.10.010

152. Benarroch EE. The arterial baroreflex: functional organization and involvement in neurologic disease. *Neurology*. 2008;71(21):1733-1738. doi:10.1212/01.wnl.0000335246.93495.92

153. Wehrwein EA, Joyner MJ. Regulation of blood pressure by the arterial baroreflex and autonomic nervous system. *Handb Clin Neurol*. 2013;117:89-102. doi:10.1016/B978-0-444-53491-0.00008-0

154. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med*. 2008;358(6):615-624. doi:10.1056/NEJMcp074189

155. Kimmerly DS. A review of human neuroimaging investigations involved with central autonomic regulation of baroreflex-mediated cardiovascular control. *Auton Neurosci*. May 2017. doi:10.1016/j.autneu.2017.05.008

156. Gupta V, Lipsitz LA. Orthostatic Hypotension in the Elderly: Diagnosis and Treatment. *Am J Med*. 2007;120(10):841-847. doi:10.1016/j.amjmed.2007.02.023

157. Taylor CE, Willie CK, Ainslie PN, Tzeng Y-C. Assessment of human baroreflex function using carotid ultrasonography: what have we learnt? *Acta Physiol*. 2014;211(2):297–313.

158. Ferrari AU, Radaelli A, Centola M. Invited Review: Aging and the cardiovascular system. *J Appl Physiol*. 2003;95(6):2591-2597. doi:10.1152/japplphysiol.00601.2003

159. Arnold AC, Gallagher PE, Diz DI. Brain renin–angiotensin system in the nexus of hypertension and aging. *Hypertens Res*. 2013;36(1):5-13. doi:10.1038/hr.2012.161

160. Monahan KD. Effect of aging on baroreflex function in humans. *Am J Physiol Regul Integr Comp Physiol*. 2007;293(1):R3-R12. doi:10.1152/ajpregu.00031.2007

161. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res*. 2011;21(2):69-72. doi:10.1007/s10286-011-0119-5

162. Harris T, Lipsitz LA, Kleinman JC, Cornoni-Huntley J. Postural change in blood pressure associated with age and systolic blood pressure. The National Health and Nutrition Examination Survey II. *J Gerontol*. 1991;46(5):M159-163.

163. Lipsitz LA. Orthostatic Hypotension and Falls. *J Am Geriatr Soc*. 2017;65(3):470-471. doi:10.1111/jgs.14745

164. Frewen J, Finucane C, Savva GM, Boyle G, Kenny RA. Orthostatic Hypotension Is Associated With Lower Cognitive Performance in Adults Aged 50 Plus With Supine Hypertension. *J Gerontol A Biol Sci Med Sci*. November 2013. doi:10.1093/gerona/glt171

165. Ricci F, De Caterina R, Fedorowski A. Orthostatic Hypotension: Epidemiology, Prognosis, and Treatment. *J Am Coll Cardiol*. 2015;66(7):848-860. doi:10.1016/j.jacc.2015.06.1084

166. Nardo CJ, Chambless LE, Light KC, et al. Descriptive Epidemiology of Blood Pressure Response to Change in Body Position The ARIC Study. *Hypertension*. 1999;33(5):1123-1129. doi:10.1161/01.HYP.33.5.1123

167. Arnold AC, Raj SR. Orthostatic Hypotension: A Practical Approach to Investigation and Management. *Can J Cardiol*. 2017;33(12):1725-1728. doi:10.1016/j.cjca.2017.05.007

168. Developed in collaboration with, European Heart Rhythm Association (EHRA), Heart Failure Association (HFA), et al. Guidelines for the diagnosis and management of syncope (version 2009): The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). *Eur Heart J*. 2009;30(21):2631-2671. doi:10.1093/eurheartj/ehp298

169. Lipsitz LA. What's Different About Syncope in the Aged? *Am J Geriatr Cardiol*. 1993;2(6):37-41.

170. Kenny RA, Bhangu J, King-Kallimanis BL. Epidemiology of Syncope/Collapse in Younger and Older Western Patient Populations. *Prog Cardiovasc Dis*. 2013;55(4):357-363. doi:10.1016/j.pcad.2012.11.006

171. Sheldon RS, Grubb BP, Olshansky B, et al. 2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope. *Heart Rhythm*. 2015;12(6):e41-e63. doi:10.1016/j.hrthm.2015.03.029

172. Beacher FDCC, Gray MA, Mathias CJ, Critchley HD. Vulnerability to simple faints is predicted by regional differences in brain anatomy. *NeuroImage*. 2009;47(3):937-945. doi:10.1016/j.neuroimage.2009.05.038

173. Alboni P, Alboni M. Origin and Evolution of the Vasovagal Reflex. In: Alboni P, Furlan R, eds. *Vasovagal Syncope*. Springer International Publishing; 2015:3-17. http://link.springer.com.myaccess.library.utoronto.ca/chapter/10.1007/978-3-319-09102-0_1. Accessed June 30, 2015.

174. Mosqueda-Garcia R. Pathophysiology of Vasovagal Syncope: Role of Baroreceptor Mechanisms. In: Alboni P, Furlan R, eds. *Vasovagal Syncope*. Springer International Publishing; 2015:67-74. http://link.springer.com.myaccess.library.utoronto.ca/chapter/10.1007/978-3-319-09102-0_6. Accessed June 30, 2015.

175. Iacoviello M, Forleo C, Guida P, et al. Independent role of reduced arterial baroreflex sensitivity during head-up tilt testing in predicting vasovagal syncope recurrence. *EP Eur*. 2010;12(8):1149-1155. doi:10.1093/europace/euq149

176. Iacoviello M, Guida P, Forleo C, Sorrentino S, D'Alonzo L, Favale S. Impaired arterial baroreflex function before nitrate-induced vasovagal syncope during head-up tilt test. *EP Eur*. 2008;10(10):1170-1175. doi:10.1093/europace/eun217

177. Pitzalis M, Parati G, Massari F, et al. Enhanced reflex response to baroreceptor deactivation in subjects with tilt-Induced syncope. *J Am Coll Cardiol*. 2003;41(7):1167-1173. doi:10.1016/S0735-1097(03)00050-0

178. Tan MP, Parry SW. Vasovagal syncope in the older patient. *J Am Coll Cardiol*. 2008;51(6):599-606. doi:10.1016/j.jacc.2007.11.025

179. Mosqueda-Garcia R. Role of the Autonomic Nervous System in Vasovagal Syncope. In: Alboni P, Furlan R, eds. *Vasovagal Syncope*. Springer International Publishing; 2015:53-65. http://link.springer.com.myaccess.library.utoronto.ca/chapter/10.1007/978-3-319-09102-0_5. Accessed June 30, 2015.

180. Skoog J, Zachrisson H, Länne T, Lindenberger M. Reduced compensatory responses to maintain central blood volume during hypovolemic stress in women with vasovagal syncope. *Am J Physiol - Regul Integr Comp Physiol*. 2017;312(1):R55-R61. doi:10.1152/ajpregu.00166.2016

181. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: A meta-analysis. *Neurosci Biobehav Rev*. 2016;64:288-310. doi:10.1016/j.neubiorev.2016.03.007

182. Romero-Ortuno R, Cogan L, Foran T, Fan CW, Kenny RA. Using the Finometer to examine sex differences in hemodynamic responses to orthostasis in older people: *Blood Press Monit*. 2010;15(1):8-17. doi:10.1097/MBP.0b013e3283353199

183. Barnett SR, Morin RJ, Kiely DK, et al. Effects of age and gender on autonomic control of blood pressure dynamics. *Hypertens Dallas Tex 1979*. 1999;33(5):1195-1200.

184. Finucane C, O'Connell MDL, Fan CW, et al. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). *Circulation*. 2014;130(20):1780-1789. doi:10.1161/CIRCULATIONAHA.114.009831

185. Deegan BM, Sorond FA, Galica A, Lipsitz LA, O'Laighin G, Serrador JM. Elderly Women Regulate Brain Blood Flow Better Than Men Do. *Stroke*. 2011;42(7):1988-1993. doi:10.1161/STROKEAHA.110.605618

186. Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nat Rev Neurosci*. 2017;18(7):419-434. doi:10.1038/nrn.2017.48

187. Purves D, Augustine GJ, Fitzpatrick D, et al. The Blood Supply of the Brain and Spinal Cord. 2001. https://www.ncbi.nlm.nih.gov/books/NBK11042/. Accessed August 25, 2017.

188. Ainslie PN, Tzeng YC. On the regulation of the blood supply to the brain: old age concepts and new age ideas. *J Appl Physiol Bethesda Md 1985*. 2010;108(6):1447-1449. doi:10.1152/japplphysiol.00257.2010

189. Tzeng Y-C, Ainslie PN. Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. *Eur J Appl Physiol*. June 2013. doi:10.1007/s00421-013-2667-y

190. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev*. 1959;39(2):183-238. doi:10.1152/physrev.1959.39.2.183

191. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis a review. *Stroke*. 1997;28(3):652–659.

192. Willie CK, Tzeng Y-C, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. *J Physiol*. 2014. http://onlinelibrary.wiley.com/doi/10.1113/jphysiol.2013.268953/abstract. Accessed June 11, 2014.

193. Gao Y, Zhang M, Han Q, et al. Cerebral autoregulation in response to posture change in elderly subjects-assessment by wavelet phase coherence analysis of cerebral tissue oxyhemoglobin concentrations and arterial blood pressure signals. *Behav Brain Res*. 2015;278:330-336. doi:10.1016/j.bbr.2014.10.019

194. Indelicato E, Fanciulli A, Poewe W, Antonini A, Pontieri FE, Wenning GK. Cerebral autoregulation and white matter lesions in Parkinson's disease and multiple system atrophy. *Parkinsonism Relat Disord*. 2015;21(12):1393-1397. doi:10.1016/j.parkreldis.2015.10.018

195. Brickman AM, Guzman VA, Gonzalez-Castellon M, et al. Cerebral autoregulation, beta amyloid, and white matter hyperintensities are interrelated. *Neurosci Lett*. 2015;592:54-58. doi:10.1016/j.neulet.2015.03.005

196. Van Beek AH, Claassen JA, Rikkert MGO, Jansen RW. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *J Cereb Blood Flow Metab*. 2008;28(6):1071–1085.

197. Mangla R, Kolar B, Almast J, Ekholm SE. Border Zone Infarcts: Pathophysiologic and Imaging Characteristics. *RadioGraphics*. 2011;31(5):1201-1214. doi:10.1148/rg.315105014

198. Förster A, Szabo K, Hennerici MG. Pathophysiological concepts of stroke in hemodynamic risk zones--do hypoperfusion and embolism interact? *Nat Clin Pract Neurol*. 2008;4(4):216-225. doi:10.1038/ncpneuro0752

199. Ryan DJ, Kenny RA, Christensen S, Meaney JFM, Fagan AJ, Harbison J. Ischaemic stroke or TIA in older subjects associated with impaired dynamic blood pressure control in the absence of severe large artery stenosis. *Age Ageing*. February 2015:afv011. doi:10.1093/ageing/afv011

200. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9(7):689-701. doi:10.1016/S1474-4422(10)70104-6

201. Love S, Miners JS. White matter hypoperfusion and damage in dementia: post-mortem assessment. *Brain Pathol Zurich Switz*. 2015;25(1):99-107. doi:10.1111/bpa.12223

202. Binnewijzend MAA, Benedictus MR, Kuijer JPA, et al. Cerebral perfusion in the predementia stages of Alzheimer's disease. *Eur Radiol*. 2016;26(2):506-514. doi:10.1007/s00330-015-3834-9

203. Wolters FJ, Zonneveld HI, Hofman A, et al. Cerebral Perfusion and the Risk of Dementia: A Population-Based Study. *Circulation*. June 2017:CIRCULATIONAHA.117.027448. doi:10.1161/CIRCULATIONAHA.117.027448

204. Zonneveld HI, Loehrer EA, Hofman A, et al. The bidirectional association between reduced cerebral blood flow and brain atrophy in the general population. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab*. 2015;35(11):1882-1887. doi:10.1038/jcbfm.2015.157

205. Centi J, Freeman R, Gibbons CH, Neargarder S, Canova AO, Cronin-Golomb A. Effects of orthostatic hypotension on cognition in Parkinson disease. *Neurology*. 2017;88(1):17-24. doi:10.1212/WNL.0000000000003452

206. Direk N, Koudstaal PJ, Hofman A, Ikram MA, Hoogendijk WJ, Tiemeier H. Cerebral Hemodynamics and Incident Depression: The Rotterdam Study. *Biol Psychiatry*. 2012;72(4):318-323. doi:10.1016/j.biopsych.2012.01.019

207. Tiemeier H, Bakker S, Hofman A, Koudstaal P, Breteler M. Cerebral haemodynamics and depression in the elderly. *J Neurol Neurosurg Psychiatry*. 2002;73(1):34. doi:10.1136/jnnp.73.1.34

208. Bakker SLM, Leeuw F-E de, Heijer T den, Koudstaal PJ, Hofman A, Breteler MMB. Cerebral Haemodynamics in the Elderly: The Rotterdam Study. *Neuroepidemiology*. 2004;23(4):178-184. doi:10.1159/000078503

209. Dotson VM, Beason-Held L, Kraut MA, Resnick SM. Longitudinal study of chronic depressive symptoms and regional cerebral blood flow in older men and women. *Int J Geriatr Psychiatry*. 2009;24(8):809-819. doi:10.1002/gps.2298

210. Colloby SJ, Firbank MJ, He J, et al. Regional cerebral blood flow in late-life depression: arterial spin labelling magnetic resonance study. *Br J Psychiatry J Ment Sci*. 2012;200(2):150-155. doi:10.1192/bjp.bp.111.092387

211. Grade M, Hernandez Tamames JA, Pizzini FB, Achten E, Golay X, Smits M. A neuroradiologist's guide to arterial spin labeling MRI in clinical practice. *Neuroradiology*. 2015;57:1181-1202. doi:10.1007/s00234-015-1571-z

212. Abi Zeid Daou M, Boyd BD, Donahue MJ, Albert K, Taylor WD. Frontocingulate cerebral blood flow and cerebrovascular reactivity associated with antidepressant response in late-life depression. *J Affect Disord*. 2017;215:103-110. doi:10.1016/j.jad.2017.03.027

213. Karim HT, Tudorascu DL, Butters MA, Walker S, Aizenstein HJ, Andreescu C. In the grip of worry: cerebral blood flow changes during worry induction and reappraisal in late-life generalized anxiety disorder. *Transl Psychiatry*. 2017;7(8):e1204. doi:10.1038/tp.2017.180

214. Andreescu C, Gross JJ, Lenze E, et al. Altered cerebral blood flow patterns associated with pathologic worry in the elderly. *Depress Anxiety*. 2011;28(3):202-209. doi:10.1002/da.20799

215. Palma J-A, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. *Neurology*. 2014;83(3):261-271. doi:10.1212/WNL.0000000000000605

216. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin Proc*. 1993;68(10):988-1001.

217. Beissner F, Meissner K, Bär K-J, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J Neurosci Off J Soc Neurosci*. 2013;33(25):10503-10511. doi:10.1523/JNEUROSCI.1103-13.2013

218. Royall DR, Gao J-H, Kellogg DL. Insular Alzheimer's disease pathology as a cause of "age-related" autonomic dysfunction and mortality in the non-demented elderly. *Med Hypotheses*. 2006;67(4):747-758. doi:10.1016/j.mehy.2005.10.036

219. Nieuwenhuys R. The insular cortex: a review. *Prog Brain Res*. 2012;195:123-163. doi:10.1016/B978-0-444-53860-4.00007-6

220. Udow SJ, Robertson AD, MacIntosh BJ, et al. "Under pressure": is there a link between orthostatic hypotension and cognitive impairment in α-synucleinopathies? *J Neurol Neurosurg Psychiatry*. 2016;87(12):1311-1321. doi:10.1136/jnnp-2016-314123

221. Gorelick PB, Furie KL, Iadecola C, et al. Defining Optimal Brain Health in Adults: A Presidential Advisory From the American Heart Association/American Stroke Association. *Stroke*. 2017;48(10):e284-e303. doi:10.1161/STR.0000000000000148

222. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health*. 2003;57(10):778-783. doi:10.1136/jech.57.10.778

223. Jennings JR, Zanstra Y. Is the brain the essential in hypertension? *NeuroImage*. 2009;47(3):914-921. doi:10.1016/j.neuroimage.2009.04.072

224. Berens AE, Jensen SKG, Nelson CA. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. *BMC Med*. 2017;15. doi:10.1186/s12916-017-0895-4

225. Power C, Kuh D, Morton S. From Developmental Origins of Adult Disease to Life Course Research on Adult Disease and Aging: Insights from Birth Cohort Studies. *Annu Rev Public Health*. 2013;34(1):7-28. doi:10.1146/annurev-publhealth-031912-114423

226. McEwen BS, Gianaros PJ. Stress- and allostasis-induced brain plasticity. *Annu Rev Med*. 2011;62:431-445. doi:10.1146/annurev-med-052209-100430

227. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol Behav*. 2012;106(1):29-39. doi:10.1016/j.physbeh.2011.08.019

228. EL-SHEIKH M, ERATH SA. Family conflict, autonomic nervous system functioning, and child adaptation: State of the science and future directions. *Dev Psychopathol*. 2011;23(2):703-721. doi:10.1017/S0954579411000034

229. Oldehinkel AJ, Verhulst FC, Ormel J. Low heart rate: a marker of stress resilience. The TRAILS study. *Biol Psychiatry*. 2008;63(12):1141-1146. doi:10.1016/j.biopsych.2007.12.006

230. Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. *Hypertens Dallas Tex 1979*. 2010;55(4):1026-1032. doi:10.1161/HYPERTENSIONAHA.109.146621

231. Lovallo WR. Cardiovascular Responses to Stress and Disease Outcomes: A Test of the Reactivity Hypothesis. *Hypertension*. 2010;55(4):842-843. doi:10.1161/HYPERTENSIONAHA.110.149773

232. Gianaros PJ, Onyewuenyi IC, Sheu LK, Christie IC, Critchley HD. Brain Systems for Baroreflex Suppression During Stress in Humans. *Hum Brain Mapp*. 2012;33(7):1700-1716. doi:10.1002/hbm.21315

233. McGee H, Garavan R, Barra M de, Byrne J, Conroy R. The SAVI report: sexual abuse and violence in Ireland. *Psychol Rep*. January 2002. https://epubs.rcsi.ie/psycholrep/10.

234. Morgan M, Rochford S, Sheehan A. *Childhood Adversity: Lessons from Research and Practice*. Centre for Effective Services; 2016. http://www.lenus.ie/hse/handle/10147/620157. Accessed February 4, 2018.

235. McCrory C, Dooley C, Layte R, Kenny RA. The lasting legacy of childhood adversity for disease risk in later life. *Health Psychol Off J Div Health Psychol Am Psychol Assoc*. 2015;34(7):687-696. doi:10.1037/hea0000147

236. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245-258. doi:10.1016/S0749-3797(98)00017-8

237. Su S, Wang X, Pollock JS, et al. Adverse Childhood Experiences and Blood Pressure Trajectories From Childhood to Young AdulthoodCLINICAL PERSPECTIVE: The Georgia Stress and Heart Study. *Circulation*. 2015;131(19):1674-1681. doi:10.1161/CIRCULATIONAHA.114.013104

238. Feeney J, Dooley C, Finucane C, Kenny RA. Stressful Life Events and Orthostatic Blood Pressure Recovery in Older Adults. *Health Psychol*. 2014. doi:10.1037/hea0000194

239. Oddone AE, Dennis PA, Calhoun PS, et al. Orthostatic hypotension in young adults with and without posttraumatic stress disorder. *Psychol Trauma Theory Res Pract Policy*. 2015;7(3):229-233. doi:10.1037/a0036716

240. Hinton DE, Hofmann SG, Pitman RK, Pollack MH, Barlow DH. The panic attack-posttraumatic stress disorder model: applicability to orthostatic panic among Cambodian refugees. *Cogn Behav Ther*. 2008;37(2):101-116. doi:10.1080/16506070801969062

241. Park J, Marvar PJ, Liao P, et al. Baroreflex dysfunction and augmented sympathetic nerve responses during mental stress in veterans with post-traumatic stress disorder. *J Physiol*. 2017;595(14):4893-4908. doi:10.1113/JP274269

242. Bizios AS, Sheldon RS. Vasovagal syncope: state or trait? *Curr Opin Cardiol*. 2009;24(1):68-73.

243. Sheldon RS, Sheldon AG, Connolly SJ, et al. Age of First Faint in Patients with Vasovagal Syncope. *J Cardiovasc Electrophysiol*. 2006;17(1):49-54. doi:10.1111/j.1540-8167.2005.00267.x

244. Kapoor WN, Fortunato M, Hanusa BH, Schulberg HC. Psychiatric illnesses in patients with syncope. *Am J Med*. 1995;99(5):505-512.

245. Oh JH, Kapoor WN. Psychiatric illness and syncope. *Cardiol Clin*. 1997;15(2):269-275.

246. Skeldon J. The impact of neurocardiogenic syncope on young people's health related quality of life and psychological functioning: A qualitative study. 2015.

247. Bracha HS. Freeze, flight, fight, fright, faint: Adaptationist perspectives on the acute stress response spectrum. *CNS Spectr*. 2004;9(9):679–685.

248. Williamson JB, Porges EC, Lamb DG, Porges SW. Maladaptive autonomic regulation in PTSD accelerates physiological aging. *Front Psychol*. 2015;5. doi:10.3389/fpsyg.2014.01571

249. Porges SW. The polyvagal perspective. *Biol Psychol*. 2007;74(2):116-143. doi:10.1016/j.biopsycho.2006.06.009

250. Porges SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. *Cleve Clin J Med*. 2009;76 Suppl 2:S86-90. doi:10.3949/ccjm.76.s2.17

251. Tannemaat MR, van Dijk JG. The terminology of psychogenic nonepileptic seizures: a historical perspective. *Epilepsia*. 2015;56(6):978-979. doi:10.1111/epi.12992

252. Benbadis SR, Chichkova R. Psychogenic pseudosyncope: An underestimated and provable diagnosis. *Epilepsy Behav*. 2006;9(1):106-110. doi:10.1016/j.yebeh.2006.02.011

253. Emiroglu FNI, Kurul S, Akay A, Miral S, Dirik E. Assessment of Child Neurology Outpatients With Headache, Dizziness, and Fainting -. *J Child Neurol*. 2004;19(5):332-336. doi:10.1177/088307380401900505

254. Tannemaat MR, Niekerk J, Reijntjes RH, Thijs RD, Sutton R, Dijk JG. The semiology of tilt-induced psychogenic pseudosyncope. *Neurology*. 2013;81(8):752-758. doi:10.1212/WNL.0b013e3182a1aa88

255. Paras ML MM. Sexual abuse and lifetime diagnosis of somatic disorders: A systematic review and meta-analysis. *JAMA*. 2009;302(5):550-561. doi:10.1001/jama.2009.1091

256. Frith J. Diagnosing orthostatic hypotension: a narrative review of the evidence. *Br Med Bull*. 2015;115(1):123-134. doi:10.1093/bmb/ldv025

257. van Wijnen VK, Finucane C, Harms MPM, et al. Noninvasive beat-to-beat finger arterial pressure monitoring during orthostasis: a comprehensive review of normal and abnormal responses at different ages. *J Intern Med*. 2017;282(6):468-483. doi:10.1111/joim.12636

258. Nordkamp LRAO, Dijk N van, Wieling W. Orthostatic Challenge Tests: Active Standing and Head-Up Tilt. In: *Electrical Diseases of the Heart*. Springer, London; 2013:197-207. doi:10.1007/978-1-4471-4978-1_12

259. Imholz BP, Settels JJ, van der Meiracker AH, Wesseling KH, Wieling W. Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. *Cardiovasc Res*. 1990;24(3):214–221.

260. Soraghan CJ, Fan CW, Hayakawa T, et al. TILDA Signal Processing Framework (SPF) for the analysis of BP responses to standing in epidemiological and clinical studies. In: *2014 IEEE-EMBS International Conference on Biomedical and Health Informatics (BHI)*. ; 2014:793-796. doi:10.1109/BHI.2014.6864483

261. O'Connell MDL, Savva GM, Fan CW, Kenny RA. Orthostatic hypotension, orthostatic intolerance and frailty: The Irish Longitudinal Study on Aging-TILDA. *Arch Gerontol Geriatr*. 2015;60(3):507-513. doi:10.1016/j.archger.2015.01.008

262. Kearney PM, Cronin H, O'Regan C, Kamiya Y, Whelan BJ, Kenny RA. Comparison of centre and home-based health assessments: early experience from the Irish Longitudinal Study on Ageing (TILDA). *Age Ageing*. 2011;40(1):85-90. doi:10.1093/ageing/afq124

263. Cooke J, Carew S, O'Connor M, Costelloe A, Sheehy T, Lyons D. Sitting and standing blood pressure measurements are not accurate for the diagnosis of orthostatic hypotension. *QJM*. 2009;102(5):335-339. doi:10.1093/qjmed/hcp020

264. Sorond FA, Serrador JM, Jones RN, Shaffer ML, Lipsitz LA. The sit-to-stand technique for the measurement of dynamic cerebral autoregulation. *Ultrasound Med Biol*. 2009;35(1):21-29. doi:10.1016/j.ultrasmedbio.2008.08.001

265. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology*. 1996;46(5):1470.

266. Wieling W, Krediet C, Van Dijk N, Linzer M, Tschakovsky M. Initial orthostatic hypotension: review of a forgotten condition. *Clin Sci*. 2007;112:157–165.

267. Naschitz JE, Slobodin G, Elias N, Rosner I. The patient with supine hypertension and orthostatic hypotension: a clinical dilemma. *Postgrad Med J*. 2006;82(966):246-253. doi:10.1136/pgmj.2005.037457

268. van Dijk JG, Tjon-A-Tsien AM, Kamzoul BA, Kramer CG, Lemkes HH. Effects of supine blood pressure on interpretation of standing up test in 500 patients with diabetes mellitus. *J Auton Nerv Syst*. 1994;47(1-2):23-31.

269. Arbogast SD, Alshekhlee A, Hussain Z, McNeeley K, Chelimsky TC. Hypotension unawareness in profound orthostatic hypotension. *Am J Med*. 2009;122(6):574–580.

270. Rickards CA, Cohen KD, Bergeron LL, et al. Cerebral blood flow response and its association with symptoms during orthostatic hypotension. *Aviat Space Environ Med*. 2007;78(7):653-658.

271. Cooke J, Carew S, Quinn C, et al. The prevalence and pathological correlates of orthostatic hypotension and its subtypes when measured using beat-to-beat technology in a sample of older adults living in the community. *Age Ageing*. 2013;42(6):709-714. doi:10.1093/ageing/aft112

272. Regan CO, Kearney PM, Cronin H, Savva GM, Lawlor BA, Kenny R. Oscillometric measure of blood pressure detects association between orthostatic hypotension and

depression in population based study of older adults. *BMC Psychiatry*. 2013;13(1):266.

273. Bengtsson-Lindberg M, Larsson V, Minthon L, Wattmo C, Londos E. Lack of orthostatic symptoms in dementia patients with orthostatic hypotension. *Clin Auton Res Off J Clin Auton Res Soc*. April 2014. doi:10.1007/s10286-014-0244-z

274. Romero-Ortuno R, Cogan L, Foran T, Kenny RA, Fan CW. Continuous Noninvasive Orthostatic Blood Pressure Measurements and Their Relationship with Orthostatic Intolerance, Falls, and Frailty in Older People: ORTHOSTATIC BP RESPONSES AND FRAILTY IN ELDERS. *J Am Geriatr Soc*. 2011;59(4):655-665. doi:10.1111/j.1532-5415.2011.03352.x

275. Nishime EO. Heart Rate Recovery and Treadmill Exercise Score as Predictors of Mortality in Patients Referred for Exercise ECG. *JAMA*. 2000;284(11):1392. doi:10.1001/jama.284.11.1392

276. Birkett MA. The Trier Social Stress Test Protocol for Inducing Psychological Stress. *J Vis Exp JoVE*. 2011;(56). doi:10.3791/3238

277. Allan LM, Ballard CG, Allen J, et al. Autonomic dysfunction in dementia. *J Neurol Neurosurg Psychiatry*. 2007;78(7):671-677. doi:10.1136/jnnp.2006.102343

278. Elmståhl S, Widerström E. Orthostatic intolerance predicts mild cognitive impairment: incidence of mild cognitive impairment and dementia from the Swedish general population cohort Good Aging in Skåne. *Clin Interv Aging*. 2014;9:1993-2002. doi:10.2147/CIA.S72316

279. Lagro J. Impaired Systolic Blood Pressure Recovery Directly After Standing Predicts Mortality in Older Falls Clinic Patients. *J Gerontol Ser Biomed Sci Med Sci*. 2014;69(4):471-478.

280. Hayakawa T, McGarrigle CA, Coen RF, et al. Orthostatic Blood Pressure Behavior in People with Mild Cognitive Impairment Predicts Conversion to Dementia. *J Am Geriatr Soc*. 2015;63(9):1868-1873. doi:10.1111/jgs.13596

281. Feeney J, O'Leary N, Kenny RA. Impaired orthostatic blood pressure recovery and cognitive performance at two-year follow up in older adults: The Irish Longitudinal Study on Ageing. *Clin Auton Res*. 2016;26(2):127–133.

282. Kario K. Orthostatic Hypertension. *Circ J*. 2009;73(6):1002–1007.

283. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic Hypotension as a Risk Factor for Stroke : The Atherosclerosis Risk in Communities (ARIC) Study, 1987-1996. *Stroke*. 2000;31(10):2307-2313. doi:10.1161/01.STR.31.10.2307

284. Yatsuya H, Folsom AR, Alonso A, Gottesman RF, Rose KM. Postural Changes in Blood Pressure and Incidence of Ischemic Stroke Subtypes The ARIC Study. *Hypertension*. 2011;57(2):167-173. doi:10.1161/HYPERTENSIONAHA.110.161844

285. Ní Bhuachalla B, McGarrigle CA, Kenny RA. Neurocardiovascular instability may modulate end-organ damage: A review of this hypothesis investigating the eye and manifestations of NCVI. *Med Hypotheses*. 2015;85(5):594-602. doi:10.1016/j.mehy.2015.07.020

286. Ní Bhuachalla B, McGarrigle CA, Akuffo KO, Peto T, Beatty S, Kenny RA. Phenotypes of orthostatic blood pressure behaviour and association with visual acuity. *Clin Auton Res Off J Clin Auton Res Soc*. 2015;25(6):373-381. doi:10.1007/s10286-015-0315-9

287. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2016;354:i4098. doi:10.1136/bmj.i4098

288. Wolters FJ, Mattace-Raso FUS, Koudstaal PJ, Hofman A, Ikram MA, Heart Brain Connection Collaborative Research Group. Orthostatic Hypotension and the Long-Term Risk of Dementia: A Population-Based Study. *PLoS Med*. 2016;13(10):e1002143. doi:10.1371/journal.pmed.1002143

289. Ballard C, O'brien J, Barber B, et al. Neurocardiovascular instability, hypotensive episodes, and MRI lesions in neurodegenerative dementia. *Ann N Y Acad Sci*. 2000;903(1):442–445.

290. Collins O, Dillon S, Finucane C, Lawlor B, Kenny RA. Parasympathetic autonomic dysfunction is common in mild cognitive impairment. *Neurobiol Aging*. 2012;33(10):2324-2333. doi:10.1016/j.neurobiolaging.2011.11.017

291. Curreri C, Giantin V, Veronese N, et al. Orthostatic Changes in Blood Pressure and Cognitive Status in the Elderly: The Progetto Veneto Anziani Study. *Hypertens Dallas Tex 1979*. 2016;68(2):427-435. doi:10.1161/HYPERTENSIONAHA.116.07334

292. Viramo P, Luukinen H, Koski K. Orthostatic hypotension and cognitive decline in older people. *J Am Geriatr Soc*. 1999;47(5):600-604.

293. Yap PLK, Niti M, Yap KB, Ng TP. Orthostatic Hypotension, Hypotension and Cognitive Status: Early Comorbid Markers of Primary Dementia? *Dement Geriatr Cogn Disord*. 2008;26(3):239-246. doi:10.1159/000160955

294. Rose KM, Couper D, Eigenbrodt ML, Mosley TH, Sharrett AR, Gottesman RF. Orthostatic Hypotension and Cognitive Function: The Atherosclerosis Risk in Communities Study. *Neuroepidemiology*. 2010;34(1):1-7. doi:10.1159/000255459

295. Colloby SJ, Vasudev A, O'Brien JT, Firbank MJ, Parry SW, Thomas AJ. Relationship of orthostatic blood pressure to white matter hyperintensities and subcortical volumes in late-life depression. *Br J Psychiatry*. 2011;199(5):404-410. doi:10.1192/bjp.bp.110.090423

296. Haley RW, Charuvastra E, Shell WE, et al. Cholinergic Autonomic Dysfunction in Veterans With Gulf War Illness: Confirmation in a Population-Based Sample. *JAMA Neurol*. 2013;70(2):191. doi:10.1001/jamaneurol.2013.596

297. Räihä I, Tarvonen S, Kurki T, Rajala T, Sourander L. Relationship between vascular factors and white matter low attenuation of the brain. *Acta Neurol Scand*. 1993;87(4):286-289. doi:10.1111/j.1600-0404.1993.tb05509.x

298. Soennesyn H, Nilsen DW, Oppedal K, Greve OJ, Beyer MK, Aarsland D. Relationship between orthostatic hypotension and white matter hyperintensity load in older patients with mild dementia. *PloS One*. 2012;7(12):e52196. doi:10.1371/journal.pone.0052196

299. Kario K, Eguchi K, Hoshide S, et al. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. *J Am Coll Cardiol*. 2002;40(1):133–141.

300. Eguchi K, Kario K, Hoshide S, et al. Greater change of orthostatic blood pressure is related to silent cerebral infarct and cardiac overload in hypertensive subjects. *Hypertens Res Off J Jpn Soc Hypertens*. 2004;27(4):235-241.

301. Matsubayashi K, Okumiya K, Wada T, et al. Postural Dysregulation in Systolic Blood Pressure Is Associated With Worsened Scoring on Neurobehavioral Function Tests and Leukoaraiosis in the Older Elderly Living in a Community. *Stroke*. 1997;28(11):2169-2173. doi:10.1161/01.STR.28.11.2169

302. Steffens DC, Chung H, Krishnan KRR, Longstreth WT, Carlson M, Burke GL. Antidepressant treatment and worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2008;39(3):857-862. doi:10.1161/STROKEAHA.107.498097

303. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Hypertension*. 1992;19(6 Pt 1):508-519.

304. Longstreth WT, Arnold AM, Beauchamp NJ, et al. Incidence, Manifestations, and Predictors of Worsening White Matter on Serial Cranial Magnetic Resonance Imaging in the Elderly: The Cardiovascular Health Study. *Stroke*. 2005;36(1):56-61. doi:10.1161/01.STR.0000149625.99732.69

305. Longstreth WT, Dulberg C, Manolio TA, et al. Incidence, Manifestations, and Predictors of Brain Infarcts Defined by Serial Cranial Magnetic Resonance Imaging in the Elderly The Cardiovascular Health Study. *Stroke*. 2002;33(10):2376-2382. doi:10.1161/01.STR.0000032241.58727.49

306. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in Midlife Systolic Blood Pressure Is Related to Late-Life Brain White Matter Lesions: The Honolulu-Asia Aging Study. *Stroke*. 2002;33(1):26-30. doi:10.1161/hs0102.101890

307. DeCarli C, Miller BL, Swan GE, et al. Predictors of Brain Morphology for the Men of the NHLBI Twin Study. *Stroke*. 1999;30(3):529-536. doi:10.1161/01.STR.30.3.529

308. Swenne CA. Baroreflex sensitivity: mechanisms and measurement. *Neth Heart J*. 2013;21(2):58-60. doi:10.1007/s12471-012-0346-y

309. Rovere MTL, Bigger Jr JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *The Lancet*. 1998;351(9101):478-484. doi:10.1016/S0140-6736(97)11144-8

310. Tarumi T, de Jong DLK, Zhu DC, et al. Central artery stiffness, baroreflex sensitivity, and brain white matter neuronal fiber integrity in older adults. *NeuroImage*. 2015;110:162-170. doi:10.1016/j.neuroimage.2015.01.041

311. Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. *J Hypertens*. 2000;18(1):7-19.

312. Persson PB, DiRienzo M, Castiglioni P, et al. Time versus frequency domain techniques for assessing baroreflex sensitivity. *J Hypertens*. 2001;19(10):1699-1705.

313. Parlow J, Viale JP, Annat G, Hughson R, Quintin L. Spontaneous cardiac baroreflex in humans. Comparison with drug-induced responses. *Hypertens Dallas Tex 1979*. 1995;25(5):1058-1068.

314. Szili-Török T, Kálmán J, Paprika D, Dibó G, Rózsa Z, Rudas L. Depressed baroreflex sensitivity in patients with Alzheimer's and Parkinson's disease. *Neurobiol Aging*. 2001;22(3):435-438.

315. Saint Martin M, Sforza E, Thomas-Anterion C, Barthélémy JC, Roche F, The PROOF Study Group. Baroreflex Sensitivity, Vascular Risk Factors, and Cognitive Function in a Healthy Elderly Population: The PROOF Cohort. *J Am Geriatr Soc*. 2013;61(12):2096-2102. doi:10.1111/jgs.12548

316. Saint Martin M, Roche F, Thomas-Anterion C, Barthélémy JC, Sforza E, the PROgnostic OF cardiovascular and cerebrovascular events study group. Eight-Year Parallel Change in Baroreflex Sensitivity and Memory Function in a Sample of Healthy Older Adults. *J Am Geriatr Soc*. 2015;63(2):270-275. doi:10.1111/jgs.13252

317. Watkins LL, Blumenthal JA, Carney RM. Association of anxiety with reduced baroreflex cardiac control in patients after acute myocardial infarction. *Am Heart J*. 2002;143(3):460-466.

318. Watkins LL, Grossman P. Association of depressive symptoms with reduced baroreflex cardiac control in coronary artery disease. *Am Heart J*. 1999;137(3):453-457.

319. Vasudev A, O'Brien JT, Tan MP, Parry SW, Thomas AJ. A study of orthostatic hypotension, heart rate variability and baroreflex sensitivity in late-life depression. *J Affect Disord*. 2011;131(1-3):374-378. doi:10.1016/j.jad.2010.11.001

320. Dauphinot V, Rouch I, Kossovsky MP, et al. Depressive symptoms and autonomic nervous system dysfunction in an elderly population-based study: The PROOF study. *J Affect Disord*. 2012;143(1-3):153-159. doi:10.1016/j.jad.2012.05.045

321. Empana J-P, Prugger C, Thomas F, et al. Serotonin and norepinephrine reuptake inhibitors antidepressant use is related to lower baroreflex sensitivity independently of the severity of depressive symptoms. A community-study of 9213 participants from the Paris Prospective Study III. *Atherosclerosis*. 2016;251:55–62.

322. Laosiripisan J, Tarumi T, Gonzales MM, Haley AP, Tanaka H. Association between cardiovagal baroreflex sensitivity and baseline cerebral perfusion of the hippocampus. *Clin Auton Res*. 2015;4(25):213-218. doi:10.1007/s10286-015-0296-8

323. Shen W-K, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *Circulation*. January 2017:CIR.0000000000000499. doi:10.1161/CIR.0000000000000499

324. Transient loss of consciousness ('blackouts') in over 16s | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/cg109. Accessed June 18, 2017.

325. O'Dwyer C, Bennett K, Langan Y, Fan CW, Kenny RA. Amnesia for loss of consciousness is common in vasovagal syncope. *Europace*. 2011;13(7):1040–1045.

326. Savage DD, Corwin L, McGee DL, Kannel WB, Wolf PA. Epidemiologic features of isolated syncope: the Framingham Study. *Stroke*. 1985;16(4):626–629.

327. Flint B, Baker C, Freeston M, Newton JL. Level of psychosocial impairment predicts early response to treatment in vasovagal syncope. *Europace*. 2009;11(2):231–236.

328. Chen LY, Shen W-K, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Prevalence of syncope in a population aged more than 45 years. *Am J Med*. 2006;119(12):1088–e1.

329. Bhangu JS, King-Kallimanis B, Cunningham C, Kenny RA. The relationship between syncope, depression and anti-depressant use in older adults. *Age Ageing*. 2014;43(4):502-509. doi:10.1093/ageing/afu003

330. Frewen J, King-Kallimanis B, Boyle G, Kenny RA. Recent syncope and unexplained falls are associated with poor cognitive performance. *Age Ageing*. 2015;44(2):282-286. doi:10.1093/ageing/afu191

331. Thijs RD, Kruit MC, Van Buchem MA, Ferrari MD, Launer LJ, Van Dijk JG. Syncope in migraine The population-based CAMERA study. *Neurology*. 2006;66(7):1034–1037.

332. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, Van Dijk N. Lifetime Cumulative Incidence of Syncope in the General Population: A Study of 549 Dutch Subjects Aged 35–60 Years. *J Cardiovasc Electrophysiol*. 2006;17(11):1172-1176. doi:10.1111/j.1540-8167.2006.00595.x

333. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med*. 2002;347(12):878-885.

334. Lipsitz LA, Wei JY, Rowe JW. Syncope in an Elderly, Institutionalised Population: Prevalence, Incidence, and Associated Risk. *QJM Int J Med*. 1985;55(1):45-54. doi:10.1093/oxfordjournals.qjmed.a067852

335. Ruiter SC de, Jonghe JFM de, Germans T, Ruiter JH, Jansen RWMM. Cognitive Impairment Is Very Common in Elderly Patients With Syncope and Unexplained Falls. *J Am Med Dir Assoc*. 2017;18(5):409-413. doi:10.1016/j.jamda.2016.11.012

336. Ungar A, Mussi C, Nicosia F, et al. The “syncope and dementia” study: a prospective, observational, multicenter study of elderly patients with dementia and episodes of “suspected” transient loss of consciousness. *Aging Clin Exp Res*. 2015;27(6):877-882. doi:10.1007/s40520-015-0354-z

337. D’Antono B, Dupuis G, St-Jean K, et al. Prospective evaluation of psychological distress and psychiatric morbidity in recurrent vasovagal and unexplained syncope. *J Psychosom Res*. 2009;67(3):213-222. doi:10.1016/j.jpsychores.2009.03.012

338. Ungar A, Galizia G, Morrione A, et al. Two-year morbidity and mortality in elderly patients with syncope. *Age Ageing*. 2011;40(6):696-702. doi:10.1093/ageing/afr109

339. Kruit MC, Thijs RD, Ferrari MD, Launer LJ, van Buchem MA, van Dijk JG. Syncope and orthostatic intolerance increase risk of brain lesions in migraineurs and controls. *Neurology*. 2013;80(21):1958-1965. doi:10.1212/WNL.0b013e318293e1c7

340. Kuo H-K, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci*. 2004;59(8):M818–M826.

341. Kim JB, Suh S -i, Seo W-K, Koh S-B, Kim JH. Right Insular Atrophy in Neurocardiogenic Syncope: A Volumetric MRI Study. *Am J Neuroradiol*. 2014;35(1):113-118. doi:10.3174/ajnr.A3611

342. Rönnlund M, Sundström A, Adolfsson R, Nilsson L-G. Subjective memory impairment in older adults predicts future dementia independent of baseline memory performance: Evidence from the Betula prospective cohort study. *Alzheimers Dement*. doi:10.1016/j.jalz.2014.11.006

343. Ainslie PN. Regional brain blood flow regulation during orthostatic stress: new insights from volumetric brain blood flow measurements. *Exp Physiol*. 2012;97(12):1247-1248. doi:10.1113/expphysiol.2012.067751

344. Hohman TJ, Beason-Held LL, Lamar M, Resnick SM. Subjective cognitive complaints and longitudinal changes in memory and brain function. *Neuropsychology*. 2011;25(1):125-130. doi:10.1037/a0020859

345. Ricci F, Fedorowski A, Radico F, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. *Eur Heart J*. 2015:ehv093.

346. Freidenberg DL, Shaffer LE, Macalester S, Fannin EA. Orthostatic Hypotension in Patients with Dementia: Clinical Features and Response to Treatment. *Cogn Behav Neurol*. 2013;26(3):105–120.

347. Passant U, Warkentin S, Karlson S, Nilsson K, Edvinsson L, Gustafson L. Orthostatic hypotension in organic dementia: Relationship between blood pressure, cortical blood flow and symptoms. *Clin Auton Res*. 1996;6(1):29-36. doi:10.1007/BF02291403

348. Frewen J, Savva GM, Boyle G, Finucane C, Kenny RA. Cognitive Performance in Orthostatic Hypotension: Findings from a Nationally Representative Sample. *J Am Geriatr Soc*. 2014;62(1):117-122. doi:10.1111/jgs.12592

349. Kearney PM, Cronin H, O'Regan C, et al. Cohort profile: the Irish longitudinal study on ageing. *Int J Epidemiol*. 2011;40(4):877–884.

350. Langa KM, Plassman BL, Wallace RB, et al. The Aging, Demographics, and Memory Study: study design and methods. *Neuroepidemiology*. 2005;25(4):181–191.

351. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of Cognitive Impairment without Dementia in the United States. *Ann Intern Med*. 2008;148(6):427-434.

352. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x

353. Sawyer Radloff L, Teri L. 6/Use of the Center for Epidemiological Studies-Depression Scale with Older Adults. *Clin Gerontol*. 1986;5(1-2):119-136. doi:10.1300/J018v05n01_06

354. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med*. 1997;27(1):231-235.

355. Cheshire WP. Highlights in clinical autonomic neurosciences: Brain volume and autonomic regulation. *Auton Neurosci*. 2014;183:4-7. doi:10.1016/j.autneu.2014.05.001

356. Collins O, Kenny RA. Is neurocardiovascular instability a risk factor for cognitive decline and/or dementia? The science to date. *Rev Clin Gerontol*. 2007;17(03). doi:10.1017/S0959259808002529

357. Oyetunji TA, Chang DC, Crompton JG, et al. Redefining hypotension in the elderly: normotension is not reassuring. *Arch Surg Chic Ill 1960*. 2011;146(7):865-869. doi:10.1001/archsurg.2011.154

358. Musini VM, Nazer M, Bassett K, Wright JM. Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. *Cochrane Database Syst Rev*. 2014;5:CD003824. doi:10.1002/14651858.CD003824.pub2

359. Hellman AM, Shah SP, Pawlowski SM, Duda JE, Morley JF. Continuous non-invasive monitoring to detect covert autonomic dysfunction in Parkinson's disease. *Parkinsonism Relat Disord*. doi:10.1016/j.parkreldis.2015.04.016

360. Abdulrab K, Heun R. Subjective Memory Impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. *Eur Psychiatry*. 2008;23(5):321-330. doi:10.1016/j.eurpsy.2008.02.004

361. Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment: Effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry*. 2010;67(4):414-422. doi:10.1001/archgenpsychiatry.2010.30

362. Carney RM, Blumenthal JA, Stein PK, et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation*. 2001;104(17):2024–2028.

363. Logan IC, Witham MD. Efficacy of treatments for orthostatic hypotension: a systematic review. *Age Ageing*. 2012;41(5):587-594. doi:10.1093/ageing/afs061

364. Jindal RD, Vasko RC, Jennings JR, Fasiczka AL, Thase ME, Reynolds CF. Heart Rate Variability in Depressed Elderly. *Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry*. 2008;16(11):861-866. doi:10.1097/JGP.0b013e318180053d

365. van der Kooy KG, van Hout HPJ, van Marwijk HWJ, de Haan M, Stehouwer CDA, Beekman ATF. Differences in heart rate variability between depressed and non-depressed elderly. *Int J Geriatr Psychiatry*. 2006;21(2):147-150. doi:10.1002/gps.1439

366. O'Regan C, Kenny RA, Cronin H, Finucane C, Kearney PM. Antidepressants strongly influence the relationship between depression and heart rate variability: findings from The Irish Longitudinal Study on Ageing (TILDA). *Psychol Med*. July 2014:1-14. doi:10.1017/S0033291714001767

367. La Rovere MT, Pinna GD, Hohnloser SH, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation*. 2001;103(16):2072-2077.

368. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Glob Health*. 2017;2(2):e000298. doi:10.1136/bmjgh-2017-000298

369. Verkuil B, Brosschot JF, Marques AH, Kampschroer K, Sternberg EM, Thayer JF. Gender differences in the impact of daily sadness on 24-h heart rate variability: Gender, sadness, and HRV. *Psychophysiology*. 2015;52(12):1682-1688. doi:10.1111/psyp.12541

370. Chen H-C, Yang CCH, Kuo TBJ, Su T-P, Chou P. Gender differences in the relationship between depression and cardiac autonomic function among community elderly. *Int J Geriatr Psychiatry*. 2010;25(3):314-322. doi:10.1002/gps.2341

371. Johnson MS, DeMarco VG, Heesch CM, et al. Sex differences in baroreflex sensitivity, heart rate variability, and end organ damage in the TGR(mRen2)27 rat. *Am J Physiol Heart Circ Physiol*. 2011;301(4):H1540-1550. doi:10.1152/ajpheart.00593.2011

372. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617–627.

373. Mackenzie CS, Reynolds K, Chou K-L, Pagura J, Sareen J. Prevalence and Correlates of Generalized Anxiety Disorder in a National Sample of Older Adults. *Am J Geriatr Psychiatry*. 2011;19(4):305-315. doi:10.1097/JGP.0b013e318202bc62

374. Wuthrich VM, Johnco C, Knight A. Comparison of the Penn State Worry Questionnaire (PSWQ) and abbreviated version (PSWQ-A) in a clinical and non-clinical population of older adults. *J Anxiety Disord*. 2014;28(7):657-663. doi:10.1016/j.janxdis.2014.07.005

375. Middleton N, Gunnell D, Whitley E, Dorling D, Frankel S. Secular trends in antidepressant prescribing in the UK, 1975-1998. *J Public Health Med*. 2001;23(4):262-267.

376. Licht CMM, de Geus EJC, van Dyck R, Penninx BWJH. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biol Psychiatry*. 2010;68(9):861-868. doi:10.1016/j.biopsych.2010.06.032

377. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370.

378. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*. 2002;52(2):69-77.

379. Hopko DR, Stanley MA, Reas DL, et al. Assessing worry in older adults: confirmatory factor analysis of the Penn State Worry Questionnaire and psychometric properties of an abbreviated model. *Psychol Assess*. 2003;15(2):173-183.

380. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas*. 1977;1(3):385-401. doi:10.1177/014662167700100306

381. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-1395. doi:10.1249/01.MSS.0000078924.61453.FB

382. Multivariate Regression Analysis | Stata Data Analysis Examples. *IDRE Stats*. https://stats.idre.ucla.edu/stata/dae/multivariate-regression-analysis/. Accessed March 1, 2018.

383. Lenze EJ, Mulsant BH, Shear MK, Alexopoulos GS, Frank E, Reynolds CF. Comorbidity of depression and anxiety disorders in later life. *Depress Anxiety*. 2001;14(2):86–93.

384. Watkins LL, Grossman P, Krishnan R, Blumenthal JA. Anxiety reduces baroreflex cardiac control in older adults with major depression. *Psychosom Med*. 1999;61(3):334-340.

385. Thayer JF, Smith M, Rossy LA, Sollers JJ, Friedman BH. Heart period variability and depressive symptoms: gender differences. *Biol Psychiatry*. 1998;44(4):304-306. doi:10.1016/S0006-3223(98)00008-0

386. Merz AA, Cheng S. Sex differences in cardiovascular ageing. *Heart*. February 2016:heartjnl-2015-308769. doi:10.1136/heartjnl-2015-308769

387. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol Psychiatry*. 2010;67(11):1067-1074. doi:10.1016/j.biopsych.2009.12.012

388. Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *Am J Psychiatry*. 2010;167(7):748-751. doi:10.1176/appi.ajp.2010.09091379

389. Gallagher D, O'Regan C, Savva GM, Cronin H, Lawlor BA, Kenny RA. Depression, anxiety and cardiovascular disease: Which symptoms are associated with increased risk in community dwelling older adults? *J Affect Disord*. 2012;142(1-3):132-138. doi:10.1016/j.jad.2012.04.012

390. Anang JBM, Gagnon J-F, Bertrand J-A, et al. Predictors of dementia in Parkinson disease: A prospective cohort study. *Neurology*. August 2014. doi:10.1212/WNL.0000000000000842

391. Czajkowska J, Ozhog S, Smith E, Perlmuter LC. Cognition and Hopelessness in Association With Subsyndromal Orthostatic Hypotension. *J Gerontol A Biol Sci Med Sci*. 2010;65A(8):873-879. doi:10.1093/gerona/glq068

392. Suter O-C, Sunthorn T, Kraftsik R, et al. Cerebral Hypoperfusion Generates Cortical Watershed Microinfarcts in Alzheimer Disease. *Stroke*. 2002;33(8):1986-1992. doi:10.1161/01.STR.0000024523.82311.77

393. Pilleri M, Facchini S, Gasparoli E, et al. Cognitive and MRI correlates of orthostatic hypotension in Parkinson's disease. *J Neurol*. 2013;260(1):253-259. doi:10.1007/s00415-012-6627-y

394. Wu M, Rosano C, Butters M, et al. A fully automated method for quantifying and localizing white matter hyperintensities on MR images. *Psychiatry Res Neuroimaging*. 2006;148(2):133–142.

395. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15(1):273–289.

396. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, al et. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology*. 2003;22(1):1-12.

397. Metti AL, Yaffe K, Boudreau RM, et al. Change in Inflammatory Markers and Cognitive Status in the Oldest-Old Women from the Study of Osteoporotic Fractures. *J Am Geriatr Soc*. 2014;62(4):662-666. doi:10.1111/jgs.12739

398. Brookmeyer R, Evans DA, Hebert L, et al. National estimates of the prevalence of Alzheimer's disease in the United States*. *Alzheimers Dement J Alzheimers Assoc*. 2011;7(1):61-73. doi:10.1016/j.jalz.2010.11.007

399. Volpato S, Pahor M, Ferrucci L, et al. Relationship of alcohol intake with inflammatory markers and plasminogen activator inhibitor-1 in well-functioning older adults: the Health, Aging, and Body Composition study. *Circulation*. 2004;109(5):607-612. doi:10.1161/01.CIR.0000109503.13955.00

400. Townsend RR, Chang TI, Cohen DL, et al. Orthostatic changes in systolic blood pressure among SPRINT participants at baseline. *J Am Soc Hypertens*. 2016;10(11):847–856.

401. Thomas RJ, Liu K, Jacobs DR, Bild DE, Kiefe CI, Hulley SB. Positional change in blood pressure and 8-year risk of hypertension: the CARDIA Study. *Mayo Clin Proc*. 2003;78(8):951-958. doi:10.4065/78.8.951

402. Goswami N, Gorur P, Pilsl U, et al. Effect of Orthostasis on Endothelial Function: A Gender Comparative Study. Quintas LEM, ed. *PLoS ONE*. 2013;8(8):e71655. doi:10.1371/journal.pone.0071655

403. Masoud M, Sarig G, Brenner B, Jacob G. Orthostatic hypercoagulability: a novel physiological mechanism to activate the coagulation system. *Hypertension*. 2008;51(6):1545-1551. doi:10.1161/HYPERTENSIONAHA.108.112003

404. Wong EH, Pullicino PM, Benedict R. Deep Cerebral Infarcts Extending to the Subinsular Region. *Stroke*. 2001;32(10):2272-2277. doi:10.1161/hs1001.096622

405. Fagard RH, De Cort P. Orthostatic Hypotension Is a More Robust Predictor of Cardiovascular Events Than Nighttime Reverse Dipping in Elderly. *Hypertension*. 2010;56(1):56-61. doi:10.1161/HYPERTENSIONAHA.110.151654

406. Kapoor WN. Current evaluation and management of syncope. *Circulation*. 2002;106(13):1606-1609.

407. Alboni P. The different clinical presentations of vasovagal syncope. *Heart*. 2015;101(9):674-678. doi:10.1136/heartjnl-2014-307096

408. Eccles JA, Owens AP, Mathias CJ, Umeda S, Critchley HD. Neurovisceral phenotypes in the expression of psychiatric symptoms. *Front Neurosci*. 2015;9. doi:10.3389/fnins.2015.00004

409. Giada F, Silvestri I, Rossillo A, Nicotera P, Manzillo G, Raviele A. Psychiatric profile, quality of life and risk of syncopal recurrence in patients with tilt-induced vasovagal syncope. *Europace*. 2005;7(5):465-471. doi:10.1016/j.eupc.2005.05.008

410. Springer KW, Sheridan J, Kuo D, Carnes M. The Long-term Health Outcomes of Childhood Abuse. *J Gen Intern Med*. 2003;18(10):864-870. doi:10.1046/j.1525-1497.2003.20918.x

411. Thurston RC, Chang Y, Derby CA, et al. Abuse and subclinical cardiovascular disease among midlife women: the study of women's health across the nation. *Stroke J Cereb Circ*. 2014;45(8):2246-2251. doi:10.1161/STROKEAHA.114.005928

412. Cappelleri JC, Eckenrode J, Powers JL. The epidemiology of child abuse: findings from the Second National Incidence and Prevalence Study of Child Abuse and Neglect. *Am J Public Health*. 1993;83(11):1622-1624.

413. Colman N, Nahm K, Ganzeboom KS, et al. Epidemiology of reflex syncope. *Clin Auton Res Off J Clin Auton Res Soc*. 2004;14 Suppl 1:9-17. doi:10.1007/s10286-004-1003-3

414. Grubb BP. Once a fainter, always a fainter? *J Cardiovasc Electrophysiol*. 2006;17(1):55. doi:10.1111/j.1540-8167.2005.00283.x

415. Kapoor W, Snustad D, Peterson J, Wieand HS, Cha R, Karpf M. Syncope in the elderly. *Am J Med*. 1986;80(3):419-428. doi:10.1016/0002-9343(86)90716-3

416. Ventura R. Psychiatric conditions in patients with recurrent unexplained syncope. *Europace*. 2001;3(4):311-316. doi:10.1053/eupc.2001.0182

417. Holman N, Kirkby A, Duncan S, Brown RJ. Adult attachment style and childhood interpersonal trauma in non-epileptic attack disorder. *Epilepsy Res*. 2008;79(1):84-89. doi:10.1016/j.eplepsyres.2007.12.015

418. Stone J, LaFrance WC, Brown R, Spiegel D, Levenson JL, Sharpe M. Conversion Disorder: Current problems and potential solutions for DSM-5. *J Psychosom Res*. 2011;71(6):369-376. doi:10.1016/j.jpsychores.2011.07.005

419. WHO 2012. *WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC Classification and DDD Assignment 2013. Oslo,2012* .

420. Arbor A. *HRS/AHEAD Documentation Report Documentation of Cognitive Functioning Measures in the Health and Retirement Study*.; 2005.

421. MacKinnon DP, Dwyer JH. Estimating mediated effects in prevention studies. *Eval Rev*. 1993;17(2):144–158.

422. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods*. 2008;40(3):879–891.

423. Blad H, Lamberts RJ, van Dijk GJ, Thijs RD. Tilt-induced vasovagal syncope and psychogenic pseudosyncope: Overlapping clinical entities. *Neurology*. 2015;85(23):2006-2010. doi:10.1212/WNL.0000000000002184

424. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. *Eur Arch Psychiatry Clin Neurosci*. 2006;256(3):174-186. doi:10.1007/s00406-005-0624-4

425. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychol Bull*. 2011;137(6):959-997. doi:10.1037/a0024768

426. Marx BP, Forsyth JP, Gallup GG, Fusé T, Lexington JM. Tonic Immobility as an Evolved Predator Defense: Implications for Sexual Assault Survivors. *Clin Psychol Sci Pract*. 2008;15(1):74-90. doi:10.1111/j.1468-2850.2008.00112.x

427. Katon WJ. Panic Disorder. *N Engl J Med*. 2006;354(22):2360-2367.

428. Pitman RK, Rasmusson AM, Koenen KC, et al. Biological studies of post-traumatic stress disorder. *Nat Rev Neurosci*. 2012;13(11):769+.

429. Saleh A, Potter GG, McQuoid DR, et al. Effects of early life stress on depression, cognitive performance and brain morphology. *Psychol Med*. 2017;47(1):171-181. doi:10.1017/S0033291716002403

430. Gracie J, Newton JL, Norton M, Baker C, Freeston M. The role of psychological factors in response to treatment in neurocardiogenic (vasovagal) syncope. *Europace*. 2006;8(8):636-643. doi:10.1093/europace/eul073

431. Mendu ML, McAvay G, Lampert R, Stoehr J, Tinetti ME. Yield of diagnostic tests in evaluating syncopal episodes in older patients. *Arch Intern Med*. 2009;169(14):1299.

432. Dube SR, Williamson DF, Thompson T, Felitti VJ, Anda RF. Assessing the reliability of retrospective reports of adverse childhood experiences among adult HMO members attending a primary care clinic. *Child Abuse Negl*. 2004;28(7):729-737. doi:10.1016/j.chiabu.2003.08.009

433. Tsakiris M, Critchley H. Interoception beyond homeostasis: affect, cognition and mental health. *Philos Trans R Soc Lond B Biol Sci*. 2016;371(1708). doi:10.1098/rstb.2016.0002

434. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003

435. Borst C, Van Brederode JFM, Wieling W, Van Montfrans GA, Dunning AJ. Mechanisms of initial blood pressure response to postural change. *Clin Sci*. 1984;67(Pt 3):321–327.

436. Mattace-Raso FU, van der Cammen TJ, Knetsch AM, et al. Arterial stiffness as the candidate underlying mechanism for postural blood pressure changes and orthostatic hypotension in older adults: the Rotterdam Study. *J Hypertens Febr 2006*. 2006;24(2):339-344.

437. Kenny RA. Syncope in the Elderly: *J Cardiovasc Electrophysiol*. 2003;14:S74-S77. doi:10.1046/j.1540-8167.14.s9.8.x

438. Byars KC, Brown RT, Campbell RM, Hobbs SA. Psychological adjustment and coping in a population of children with recurrent syncope. *J Dev Behav Pediatr*. 2000;21(3):189-197.

439. O'Riordan S, Vasilakis N, Hussain L, et al. Measurement of lying and standing blood pressure in hospital. *Nurs Older People*. 2017;29(8):20-26. doi:10.7748/nop.2017.e961

440. Schulman EA, Hohler AD. The American Academy of Neurology position statement on abuse and violence. *Neurology*. 2012;78(6):433-435. doi:10.1212/WNL.0b013e318245d21c

441. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol*. 2015;12. doi:10.1186/s12982-015-0037-4

442. Bennett DA, Holmes MV. Mendelian randomisation in cardiovascular research: an introduction for clinicians. *Heart Br Card Soc*. 2017;103(18):1400-1407. doi:10.1136/heartjnl-2016-310605

443. Matthews FE, Chatfield M, Freeman C, McCracken C, Brayne C, MRC CFAS. Attrition and bias in the MRC cognitive function and ageing study: an epidemiological investigation. *BMC Public Health*. 2004;4:12. doi:10.1186/1471-2458-4-12

444. Helliwell B, Aylesworth R, McDowell I, Baumgarten M, Sykes E. Correlates of nonparticipation in the Canadian Study of Health and Aging. *Int Psychogeriatr*. 2001;13 Supp 1:49-56.

445. Whelan BJ, Savva GM. Design and methodology of the Irish Longitudinal Study on Ageing. *J Am Geriatr Soc*. 2013;61 Suppl 2:S265-268. doi:10.1111/jgs.12199

446. Rothman KJ, Gallacher JEJ, Hatch EE. Why representativeness should be avoided. *Int J Epidemiol*. 2013;42(4):1012-1014. doi:10.1093/ije/dys223

447. Rothman KJ, Gallacher JEJ, Hatch EE. Rebuttal: When it comes to scientific inference, sometimes a cigar is just a cigar. *Int J Epidemiol*. 2013;42(4):1026-1028. doi:10.1093/ije/dyt124

448. Swanson JM. The UK Biobank and selection bias. *Lancet Lond Engl*. 2012;380(9837):110. doi:10.1016/S0140-6736(12)61179-9

449. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annu Rev Public Health*. 1997;18:341-378. doi:10.1146/annurev.publhealth.18.1.341

450. Zhivan NA, Ang A, Amaro H, Vega WA, Markides KS. Ethnic/race differences in the attrition of older American survey respondents: implications for health-related research. *Health Serv Res*. 2012;47(1 Pt 1):241-254. doi:10.1111/j.1475-6773.2011.01322.x

451. Chatfield MD, Brayne CE, Matthews FE. A systematic literature review of attrition between waves in longitudinal studies in the elderly shows a consistent pattern of dropout between differing studies. *J Clin Epidemiol*. 2005;58(1):13-19. doi:10.1016/j.jclinepi.2004.05.006

452. Newman AB. An overview of the design, implementation, and analyses of longitudinal studies on aging. *J Am Geriatr Soc*. 2010;58 Suppl 2:S287-291. doi:10.1111/j.1532-5415.2010.02916.x

453. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J*. 2003;20(1):54-60. doi:10.1136/emj.20.1.54

454. Fan CW, Savva GM, Finucane C, et al. Factors affecting continuous beat-to-beat orthostatic blood pressure response in community-dwelling older adults. *Blood Press Monit*. 2012;17(4):160-163. doi:10.1097/MBP.0b013e328356821f

455. Finucane C, Savva GM, Kenny RA. Reliability of orthostatic beat-to-beat blood pressure tests: implications for population and clinical studies. *Clin Auton Res*. 2017;27(1):31-39. doi:10.1007/s10286-016-0393-3

456. Frøslie KF, Røislien J, Laake P, Henriksen T, Qvigstad E, Veierød MB. Categorisation of continuous exposure variables revisited. A response to the

Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study. *BMC Med Res Methodol*. 2010;10:103. doi:10.1186/1471-2288-10-103

457. Hajjar I, Hart M, Chen Y-L, et al. Antihypertensive Therapy and Cerebral Hemodynamics in Executive Mild Cognitive Impairment: Results of a Pilot Randomized Clinical Trial. *J Am Geriatr Soc*. 2013;61(2):194-201. doi:10.1111/jgs.12100

458. Juraschek SP, Daya N, Rawlings AM, et al. Association of History of Dizziness and Long-term Adverse Outcomes With Early vs Later Orthostatic Hypotension Assessment Times in Middle-aged Adults. *JAMA Intern Med*. 2017;177(9):1316. doi:10.1001/jamainternmed.2017.2937

459. Sheldon R. Syncope Diagnostic Scores. *Prog Cardiovasc Dis*. 2013;55(4):390-395. doi:10.1016/j.pcad.2012.10.011

460. Widom CS, Raphael KG, DuMont KA. The case for prospective longitudinal studies in child maltreatment research: commentary on Dube, Williamson, Thompson, Felitti, and Anda (2004). *Child Abuse Negl*. 2004;28(7):715-722. doi:10.1016/j.chiabu.2004.03.009

461. Kendall-Tackett K, Becker-Blease K. The importance of retrospective findings in child maltreatment research. *Child Abuse Negl*. 2004;28(7):723-727. doi:10.1016/j.chiabu.2004.02.002

462. Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J Child Psychol Psychiatry*. 2004;45(2):260-273.

463. Frissa S, Hatch SL, Fear NT, Dorrington S, Goodwin L, Hotopf M. Challenges in the retrospective assessment of trauma: comparing a checklist approach to a single item trauma experience screening question. *BMC Psychiatry*. 2016;16:20. doi:10.1186/s12888-016-0720-1

464. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

465. Davis DHJ, Creavin ST, Yip JLY, Noel-Storr AH, Brayne C, Cullum S. Montreal Cognitive Assessment for the diagnosis of Alzheimer's disease and other dementias. *Cochrane Database Syst Rev*. 2015;(10):CD010775. doi:10.1002/14651858.CD010775.pub2

466. Creavin ST, Wisniewski S, Noel-Storr AH, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst Rev*. 2016;(1):CD011145. doi:10.1002/14651858.CD011145.pub2

467. Gorelick PB, Counts SE, Nyenhuis D. Vascular cognitive impairment and dementia. *Biochim Biophys Acta*. 2016;1862(5):860-868. doi:10.1016/j.bbadis.2015.12.015

468. Coen RF. Strengths and Limitations of the MoCA for Assessing Cognitive Functioning. 2016;29(1):18-24.

469. Weir DR, Wallace RB, Langa KM, et al. Reducing case ascertainment costs in U.S. population studies of Alzheimer's disease, dementia, and cognitive impairment-Part 1. *Alzheimers Dement J Alzheimers Assoc*. 2011;7(1):94-109. doi:10.1016/j.jalz.2010.11.004

470. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *J Gerontol B Psychol Sci Soc Sci*. 2011;66 Suppl 1:i162-171. doi:10.1093/geronb/gbr048

471. Bourdon KH, Rae DS, Locke BZ, Narrow WE, Regier DA. Estimating the prevalence of mental disorders in U.S. adults from the Epidemiologic Catchment Area Survey. *Public Health Rep*. 1992;107(6):663-668.

472. WHO WMH-CIDI – The World Health Organization World Mental Health Composite International Diagnostic Interview. https://www.hcp.med.harvard.edu/wmhcidi/. Accessed January 28, 2018.

473. Blazer DG, Kessler RC, Swartz MS. Epidemiology of recurrent major and minor depression with a seasonal pattern. The National Comorbidity Survey. *Br J Psychiatry*. 1998;172(2):164–167.

474. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry*. 1999;174(4):307-311. doi:10.1192/bjp.174.4.307

475. Rajtmajer SM, Roy A, Albert R, Molenaar PCM, Hillary FG. A voxelwise approach to determine consensus regions-of-interest for the study of brain network plasticity. *Front Neuroanat*. 2015;9. doi:10.3389/fnana.2015.00097

476. Blane D. Commentary: the place in life course research of validated measures of socioeconomic position. *Int J Epidemiol*. 2006;35(1):139-140. doi:10.1093/ije/dyi217

477. McCrory C, Finucane C, O'Hare C, et al. Social Disadvantage and Social Isolation Are Associated With a Higher Resting Heart Rate: Evidence From The Irish Longitudinal Study on Ageing. *J Gerontol B Psychol Sci Soc Sci*. 2016;71(3):463-473. doi:10.1093/geronb/gbu163

478. McCrory C, Berkman LF, Moore PV, Kenny RA. What Explains Socioeconomic Differences in the Speed of Heart Rate Recovery to Postural Challenge? *J Gerontol A Biol Sci Med Sci*. 2017;72(12):1717-1723. doi:10.1093/gerona/glx060

479. Verma AA, Jimenez MP, Subramanian SV, Sniderman AD, Razak F. Race and Socioeconomic Differences Associated With Changes in Statin Eligibility Under the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines. *Circ Cardiovasc Qual Outcomes*. 2017;10(9):e003764. doi:10.1161/CIRCOUTCOMES.117.003764

480. Division (DCD) DC. Who is eligible for Medicare? HHS.gov. https://www.hhs.gov/answers/medicare-and-medicaid/who-is-elibible-for-medicare/index.html. Published June 7, 2015. Accessed January 28, 2018.

481. McCrory C, Henretta JC, O'Connell MDL, Kenny RA. Intergenerational Occupational Mobility and Objective Physical Functioning in Midlife and Older Ages. *J Gerontol Ser B*. 2018;73(2):279-291. doi:10.1093/geronb/gbv084

482. Richardson K, Kenny RA, Peklar J, Bennett K. Agreement between patient interview data on prescription medication use and pharmacy records in those aged older than 50 years varied by therapeutic group and reporting of indicated health conditions. *J Clin Epidemiol*. 2013;66(11):1308-1316. doi:10.1016/j.jclinepi.2013.02.016

483. Marcum ZA, Perera S, Thorpe JM, et al. Antidepressant Use and Recurrent Falls in Community-Dwelling Older Adults: Findings From the Health ABC Study. *Ann Pharmacother*. 2016;50(7):525-533. doi:10.1177/1060028016644466

484. Butler J, Kalogeropoulos A, Georgiopoulou V, et al. Incident Heart Failure Prediction in the Elderly: The Health ABC Heart Failure Score. *Circ Heart Fail*. 2008;1(2):125-133. doi:10.1161/CIRCHEARTFAILURE.108.768457

485. van den Berg MP, Almomani R, Biaggioni I, et al. Mutations in CYB561 Causing a Novel Orthostatic Hypotension Syndrome. *Circ Res*. January 2018. doi:10.1161/CIRCRESAHA.117.311949

486. Nolte IM, Munoz ML, Tragante V, et al. Genetic loci associated with heart rate variability and their effects on cardiac disease risk. *Nat Commun*. 2017;8:15805. doi:10.1038/ncomms15805

487. Wainer H. Adjusting for differential base rates: Lord's paradox again. *Psychol Bull*. 1991;109(1):147-151.

488. Ravindrarajah R, Hazra NC, Hamada S, et al. Systolic Blood Pressure Trajectory, Frailty, and All-Cause Mortality >80 Years of AgeClinical Perspective: Cohort Study Using Electronic Health Records. *Circulation*. 2017;135(24):2357-2368. doi:10.1161/CIRCULATIONAHA.116.026687

489. SPRINT Research Group, Wright JT, Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373(22):2103-2116. doi:10.1056/NEJMoa1511939

490. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial. *JAMA*. 2016;315(24):2673-2682. doi:10.1001/jama.2016.7050

491. Pajewski NM, Williamson JD, Applegate WB, et al. Characterizing Frailty Status in the Systolic Blood Pressure Intervention Trial. *J Gerontol A Biol Sci Med Sci*. 2016;71(5):649-655. doi:10.1093/gerona/glv228

492. Frith J, Parry SW. New Horizons in orthostatic hypotension. *Age Ageing*. 2017;46(2):168-174. doi:10.1093/ageing/afw211

493. Sexton DJ, Canney M, O'Connell MDL, et al. Injurious Falls and Syncope in Older Community-Dwelling Adults Meeting Inclusion Criteria for SPRINT. *JAMA Intern Med*. 2017;177(9):1385-1387. doi:10.1001/jamainternmed.2017.2924

494. Pajewski NM, Supiano MA, Williamson JD. Limitations of Observational Data in Interpreting SPRINT Results. *JAMA Intern Med*. 2018;178(1):154-155. doi:10.1001/jamainternmed.2017.7215

495. Supiano MA, Williamson JD. Applying the Systolic Blood Pressure Intervention Trial Results to Older Adults. *J Am Geriatr Soc*. 2017;65(1):16-21. doi:10.1111/jgs.14681

496. Kenny RA, Coen RF, Frewen J, Donoghue OA, Cronin H, Savva GM. Normative values of cognitive and physical function in older adults: findings from the Irish Longitudinal Study on Ageing. *J Am Geriatr Soc*. 2013;61 Suppl 2:S279-290. doi:10.1111/jgs.12195

497. Berlowitz DR, Foy CG, Kazis LE, et al. Effect of Intensive Blood-Pressure Treatment on Patient-Reported Outcomes. http://dx.doi.org/10.1056/NEJMoa1611179. doi:10.1056/NEJMoa1611179

498. Lipsitz LA, Habtemariam D, Gagnon M, et al. RE-EXAMINING THE EFFECT OF ANTIHYPERTENSIVE MEDICATIONS ON FALLS IN OLD AGE. *Hypertension*. 2015;66(1):183-189. doi:10.1161/HYPERTENSIONAHA.115.05513

499. Lipsitz LA, Gagnon M, Vyas M, et al. Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertens Dallas Tex 1979*. 2005;45(2):216-221. doi:10.1161/01.HYP.0000153094.09615.11

500. Khalaf A, Edelman K, Tudorascu D, Andreescu C, Reynolds CF, Aizenstein H. White Matter Hyperintensity Accumulation During Treatment of Late-Life Depression. *Neuropsychopharmacology*. 2015;40(13):3027-3035. doi:10.1038/npp.2015.158

501. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288(6):701-709.

502. Ryan J, Carriere I, Ritchie K, et al. Late-life depression and mortality: influence of gender and antidepressant use. *Br J Psychiatry J Ment Sci*. 2008;192(1):12-18. doi:10.1192/bjp.bp.107.039164

503. Joynt KE, O'Connor CM. Lessons from SADHART, ENRICHD, and other trials. *Psychosom Med*. 2005;67 Suppl 1:S63-66. doi:10.1097/01.psy.0000163454.25036.fc

504. Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol*. 2017;14(3):145-155. doi:10.1038/nrcardio.2016.181

505. Torres RV, Elias MF, Crichton GE, Dore GA, Davey A. Systolic orthostatic hypotension is related to lowered cognitive function: Findings from the Maine-Syracuse Longitudinal Study. *J Clin Hypertens Greenwich Conn*. 2017;19(12):1357-1365. doi:10.1111/jch.13095

506. Huang H, Zheng T, Liu F, Wu Z, Liang H, Wang S. Orthostatic Hypotension Predicts Cognitive Impairment in the Elderly: Findings from a Cohort Study. *Front Neurol*. 2017;8:121. doi:10.3389/fneur.2017.00121

507. Holm H, Nägga K, Nilsson ED, et al. Longitudinal and postural changes of blood pressure predict dementia: the Malmö Preventive Project. *Eur J Epidemiol*. 2017;32(4):327-336. doi:10.1007/s10654-017-0228-0

508. McIntosh AM, Stewart R, John A, et al. Data science for mental health: a UK perspective on a global challenge. *Lancet Psychiatry*. 2016;3(10):993-998. doi:10.1016/S2215-0366(16)30089-X

509. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217. doi:10.1016/j.cell.2013.05.039

510. Lipsitz LA, Goldberger AL. Loss of "complexity" and aging. Potential applications of fractals and chaos theory to senescence. *JAMA*. 1992;267(13):1806-1809.