Clinical clustering of eight orthostatic haemodynamic patterns in The Irish Longitudinal Study on Ageing (TILDA)

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MB, BCh, BAO

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Medicine

University of Dublin,
Trinity College
2021
Declaration

I declare that the work in this thesis is entirely my own, except where credit is given in the acknowledgements.

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

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. I agree to deposit this thesis in the University’s open access institutional repository or allow the Library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement. I consent to the examiner retaining a copy of the thesis beyond the examining period, should they so wish (EU GDPR May 2018).

Signed ________________________________________ David Moloney
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P.S. I wish to acknowledge the existence of my two siblings, Kevin and Catriona.
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<td>AAN</td>
<td>American Academy of Neurology</td>
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<tr>
<td>ACEI</td>
<td>Angiotensin-converting-enzyme inhibitors</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention deficit hyperactivity disorder</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>Ans</td>
<td>Autonomic nervous system</td>
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<td>ARB</td>
<td>Angiotensin II receptor blockers</td>
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<tr>
<td>AS</td>
<td>Active stand</td>
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<td>BP</td>
<td>Blood pressure</td>
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<td>BZD</td>
<td>Benzodiazepines</td>
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<td>CAPI</td>
<td>Computer-assisted personal interviews</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<tr>
<td>CCB</td>
<td>Calcium Channel Blockers</td>
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<tr>
<td>CO</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>CO2</td>
<td>Carbon dioxide</td>
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<tr>
<td>cOH</td>
<td>Classical Orthostatic Hypotension</td>
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<td>CVR</td>
<td>Cerebrovascular reactivity</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>dCA</td>
<td>Dynamic cerebral autoregulation</td>
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<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>EPO</td>
<td>Erythropoietin</td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>FinAP</td>
<td>Finger arterial blood pressure</td>
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<td>FOF</td>
<td>Fear of Falling</td>
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<tr>
<td>HbA1c</td>
<td>Glycosylated haemoglobin</td>
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<td>HRR</td>
<td>Heart rate recovery</td>
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<tr>
<td>HUT</td>
<td>Head up tilt</td>
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<tr>
<td>IMT</td>
<td>Intime-media thickness</td>
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<tr>
<td>iOH</td>
<td>Initial Orthostatic Hypotension</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>MACE</td>
<td>Major adverse cardiovascular events</td>
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<tr>
<td>MAP</td>
<td>Mean arterial blood pressure</td>
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<tr>
<td>MEloR</td>
<td>The Malaysian Elders Longitudinal Research</td>
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<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<td>MSA</td>
<td>Multiple system atrophy</td>
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<tr>
<td>NET</td>
<td>Norepinephrine transporter</td>
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<tr>
<td>NIRS</td>
<td>near-infrared spectroscopy</td>
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<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>nOH</td>
<td>Neurogenic orthostatic hypotension</td>
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<tr>
<td>OH</td>
<td>Orthostatic hypotension</td>
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<tr>
<td>OI</td>
<td>Orthostatic intolerance</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PCM</td>
<td>Physical counter manoeuvres</td>
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<tr>
<td>pCO2</td>
<td>Partial pressure of carbon dioxide</td>
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<tr>
<td>PIP</td>
<td>Potentially inappropriate prescribing</td>
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<td>POTS</td>
<td>Postural orthostatic tachycardia syndrome</td>
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<tr>
<td>ProFANE</td>
<td>Prevention of Falls Network Europe group</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>RHR</td>
<td>Resting heart rate</td>
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<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>SCQ</td>
<td>Self-completion questionnaires</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SHU</td>
<td>Sleeping ‘head up’</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin–norepinephrine reuptake inhibitors</td>
</tr>
<tr>
<td>SPRINT</td>
<td>Systolic Blood Pressure Intervention Trial</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitors</td>
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<tr>
<td>START</td>
<td>Screening Tool to Alert doctors to Right Treatment</td>
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<tr>
<td>STOPP</td>
<td>Screening Tool of Older Person’s Prescriptions</td>
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<tr>
<td>SYD</td>
<td>Syncope and Dementia registry</td>
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<tr>
<td>TCA</td>
<td>Tricyclic Antidepressants</td>
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<td>TILDA</td>
<td>The Irish Longitudinal Study on Ageing</td>
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<tr>
<td>TLOC</td>
<td>total loss of consciousness</td>
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<tr>
<td>TPR</td>
<td>Total peripheral resistance</td>
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<tr>
<td>TRIL</td>
<td>Technology Research for Independent Living study</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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Abstract

INTRODUCTION
Orthostatic hypotension (OH) can be assessed with non-invasive continuous beat-to-beat haemodynamic monitoring during active stand (AS) testing; this yields large volumes of data outside the scope of the traditional OH definition. I explored clinical associations of different AS patterns in participants from Wave 1 of The Irish Longitudinal Study on Ageing (TILDA).

METHODS
AS patterns were generated based on three sequential binary BP features: drop ≥40/20mmHg SBP/DBP within 10s post-stand (“immediate deficit”), failure to return to within 20/10mmHg SBP/DBP of supine level at 40s after standing (“stabilisation deficit”), and drop ≥20/10mmHg SBP/DBP between >40 and 120s post-stand (“late deficit”). Eight AS groups (for SBP and DBP each) resulted from combining the presence/absence of these three features. The groups were cross-sectionally characterised, and their ability to independently predict orthostatic intolerance (OI), falls or syncope in the past year, was evaluated using multivariable logistic regression models. The heart rate features of the eight SBP/DBP groups were then analysed including: resting heart rate (RHR), meanHR, maxHR, deltaHR and heart rate recovery.

RESULTS
4899 participants were included, with a mean age of 61 and of whom 55% were female. The largest group was the one with no deficits (SBP: 68% vs DBP: 49.41%). In both SBP and DBP groups, older age was associated with stabilisation deficit and late deficits were seen in groups with higher proportions of beta blockers and psychotropic medications. There were higher rates of cardiovascular risk factors/disease in the DBP groups.
In both SBP and DBP groups, regression models identified independent associations between OI and three immediate-deficit groups; associations became stronger as more deficits were present. There was a significant association between falls history and the three-deficit group (SBP: OR 1.54, 95% CI: 1.15-2.07, p=0.004, DBP: OR 1.56, 95% CI: 1.18-2.07, p=0.002).
Groups 1 and 3 have the lowest RHR and Group 8 has the quickest HRR10_20 recovery (-6.69, -6.81) when defined by either SBP or DBP criteria.

CONCLUSIONS
The accumulation of AS deficits was reflective of a frailer and more multimorbid population and was associated with higher risk of OI and falls history. During an AS the recovery pattern after the drop is as important, if not more than the initial BP drop alone. The current practice of using SBP or DBP to identify OH may result in two OH populations with different underlying pathophysiology being grouped together.
Lay Abstract

INTRODUCTION
The ability to change the body position from lying to standing is a remarkable feat that not many animals have mastered, and the major challenge is posed by gravity. When we go from lying to standing, gravity forces some blood (~15-20% of our total blood volume) to pool into the veins of our gut and legs. This causes a drop in blood pressure that our body rapidly compensates for to try to maintain a stable blood pressure. The body adapts by increasing the heart rate and the blood pressure in the arteries by narrowing their diameter. The lower limb muscles also have a role in ‘squeezing’ the veins where the blood has pooled to return as much blood as possible to the heart. Throughout, our brain also alters its circulation to try to keep a constant supply of oxygen to the brain.

This complex response is controlled by our autonomic nervous system but is influenced by many factors including age, hydration status, medication usage, and cardiovascular and neurological diseases. By standing a person up and monitoring their blood pressure and heart rate responses to this gravitational challenge, we can gain information as to how intact the compensatory systems are, which may hint at underlying disease.

There is now technology to non-invasively measure beat-to-beat heart rate and blood pressure changes during a test where the person is asked to rapidly go from lying to standing (active stand test). This results in an interpretation challenge for the clinician, as it is difficult to know which part of the stand is the most important. Previous literature has identified three separate points of possible relevance: the initial blood pressure drop (in the first 15 seconds after standing), the impaired stabilisation (the pattern from 15 to 40 seconds), and the classical definition (which is any change within the 3 minutes post-stand).

MD hypothesis
Accumulation of health deficits is associated with higher cardiovascular morbidity and mortality. By applying this principle to adverse blood pressure features during the AS, I hypothesised that their sequential accumulation may be associated with more adverse clinical features such as higher risk of orthostatic intolerance and history of falls or syncope. To test that hypothesis, I manually modelled AS patterns according to the presence/absence of immediate, early and late blood pressure deficits, and explored their clinical associations in participants from Wave 1 of The Irish Longitudinal Study on Ageing (TILDA).

My secondary hypothesis was that using purely SBP or DBP criteria to define OH would result in identifying different populations with different underlying health deficits.

Finally, I wanted to explore the role heart rate response has in generating these patterns.
Outputs

Publications:

Clinical clustering of eight orthostatic haemodynamic patterns in The Irish Longitudinal Study on Ageing (TILDA)
David Moloney, John O’Connor, Louise Newman, Siobhan Scarlett, Belinda Hernandez, Rose Anne Kenny, Roman Romero-Ortuno
Age and Ageing, Sept 2020

Presentations:

Clinical clustering of eight orthostatic haemodynamic patterns in The Irish Longitudinal Study on Ageing (TILDA)
David Moloney
Oral presentation
European Union Geriatric Medicine Society 2020 Congress
CHAPTER ONE: GENERAL INTRODUCTION
SECTION 1: History of Orthostatic Hypotension

'We wish to report the clinical and pharmacological observations upon three patients whose blood pressure readings show extremely wide variations upon change of position of the body'.

It was with these lines that, in 1925, Bradbury and Eggleston first described and defined orthostatic hypotension in their landmark case series.[1] This initial case series ignited a discussion about patients who have profound orthostatic drops in blood pressure and up to seven associated clinical phenomena: ‘(1) syncopal attacks on change of posture with a drop of the systolic blood pressure to the shock levels; (2) anhidrosis; (3) increased distress during the heat of the summer months; (4) slow and unchanging pulse rate with marked variation in the blood pressure; (5) slight decrease in the basal metabolic rate; (6) signs of slight and indefinite changes in the central nervous system; and (7) blood urea at the upper normal level.’[1]

However, the honour of ‘coining’ the term orthostatic hypotension (OH) went to Laubry and Doumer who first used the term (in French) in their case series entitled ‘L’hypotension orthostatique’ in 1932.[2]

Barker in his paper entitled ‘Postural Hypotension: Report of a Case and Review of the Literature’ (published in 1933) described OH as being a syndrome ‘in which there is an immediate, persistent and marked fall in the systolic blood pressure when the patient stands and a similar but somewhat smaller drop in the diastolic blood pressure, frequently accompanied with dizziness, fainting and other symptoms.’[3]

In the same year, Wann Langston collated the data from all the published case reports in OH (18 in total) and summarised the most common clinical features associated with postural hypotension such as syncope, anhidrosis, and slow or unchanging pulse rate with changing position. [4]

The research that followed was mainly consisting of case reports or series describing OH associated with different disease processes such as tabes dorsalis, Addison’s disease, diabetes or hypoadrenalism.[5]
In 1956, Wagner and Braunwald identified a series of 3 patients who ‘had severe postural hypotension, hypohidrosis and impotence, a clinical syndrome distinct from the postural hypotension associated with general debility, diabetes mellitus, amyloidosis, Addison's disease and various neurological disorders.’ They described these patients as having ‘primary autonomic failure’ or ‘idiopathic orthostatic hypotension’. [6]

In 1960, Shy and Drager furthered the understanding of idiopathic orthostatic hypotension when they described two cases with ‘signs and symptoms compatible with automatic nervous system involvement and a Parkinson-like syndrome, manifested by rigidity, loss of associated movements, poverty of movements, and a mask-like facies.’ [7] This syndrome is now known as multiple system atrophy (MSA).

In 1976, Davidson and Morgan suggested that idiopathic orthostatic hypotension is a spectrum of disease and noted that patients with OH with no neurological involvement had much better life expectancy than those described by Shy and Drager. [8] This idea was crucial in separating MSA from primary autonomic failure.

The way we currently conceptualise OH was shaped mainly by the 1996 meeting of The Consensus Committee of the American Autonomic Society and the American Academy of Neurology, who issued a definitive statement: ‘Orthostatic hypotension (OH) is a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing. It is a physical sign and not a disease.’ [9] This definition was based on the technology available at the time which was intermittent blood pressure measurements via sphygmomanometer and not the beat-to-beat technology we use today.

Regarding the history of treatments for OH, it is interesting that the non-pharmacological treatments trialled initially by Bradbury and Eggleston, such as increasing fluid intake and abdominal binders, are still in use today.

In 1945, Gregory proposed the use of Desoxycosterone ‘to increase blood volume as a method of maintaining an adequate blood pressure in the upright position’. [10] The idea of using a mineralocorticoid to increase blood volume and therefore improve OH is the same as the underlying principle for the use of Fludrocortisone that is commonly used today.
It was in 1969 that Hickler et al. published a case report in the New England Journal of Medicine describing their success in treating a patient with neurogenic OH with Fludrocortisone.[11]

Ephedrine, which can be considered the therapeutic precursor to Midodrine, was used in the treatment of OH in the 1930s. Wann Langston investigated a patient’s blood pressure response to head up tilt table pre and post Ephedrine administration, and in an interesting diagram showed that there was a much smaller BP nadir and a quicker SBP recovery post Ephedrine administration. It would take until 1981 for Midodrine to be used as a potential treatment for OH.[12]
Figure 1. Timeline of the history of the measurement, definition, and treatment of OH
SECTION 2: Classical Orthostatic Hypotension

2.1 Classical Orthostatic Hypotension (cOH) definition
OH is traditionally defined by consensus statement as a reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing.\[9\] This definition is based on intermittent blood pressure (BP) measurements via sphygmomanometer during a 3-minute assessment.

2.2 Epidemiology of cOH
Orthostatic hypotension is common in older adults and increases in prevalence as we age.\[13-15\] The estimated prevalence of cOH in community dwelling older adults varies from 6-81%, however the pooled analysis from a recent meta-analysis found OH in approximately one in five community-dwelling older people and almost one in four older people in long-term care;\[16\] however, one issue with the estimated prevalence of OH across populations was the significant heterogeneity in the studies included and variability in methods used.

2.3 Symptoms of Orthostatic Hypotension
OH may be symptomatic or asymptomatic and symptoms are often attributed to organ hypoperfusion secondary to the drop in blood pressure.\[17\] As per the consensus definition, symptoms may include ‘light-headedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, and neck ache.’\[18, 19\] The posterior head and neck ache (often in a ‘coat hanger’ distribution) is thought to be due to ischemia of large neck muscles (such as the trapezius).\[20\] The other symptoms such as palpitations, tremulousness, nausea, and vasomotor changes are due to sympathetic hyperactivity and occur in patients with only partial autonomic failure.\[17\]

2.4 The body’s normal physiological response to orthostatic challenge
When a person changes position from lying to standing, approximately 500-1000 mL of blood pools in the veins of the lower limbs and pelvis due to the effect of gravity.\[21\] In addition, this movement of blood to the lower limb/pelvic blood vessels increases the local pressure in those vessels causing a shift of approximately 10% of the fluid into the interstitial space.\[22\] This sudden drop in circulating blood volume causes a decrease in venous return to the heart and, as a result, there is a reduction in stroke volume, cardiac output and arterial blood pressure.\[23\]
In response to this, the body has multiple compensatory mechanisms to counteract the blood pressure drop that include the arterial baroreflex and the skeletal muscle-pump effect. The baroreceptors are in the carotid sinus and the aortic arch and are very sensitive to changes in arterial stretch i.e. arterial blood pressure changes. When arterial blood pressure suddenly falls, the decreased stretch of the baroreceptor walls causes a drop in receptor firing. This results in a parasympathetic ‘vagal withdrawal’ and an increase in sympathetic action from the medulla. These autonomic changes increase cardiac output (by increasing the heart rate) and total peripheral resistance (via arterial vasoconstriction), which results in a temporary improvement in the arterial blood pressure. [23]

This improvement in blood pressure only lasts for a 3-5 beats and to sustain this compensatory response, the amount of blood being returned to the heart needs to be increased. This is where the skeletal muscle-pump effect and postural sway come into action to increase blood return to the heart.[24]

If a person was to stay entirely still while standing, there would be a large amount of venous pooling in the lower limbs. Thankfully this is not the case and we tend to ‘shift’ or sway while standing, alternating pressure from one leg to the other. As a result of this swaying, the muscles of our legs contract and force blood through the one-way valves in the veins and back to the heart. This increase in blood return to the heart, the ‘preload’, helps maintain adequate cardiac output.[25]

2.5 Aetiology of Orthostatic Hypotension
There is a wide variety of causes of OH and often it is multifactorial. One way to approach the assessment and diagnosis of OH is to classify it into neurogenic and non-neurogenic.

2.6 Neurogenic Orthostatic Hypotension
Neurogenic OH refers to a complex group of disorders that can be organised into four categories:[26]

- Autonomic disorders with brain involvement such as synculeinopathies (Multiple System Atrophy, Lewy Body Dementia and Parkinson's Disease) and Wernicke-Korsakoff syndrome.
- Autonomic disorders with spinal cord involvement such as traumatic tetraplegia, spinal cord tumours and multiple sclerosis.
• Acute autonomic neuropathies (e.g. Guillain-Barre syndrome and Botulism).
• Chronic autonomic neuropathies (e.g. diabetic neuropathy, amyloid neuropathy and pure autonomic failure).

There are two recognised pathophysiological mechanisms that impair the ability of a person with neurogenic orthostatic hypotension to compensate for an orthostatic stress:[27]

1. Impaired vasoconstriction due to inadequate release of norepinephrine from sympathetic vasomotor neurons.
2. A blunted ability to increase the heart rate.

A new variant of neurogenic OH called neurogenic hyperadrenergic orthostatic hypotension was proposed by Mar et al. in 2015.[28] This variant appears to behave the same as neurogenic OH with regards blood pressure drops and blunted HR response, but it displays elevated levels of circulating norepinephrine. Unfortunately, there appear to have been no further studies investigating this proposed variant, so little is known about it.

### 2.7 Non-neurogenic Orthostatic Hypotension

Non-neurogenic orthostatic hypotension is most commonly due to ageing, hypovolaemia (dehydration/anaemia/diarrhoea/vomiting/burns), cardiac disease resulting in impaired cardiac output (myocardial infarction, arrhythmia, aortic stenosis), excessive venous pooling (deconditioning, hot environment, prolonged standing) or the use of prescribed medications (diuretics/anti-hypertensives/anti-depressants).[29]

One important contributor to OH, especially in the older adult, is sarcopenia which is strongly associated with OH.[30] Sarcopenia is a complex and multifactorial disease that is traditionally defined as ‘the age-associated loss of skeletal muscle mass and function’[31, 32]. Frailty is conceptualised as a syndrome of reduced physiological reserve resulting in an impaired ability to respond to stressors and an increased vulnerability to adverse outcomes.[33] Sarcopenia is a major factor for the development of frailty if one is conceptualising frailty using the physical phenotype model proposed by Fried et al (a person is frail if they present with three or more of: poor grip strength, slow walking speed, low levels of physical activity, self-reported exhaustion and unintentional weight loss).[34]

A more detailed list of potential causes of OH is outlined in the table below.
Table 1. Causes of OH

| Central Nervous System | Multiple System Atrophy  
Lewy Body Dementia  
Parkinson's Disease  
Wernicke-Korsakoff syndrome  
Pure Autonomic Failure | Cardiac disease | Myocardial infarction  
Arrhythmia  
Aortic stenosis  
Atrial myxoma  
Constrictive pericarditis |
|------------------------|--------------------------------------------------|----------------|-------------------------------|
| Spinal Cord involvement | Traumatic tetraplegia,  
Spinal cord tumours  
Multiple sclerosis  
Subacute combined degeneration  
Syringomyelia | Venous pooling | Ageing  
Frailty  
Warm environment  
Prolonged standing  
Prolonged bed rest |
| Acute autonomic neuropathies | Guillain-Barre syndrome  
Botulism  
Autoimmune autonomic neuropathy  
Porphyria | Medications | Anti-hypertensives  
Beta-blockers  
Alpha-blockers  
Nitrates  
Diuretics  
Anti-psychotics  
Anti-depressants  
Benzodiazepines  
Z-drugs |
| Hypovolaemia | Sepsis  
Burns  
Haemorrhage  
Dehydration  
Diarrhoea/vomiting  
Alcohol | | |
### Table 1 continued. Causes of OH

<table>
<thead>
<tr>
<th>Chronic autonomic neuropathies</th>
<th>Adrenal insufficiency</th>
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<tr>
<td>Diabetic neuropathy</td>
<td>Addison's disease</td>
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<tr>
<td>Amyloid neuropathy</td>
<td>Corticosteroid withdrawal</td>
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<tr>
<td>Lambert-Eaton syndrome</td>
<td>Adrenal destruction</td>
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<tr>
<td>Paraneoplastic syndrome</td>
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<tr>
<td>Familial dysautonomia</td>
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<td>HIV</td>
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2.8 Orthostatic Hypotension and Medications

Unfortunately, prescribed medications are a common cause of OH, especially in older people.[35] The classes of drugs that are often associated with OH include: antihypertensives, antidepressants, benzodiazepines, and antipsychotics.[29] One caveat we must bear in mind when discussing associations between medications and OH in cross-sectional studies is that the medication choice is not blinded in these studies; medications are prescribed for a patient in response to some existing symptoms or pathology. As a result, the pattern of prescribing may also reflect a level of underlying comorbidities or pathophysiology and the association between a medication and OH may also be mediated by the patient’s health status.

2.8.1 Orthostatic Hypotension and Angiotensin-converting-enzyme inhibitors (ACEI)/Angiotensin II receptor blockers (ARB)

There is conflicting evidence on whether ACE inhibitors are associated with OH. In a study that involved patients reporting symptoms of OH via a postal questionnaire, an association was found (Odds ratio = 2.14, 95% CI 1.42 - 3.22).[36] Another study that was a retrospective chart review of veterans attending a geriatric clinic, found that lisinopril was associated with 60% of the OH cases identified (determined by a single BP measurement after 3 minutes of standing).[35] However, in studies that had objective measurements of blood pressure during an active stand, there was no association found between ACE inhibitors and OH.[37-41] In fact, in one study the use of ACE inhibitors was found to be protective against OH in hypertensive individuals.[42] No association has been found between Angiotensin II receptor blockers (ARB) and OH in the literature so far.[41, 43, 44]

2.8.2 Orthostatic Hypotension and Calcium Channel Blockers (CCB)

The proposed mechanism of action as to how CCBs contribute to OH is that they cause a drop in the total peripheral resistance by vasodilating arterial smooth muscles more than the venous smooth muscles. They do this by acting on voltage dependent calcium channels in vascular smooth muscle and the heart. CCBs are not all the same and each drug in this class has a different vascular/cardiac effect ratio. The non-dihydropyridine CCBs (Verapamil and Diltiazem) also inhibit atrioventricular conduction, which can impair the compensatory tachycardic response to the blood pressure drop.[45] One paper looked at and compared the associations between the two classes of CCBs and OH. In that study, the authors found that non-dihydropyridine CCBs are associated with OH but dihydropyridine CCBs are not.[41]
A randomised controlled trial (RCT) looking at the safety and efficacy of Nicardipine (a dihydropyridine CCB) also found no association between Nicardipine and OH.[46] There have been numerous studies that have found an association between CCBs and OH[47-52], with odds ratios ranging from 1.66 (95% CI 1.11 - 2.48)[53] to 5.29 (1.03 - 27.14).[54]

2.8.3 Orthostatic Hypotension and Alpha-blockers
The proposed mechanism of action as to how alpha-blockers contribute to OH is that they bind to the postjunctional alpha-1-adrenergic receptors. These receptors are mainly found in the vascular smooth muscle and by binding to these receptors, alpha blockers block norepinephrine from binding. This results in arterial vasodilation and a drop in the systemic blood pressure that is exacerbated by venodilation upon standing.[55, 56] The association between alpha-blockers and OH is well established with numerous studies finding a strong association between the two.[37, 41, 42, 53, 57-60]

One important thing to note is that Tamsulosin is considered a more selective alpha-blocker than the other drugs in the class. Tamsulosin has an affinity for a specific alpha receptor called the alpha-1A-adrenergic receptor and this is posited as the reason why Tamsulosin has not been associated with OH in RCTs.[61, 62]

2.8.4 Orthostatic Hypotension and Beta-blockers
The proposed mechanism of action as to how beta-blockers contribute to OH is that they impair the ability to mount a HR response to orthostasis.[63] It has been repeatedly found that individuals with OH were more frequently treated with beta-blockers than individuals without OH. Beta-blockers are frequently found to be strongly associated with OH [40, 41, 47, 57, 58, 64] but there have been some studies suggesting that beta-blockers may improve OH.[65-67] This conflicting evidence can be explained by the fact that beta-blockers are a heterogeneous class of drugs. Each generation of beta-blockers and each beta-blocker has differing levels of affinity for the various alpha (A1 and A2) and beta (B1, B2, B3) receptors in the body and different levels of intrinsic sympathomimetic activity.[68, 69]

2.8.5 Orthostatic Hypotension and Diuretics
The proposed mechanism of action as to how diuretics contribute to OH is that they promote salt and water loss, therefore reducing blood volume and ultimately cardiac output. Loop diuretics are also thought to cause dose-dependent vasodilatation by stimulating prostaglandin production in the renal and peripheral vasculature.[70, 71]
Diuretics in general have been associated with OH that meets the DBP criteria.[52] Loop diuretics have been associated with OH in 2 studies[70, 72] and thiazide diuretics have been associated with OH in one study.[35]

2.8.6 Orthostatic Hypotension and Nitrates

The proposed mechanism of action as to how nitrates contribute to OH is that nitrates activate nitric oxide dependent signalling pathways that lead to vascular smooth muscle cell relaxation and dilatation. This hypotensive effect is well documented[73] and persists even after the nitrates have left the body.[74] Nitrate use has been associated with OH in several studies.[40, 70, 75]

2.8.7 Orthostatic Hypotension and stopping antihypertensives

There is one RCT that investigated the benefits of stopping anti-hypertensives in patients who have OH and mild cognitive impairment, which suggested that there may be a benefit in stopping anti-hypertensives as a treatment option.[76]

2.8.8 Orthostatic Hypotension and Antidepressants

Antidepressants in general have been associated with OH in the Systolic Blood Pressure Intervention Trial (SPRINT) [58] and TILDA [64] studies. They have also been associated with orthostatic intolerance symptoms in a postal questionnaire study (Odds ratio = 2.14, 95% CI 1.42 - 3.22).[36]

2.8.9 Orthostatic Hypotension and Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin–norepinephrine reuptake inhibitors (SNRIs)

The proposed mechanism of action as to how SSRIs contribute to OH is by inhibiting cardiac and vascular Na⁺, Ca²⁺ and K⁺ channels that can lead to bradycardias/arrhythmias, reduced cardiac contractility and hypotension.[77] While SSRIs are considered less likely to cause OH when compared to older antidepressants,[63] people who are prescribed SSRIs are twice as likely to have OH compared to those not prescribed them.[53, 78, 79]

SNRIs are SSRIs with additional noradrenaline re-uptake inhibition. One important point to note is that in contrast to the bradycardias associated with SSRIs, tachycardias are more commonly associated with SNRIs.[80, 81] There is very little data available on the relationship between SNRIs and OH. It has been suggested that Venlafaxine may cause OH in more than half of older adults and this has been attributed to its noradrenergic action.[82] There was an association
found between Duloxetine and OH in a meta-analysis of 42 placebo-controlled clinical trials of 8504 patients who were treated with Duloxetine.\[83\]

### 2.8.10 Orthostatic Hypotension and Tricyclic Antidepressants (TCAs)

The proposed mechanism of action as to how TCAs contribute to OH is via a blockade of postsynaptic alpha-1-adrenergic receptors.\[79, 84-86\] TCAs’ cardiovascular effects including arrhythmias and OH are well established, with odds ratios a high as 4 being found in some studies.\[53, 87\]

### 2.8.11 Orthostatic Hypotension and Benzodiazepines (BZDs)

The proposed mechanism of action as to how BZDs contribute to OH is due to a combination of BZ2- and BZ3-mediated myorelaxation, exacerbating the peripheral resistance fall and lower body venous pooling.\[88\] A negative inotropic effect has been described for BZDs.\[89, 90\] BZDs have also shown the ability to induce a depression of baroreflex responses and a sustained decrease of sympathetic tone.\[91\] BZDs can cause OH in healthy individuals including astronauts\[92\] and healthy older people.\[93\] A study with Temazepam suggested that the OH effect appears to be dose-dependent.\[93\] Another study has shown that BZDs in older people have an overall blood pressure lowering effect as well as being associated with OH.\[88\]

### 2.8.12 Orthostatic Hypotension and Antipsychotics

The proposed mechanism as to how antipsychotics contribute to OH is the same as BZDs: blockade of postsynaptic alpha-1-adrenergic receptors. All antipsychotics are associated with OH\[94, 95\] but some such as Clozapine, Quetiapine and Risperidone are more associated with a hypotensive effect, which is likely due to their higher affinity for alpha-1-adrenergic receptors.\[96, 97\] Among antipsychotics, Clozapine and Quetiapine have been reported as having the greatest association with OH, with prevalence as high as 24% and 27%.\[97\]

### 2.9 Orthostatic Hypotension and Ageing

Ageing is a complex, heterogenous, and multifactorial process that is characterised by ‘intrinsic deterioration with time that causes decreases in strength, endurance and fecundity, and increases in disease susceptibility and likelihood of death.’ \[98\] The process of ageing is unknown and there are a large variety of theories of ageing proposed across multiple different categories including evolutionary, molecular, cellular, and systemic. \[99\] The cardiovascular effects of ageing include endothelial dysfunction. Increased arterial stiffness, increased left ventricular stiffness, decreased baroreflex sensitivity and autonomic function. \[100\]
Multimorbidity becomes increasingly prevalent as we age. Barnett et al. found increasing rates of multimorbidity (at least two chronic conditions) in a cross-sectional study of Scottish community-dwelling adults; with 30.4% of adults aged 45-64yrs, increasing to 64.9% of adults aged 65-84yrs, and again increasing to >80% for adults >85yrs. [101]

OH increases with age, and the relationship is complex and likely due to a combination of factors including the following: an increased burden of chronic disease, an increased likelihood of being on more than one chronic medication,[102] decreased baroreflex sensitivity and autonomic function, increased arterial stiffness,[103] reduced capacity to vasoconstrict peripherally,[104] and/or decreased muscle strength resulting in impaired muscle pump strength.[105] Healthy older people appear to be able to maintain their blood pressure against gravity under usual circumstances. This is accomplished by less reliance on heart rate and perhaps greater dependence on peripheral vasoconstriction, as manifested by the increase in diastolic pressure during tilting.[71]

2.10 Orthostatic Hypotension and Hospital Presentations
Considering that the demographics of the western world is shifting to an increasing ageing population and that OH increases in prevalence as we age, it should not be a surprise that hospital presentations for OH are also increasing. During the year 2004 in the United States of America, there was a rate of 36 hospitalisations per 100,000 US adults. This rose to 233 per 100,000 when considering adults aged 75 years or older.[106] In the decade between 2008 and 2017, NHS England experienced a 110% increase in presentations to hospital with OH.[107]

2.11 Orthostatic Hypotension and Mortality
There appears to be an association between how long it takes for people to recover their blood pressure within 3 minutes after standing and their likelihood of dying in the following 2 years. In a study by Lagro et al., participants who did not recover their SBP by 3 minutes after standing were, compared to those who fully recovered, more likely to have died in the following 21 months.[108]

Pooled analysis from a separate meta-analysis looking at the relationship between OH and major adverse cardiovascular events, found that the relationship between OH and death could not be explained by the effect of potentially confounding factors such as cardiovascular risk factors, age or sex.[109] This suggests that OH may be an independent risk factor for major adverse cardiovascular events and death.
2.11 Reproducibility of Orthostatic Hypotension Measurements
As discussed previously, there are a wide variety of factors that can contribute to a person’s ability to compensate for the orthostatic challenge of standing up. In this context and given that people’s physiological status and extrinsic determinants (e.g. medications) may vary over time, an important consideration is the reproducibility of OH measurement within the same person. This reproducibility can be influenced by many factors including the underlying cause of OH,[110] the time of year,[111] most recent meal,[112] and hydration status.[113] A follow-up study of 125 individuals from the Irish SHARE cohort found that there was ‘moderate reliability and substantial natural variation over a 4-12 week period’ in the blood pressure and heart rate responses in the active stand.[114]

2.12 Orthostatic Hypotension and the sit to stand test
For some frail older or disabled patients, transitioning actively from lying supine to standing upright for 3 minutes may be an impossible task. In such cases, an alternative to the active stand has been proposed that consists of a sit to stand test with modified diagnostic criteria: SBP drop at least 15 mmHg or a DBP drop at least 7 mmHg.[115] However, Cooke et al. found that this approach has a low diagnostic accuracy with a sensitivity of 15.5% and a specificity of 89.9% when compared with a ‘passive’ Head-Up Tilt table test.[116] A ‘passive’ Head-Up Tilt table test involved placing a person on a tilt table and tilting them to a positive 70° angle for 3 minutes while monitoring their haemodynamic response to the tilt.

2.13 Non-Pharmacological Treatment of Orthostatic Hypotension

Education
Patient education is a common intervention in clinical practice because of its low cost and simplicity. The key components of education should include a lay explanation of how OH occurs, recognition and awareness of OH symptoms, and avoidance of precipitating factors such as sudden postural changes, alcohol, dehydration and extreme heat.[117] Another component of patient education is the advice to stand up slowly. It has been shown that standing up slowly can help reduce the initial SBP drop and aid the SBP recovery when compared to standing up at a faster speed.[118]
Physical Counter Manoeuvres (PCMs) and Compression garments

As discussed previously, approximately 500-1000 mL of venous blood pools in the lower limbs and pelvis when a person changes position from lying to standing. Physical countermaneuvers are patterns of isometric contraction of the lower limb muscles that increase both venous return to the heart (therefore cardiac output) and total peripheral resistance.[119-121] The PCMs commonly used clinically include toe-raising, leg-crossing, and contraction of the quadriceps and gluteus muscles.[117] Compression garments also aim to reduce venous pooling in the lower limbs and abdomen by compressing the capacitance beds. The capacitance beds of the legs account for less than 30% of the venous pooling when compared to the pelvic beds.[122] This can help explain why calf and thigh compression stockings appear less effective than abdominal compression.[123] While combined compression garments of the legs and abdomen is the most effective method for preventing venous pooling, abdominal binders alone provide about 2/3 of the benefits and are much better tolerated.[124] There is a minimum level of compression required for this compression to be effective, which can be uncomfortable for some wearers.[125] If these minimum levels of compression are achieved, there is level 1 evidence to support the use of compression binders in numerous different OH populations including community dwelling older adults and those with neurogenic OH.[126] Unfortunately, compression garments are generally not viewed favourably by patients due to discomfort, the difficulties taking them on/off and the general unaesthetic appearance of wearing them.[127]

Increasing fluid intake and salt supplementation

Both increasing fluid intake and salt supplementation aim to avoid hypovolaemia and improve intravascular volume by increasing fluid retention. The European Society of Cardiology (ESC) advises ‘in the absence of hypertension, patients should be instructed to have a sufficient salt and water intake, targeting 2–3 L of fluids per day and 10 g of sodium chloride’. [128] There is an additional mechanism by which increased fluid intake is thought to improve OH, which is by drinking 500 mL fluid boluses that trigger the sympathetic osmopressor response.[129, 130] In healthy subjects it has been shown that there are improvements in orthostatic intolerance, systolic blood pressure during a head-up tilt after ingesting 500 mL of water and that this effect is largely driven by increase in total peripheral resistance.[131] This effect has also been found in patients with neurogenic OH[132] and healthy older adults.[133] Interestingly, this osmopressor response is reduced if salt is added to the water ingested, as shown by this study comparing the ingestion of salt water vs plain water.[134]
A recent systematic review and meta-analysis suggested that there are both symptomatic and physiological improvements in the short term from salt supplementation in OH but that the evidence base is of low quality at present.[135]

**Sleeping with head up (SHU)**
Sleeping ‘head up’ (SHU) has been a mainstay in OH treatment since it was first described by MacLean and Allen over 70 years ago.[136] It is thought to work by reducing nocturia, therefore increasing the amount of salt and water retained in the body. This effect may be coupled with the lower limb oedema caused by SHU providing a buffer that decreases lower limb venous pooling.[137] There have been multiple case series and reports that have demonstrated a benefit to SHU in patients with OH, especially those with neurogenic OH and if used in combination with Fludrocortisone.[138] However, the only RCT that investigated the effect of SHU and OH found that there was no difference from placebo.[139]

**Exercise training**
There are two separate components to using exercise as a treatment for the prevention and management of OH. The first is to stay active and healthy and avoiding bed rest[140, 141], muscle loss[142], and malnutrition[143], as it is easier to retain function than attempt to regain it. The exercise training component mainly focuses on resistance training of the lower limbs to improve lower limb muscle strength and cardiorespiratory fitness.[144] Simple exercise regimes involving ‘10 full extensions of the lower limbs, starting from 60° flexion of hip and 90° flexion of knee and ankle joints, against the resistance of an elastic band’ have been shown to improve OH.[145]

**2.14 Pharmacological Treatment of Orthostatic Hypotension**

**Midodrine**
Midodrine is a prodrug that is converted to its active metabolite desglymidodrine and acts as a sympathomimetic agent. Desglymidodrine has a high affinity for the alpha-1-adrenergic receptors of the body, which increases blood pressure via arterial and venous vasoconstriction.[146] It is considered first line pharmacological therapy alongside Fludrocortisone for OH by the ESC.[128] There are three RCTs that have shown improvement in both objective (SBP drop changes) and subjective (orthostatic intolerance symptoms) with Midodrine therapy in neurogenic OH.[147-149] One RCT had similar results with Midodrine
therapy in severe symptomatic non-neurogenic OH.[150] There has also been a prospective observational study that confirmed its effectiveness as well as demonstrating that it is a safe and well tolerated medication in older adults.[151]

However, a retrospective analysis of the Tennessee Medicaid program database found that there are high rates of discontinuing Midodrine with a median time for discontinuation of 304 days.[152] Unfortunately, as this study is based on a Medicaid database of medications being dispensed, there is no available information on the reasons for discontinuation.

**Fludrocortisone**

Fludrocortisone is a synthetic mineralocorticoid that results in sodium and water retention and therefore increases plasma volume.[153] It is also thought to have a mechanism that increases the sensitivity of alpha-adrenoreceptors.[154] Its ability to raise blood pressure appears to persist even after the sodium and plasma increases normalise after chronic use.[155] It is considered first line pharmacological therapy alongside Midodrine for OH by the ESC.[109]

There are two RCTs that compared Fludrocortisone therapy to placebo/non-pharmacological management. One RCT was of 30 patients and demonstrated an improvement in SBP drop and recovery during an active stand after taking Fludrocortisone for 7 days compared to placebo.[156] The second RCT compared Fludrocortisone treatment (6 patients) to Domperidone (6 patients) or non-pharmacological treatment (9 patients). It found that there was a statistically significant improvement in orthostatic symptoms when compared to non-pharmacological treatment and a trend towards improvement on tilt table testing.[157] Similarly, in a case control study of 6 patients with neurogenic OH, it was shown that Fludrocortisone in combination with SHU improved SBP drop and recovery during an active stand.[158] There are multiple case series demonstrating a benefit from Fludrocortisone, sometimes in combination with SHU, in patients with neurogenic OH.[153, 159-164]

One study followed 7 patients started on Fludrocortisone for neurogenic OH for up to 14 years and reported on both the acute and chronic effects to the therapy.[155] In the first six months of treatment, most patients experienced an improvement in SBP and symptoms. However, there were significant hypertension and electrolyte related complications associated with long term use. These issues with tolerability have been replicated in a study looking at Fludrocortisone in the older adult, which found that Fludrocortisone is an effective treatment if used in the short term (less than 6 months) but that it is poorly tolerated after that due to side effects.[165] Additionally, a retrospective study of the Tennessee Medicaid program database found similar issue with the long term tolerability of Fludrocortisone.[152]
Another issue associated with chronic use of Fludrocortisone is the risk significant nocturnal hypertension which increases the risk of heart attacks and strokes.[166] When comparing the safety profiles of Midodrine vs Fludrocortisone, patients who are prescribed Fludrocortisone had higher rates of all-cause hospitalizations and this effect was particularly pronounced in patients with heart failure.[167]

**Droxidopa**

Droxidopa (L-threo-3,4-dihydroxyphenylserine) is a prodrug of norepinephrine, can be administered orally, and is a new proposed drug in the treatment of neurogenic OH.[168] As discussed previously, one of the pathological mechanisms proposed for neurogenic OH is impaired vasoconstriction due to inadequate release of norepinephrine from sympathetic vasomotor neurons. The aim of droxidopa therapy is to increase the norepinephrine levels and restore the body’s ability to vasoconstrict.

A systematic review and meta-analysis from 2016 found 4 RCTs comparing Droxidopa to placebo.[169] In their analysis, Droxidopa was effective at reducing symptoms, improving functional ability, and SBP response to standing and it also had the same rates of adverse events when compared to placebo.[169] It is unclear whether Droxidopa has lasting effects on SBP or symptoms as the longest duration of the RCTs was 8 weeks. There is currently an RCT (NCT02071459) studying the safety profile of Droxidopa in MSA over the course of 3 months that has yet to be completed. Additionally, the findings that Droxidopa is safe when compared to placebo have not been replicated and there are significant concern regarding the risks of supine hypertension.[170] In clinical practice, Droxidopa is very seldom used.

**Pyridostigmine**

Pyridostigmine bromide is a reversible inhibitor of acetylcholinesterase that is used off-label for the treatment of nOH. [171] Its mechanism of action is that by inhibiting acetylcholinesterase, there is an increase in acetylcholine signal transmission in the autonomic ganglia and an enhancement in arterial baroreflex function. There is a much greater level of activity through the autonomic ganglia during orthostasis than when supine, so the effect of Pyridostigmine was theorised to improve orthostatic BP while also not causing the supine hypertension associated with other agents such as Fludrocortisone and Midodrine. [172] Singer et al were the first to use Pyridostigmine as a treatment for nOH in an open label single dose trial of 15 patients with nOH. In this study, there were improvements in both orthostatic BP and OI with a single dose of 60mg.
Pyridostigmine. [172] Singer et al followed up that study with a double-blinded, randomized, 4-way cross-over study of Pyridostigmine alone or with low-dose Midodrine (5mg). This study found that Pyridostigmine alone can improve orthostatic BP and OI in patients with nOH without worsening supine hypertension but it was more effective when used in combination with Midodrine.[173] Pyridostigmine does not appear to be of therapeutic benefit in advanced nOH. [174] However, it may have synergistic properties when used in combination with Atomoxetine in patients with severe nOH and this combination can improve both orthostatic BP and OI. [175]

The cause of nOH appears to influence the effectiveness of Pyridostigmine as a therapeutic option, it is of benefit to patients with nOH secondary to spinal cord injury [176] but is inferior to fludrocortisone in the treatment of OH secondary to PD. [177] It can also be a useful adjunctive therapy in patients with nOH and who are suffering from other autonomic symptoms such as bladder dysfunction [178] and constipation [179]. Pyridostigmine is a well-tolerated drug, in a follow-up survey study only 3 out of 28 patients had stopped taking Pyridostigmine due to unacceptable side effects which included worsening of symptoms (2/3) and bladder problems (1/3). [180]

Atomoxetine
Atomoxetine is a selective norepinephrine transporter (NET) inhibitor, usually used in the treatment of attention deficit hyperactivity disorder (ADHD), that increases norepinephrine in the synaptic cleft. [181] This increase in norepinephrine in peripheral noradrenergic fibres results in a pressor response and increased BP. However, the increased norepinephrine levels cause central activation of alpha-2-adrenergic receptors and therefore a reduction in norepinephrine release and sympathetic activity (in a ‘Clonidine-like’ effect). It is thought that in healthy subjects, ‘these effects counteract each other, and no significant increase in BP is observed’. [182]

This view has recently been challenged by a systematic review and meta-analysis on the cardiovascular effects of Atomoxetine in young people which found atomoxetine caused significant increases in HR and SBP when compared to placebo. [183] Shibao et al were the first to propose the use of Atomoxetine in patients with nOH in a randomized, placebo-controlled crossover study that explored the haemodynamic effects of 18mg of Atomoxetine on patients with either central or peripheral autonomic failure. [184] They found that there was a significant pressor response to Atomoxetine only in patients with nOH secondary to central autonomic failure (mean 45mmHg increase for orthostatic SBP). There have been four studies [175, 185-
and one case report [188] that have found SBP and symptomatic improvements in patients with OH when treated with Atomoxetine. Two of the studies compared Atomoxetine to Midodrine [185, 186] and found that Atomoxetine may be superior to Midodrine for the improvement of orthostatic symptoms. The two other studies administered Atomoxetine with either Pyridostigmine [175] or Yohimbine [187] and found a treatment benefit from the combination therapy. Atomoxetine is currently not a licensed treatment for OH and is not used routinely.

Yohimbine

Yohimbine is an alpha-2-adrenoreceptor antagonist that increases sympathetic nervous system activity and an enhancement in arterial baroreflex function. Des Lauriers et al were the first to use Yohimbine as a therapeutic agent for OH in a case series of 11 patients with OH secondary Clomipramine. [189] Further studies have shown that Yohimbine may be effective in improving OH secondary to Clomipramine, [190, 191] diabetes, [192] and nOH. [193, 194] Yohimbine appears to be more effective than Pyridostigmine but there appears to be no synergistic effect if both are used together [174] but there does appear to be a synergistic effect when administered with Atomoxetine. [187] Yohimbine is of no treatment benefit in patients with OH secondary to PD. [195] One limitation of studies on Yohimbine is that most studies are crossover studies with no washout phase.

Erythropoietin (EPO)

Erythropoietin (EPO) is the main hormone in the regulation of erythropoiesis and its primary action is the proliferation and differentiation of erythrocytic progenitor cells in the bone marrow. Haematocrit, haemoglobin (Hb), and red cell mass levels are regulated by EPO and tissue hypoxia and anaemia are the two key drivers of increased expression of the EPO gene in the kidneys. [196]

In patients with nOH, there is reduced sympathetic innervation to the kidneys and, as a result, there is a blunted EPO response to tissue hypoxia and anaemia. [197] This blunted EPO response is thought to be the cause of anaemia in autonomic neuropathy. [198] Hoeldtke and Streeten were the first to use EPO as an adjunctive therapy to fludrocortisone in the treatment of nOH in 1993. They published a case series of 8 patients with nOH who were treated with EPO and Fludrocortisone, all patients had improvements in orthostatic BP measurements, 6/8 had improvements in orthostatic dizziness, and 3/8 developed supine hypertension. [199] There have been no RCTs studying the treatment effect of EPO in nOH but there are multiple small
studies and case series that have shown that EPO administration in nOH improves haematocrit levels and orthostatic BP. [199-204] The mechanism for how EPO causes these effects is still unknown but there are numerous theories including: increasing red cell mass and therefore blood volume, EPO administration causing increased norepinephrine levels and therefore vasoconstriction, or increased Hb resulting in increased nitric oxide (NO) binding and therefore decreased vasodilatory ability.[200]

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

Indomethacin is a prostaglandin synthetase inhibitor and the mechanism of action for how it improves OH is poorly understood. [205] One suggested mechanism is that, in patients with nOH (a pathological state with inadequate release of norepinephrine), Indomethacin inhibits prostaglandin synthesis resulting in an increased sensitivity of vascular receptors to noradrenaline and angiotensin II, [206] while another study has proposed that it may also increase reflex vasoconstriction. [207]

Smythies et al first proposed the use of aspirin to treat diarrhoea in a patient diagnosed with ‘idiopathic orthostatic hypotension’ as they believed that ‘an unbalanced action of prostaglandins’ played a role in both the hypotension and diarrhoea. [208] Four years later, Kochar et al were the first to publish evidence favouring the use of NSAIDs in their case series of 4 patients with ‘idiopathic orthostatic hypotension’ who had an improvement in BP and symptoms when treated with a yearlong course of Indomethacin (75-150mg/day). [209]

However, there have been variable results for Indomethacin as a treatment in one small RCT (n=12) [210] and subsequent case series/reports. [211, 212] Indomethacin’s use is limited in clinical practice due to the poor evidence base and its side effects which include headaches, gastrointestinal bleeding, renal failure, and electrolyte abnormalities.[205]

Ibuprofen is also a non-steroidal anti-inflammatory drug (NSAID) but it was found to have no significant pressor effect when compared to indomethacin or placebo.[194]
Table 2. Treatment of OH

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<th>Non-pharmacological</th>
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<td>Patient education</td>
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<tr>
<td>Increasing fluid intake</td>
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<tr>
<td>Salt supplementation</td>
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<tr>
<td>Sleeping with head up</td>
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<td>Exercise training</td>
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<tr>
<th>Pharmacological</th>
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<tbody>
<tr>
<td>Midodrine</td>
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<tr>
<td>2.5-10mg BD/TDS</td>
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<tr>
<td>Fludrocortisone</td>
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<tr>
<td>100-500mcg once daily</td>
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<tr>
<td>Droxidopa</td>
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<tr>
<td>100-300mg TDS</td>
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<tr>
<td>Pyridostigmine</td>
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<tr>
<td>30-60mg BD/TDS</td>
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<td>Atomoxetine</td>
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<tr>
<td>18mg once daily</td>
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<td>Yohimbine</td>
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<td>4mg TDS</td>
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<tr>
<td>Erythropoietin (EPO)</td>
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<td>25 IU/kg subcutaneously three/week</td>
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SECTION 3: FINGER ARTERIAL PRESSURE (FinAP) TECHNOLOGY AND THE ACTIVE STAND

3.1 The introduction of continuous beat-to-beat blood pressure monitoring
Since Hales first invasively measured blood pressure using a brass pipe on a horse in 1718, there have been significant changes to how we measure blood pressure. The next step was the development of the sphygmomanometer by Von Basch, the popularisation of its use by Riva Rocci, and its first application in a clinical setting by Cushing in 1903.[213] The sphygmomanometer remained as the standard method to measure blood pressure up until the 1980s, when Wesseling et al. described a new method allowing measurement of continuous beat-to-beat blood pressure measurements using finger arterial blood pressure (FinAP).[214]

3.2 Continuous beat-to-beat blood pressure methodology
FinAP is based on the volume clamp method originally described by Penaz in 1973 as a technique to measure blood pressure in the finger.[215] In this method, a cuff is placed around the finger and keeps the diameter of the digital artery constant via ‘clamping’. An infrared photoplethysmography device, built into the cuff, can measure any changes in the artery diameter/volume. In response to these fluctuations and changes, the cuff can increase or decrease the pressure it is applying to the artery so as the diameter is kept constant. The recordings attained from the FinAP device are similar in appearance to arterial waveforms and are considered a validated way to estimate intra-arterial pressure. These recording also have the advantage over traditional sphygmomanometer readings as they can provide a blood pressure value for each heartbeat. The Finometer (Finapres Medical Systems BV, Arnhem, the Netherlands) device is an updated version of the original FinAP technology and utilises a digital filter, height correction unit, dynamic set-point controller (‘Physiocal’), and a correctional algorithm to derive a more accurate brachial pressure.

3.3 Continuous beat-to-beat blood pressure validation
The Finometer has been found to give good estimations of SBP/DBP/HR and is considered accurate (but not precise) when compared to the gold standard blood pressure measurement via auscultatory sphygmomanometry.[216-219] In some units, the Finometer is used clinically to assess relative changes of blood pressure, for which, it is considered accurate.[220] When using beat-to-beat technology to assess OH, there are now 180 separate timepoints to apply the 2011 consensus definition of OH. This poses a challenge of interpretation; for example, if a person fulfils the cOH criteria for only 1 or 2 seconds, does that mean he/she has OH?
Since a beat-to-beat approach also measures the larger initial orthostatic blood pressure drop that the sphygmomanometry would miss, there is a risk of overestimating OH and it is also unclear if it would be clinically meaningful. In that regard, van der Velde et al. found that using 5 second averages of SBP/DBP is better at identifying OH when compared to beat-to-beat measurements.[221]

3.4 Active Stand Protocol

As outlined above, there are multiple factors that can affect a person’s haemodynamic response to the active stand including time of day, temperature, hydration status, most recent meal, nicotine, and caffeine. As a result, the active stand protocol aims to standardise the approach to reduce the influence of these factors so a person’s active stand result can be more easily compared with other people and with previous active stands performed by the same person.[220]

The following instructions are guidelines on how to reduce external factors on influencing the active stand: [220]

- The active stand should be performed in a quiet room kept at a temperature of 21–23 °C and should be performed in the morning if possible.
- The patients should fast for the 2 hours prior to the active stand and should avoid nicotine, caffeine, and exercise in the 12 hours prior as well.
- The patient should continue on all their regular medications for the initial active stand, but withdrawal of medications can be considered for repeat active stands to assess culprit medications.
- The patient should lie supine for 10 minutes prior to standing to allow for cardiovascular stabilisation, system calibration, and for baseline blood pressure and heart rate readings to be taken.
- The patient is then asked to stand up as quickly as possible and they should stand unaided for 3 minutes.
- During the active stand, beat-to-beat blood pressure and heart rate readings are recorded, and patients are asked whether they experience any symptoms (dizziness, light-headedness or unsteadiness) at the 1- and 3-minute marks of the active stand. Other than responding to these questions, the patient should avoid talking during the active stand as it can interfere with blood pressure measurements.
Figure 2. Labelled photograph of Finometer device connected to the doctor.
SECTION 4: INITIAL ORTHOSTATIC HYPOTENSION

4.1 Initial Orthostatic Hypotension definition (iOH)
It has been known that there is a drop in blood pressure drop immediately on standing for over 150 years but it was not possible to measure this drop until the invention of FinAP technology in the 1970s.[222] There was no formal definition of iOH until the 2011 consensus meeting of the American Academy of Neurology and the American Autonomic Society issued their diagnostic criteria for iOH as ‘a reduction in SBP of >40mmHg and/or decrease in DBP of >20mmHg, presenting within the first 15 seconds of standing, and correcting within 30-60 seconds.’[18] Other later definitions have argued that this blood pressure drop must be accompanied by symptoms such as ‘dizziness, light-headedness, unsteadiness’ to be considered iOH.[222] There are also conflicting opinions as to whether iOH represents a pathological state or is just a normal physiological reaction to gravity. Some have argued that the current definitions capture a normal physiological response and that the definition be revised to a 60/40mmHg drop instead.[223] A faster standing speed is associated with a greater initial drop but is also associated with a greater rise in HR and a quicker recovery 10 to 20 s after standing.[224]

4.2 Initial Orthostatic Hypotension prevalence
Regardless of which population is being studied, iOH appears to be a common phenomenon. It is present in 20% of teenagers and young adults and up to 58% of teenagers and young adults who experience orthostatic dizziness.[225] It is also present in 20% of community dwelling adults >50 years old if OI is included in the definition,[226] and 10% of nursing home residents.[227]

4.3 Initial Orthostatic Hypotension pathophysiology
iOH is a distinct entity when compared to traditional OH due to the more dramatic blood pressure drop (40/20mmHg vs 20/10mmHg) and the quick recovery of blood pressure as opposed to the sustained deficit in traditional OH. Its pathophysiology is not fully known but there are two key mechanisms that are thought to contribute to the rapid change in blood pressure; rapid local vasodilation after muscular activation and sympathetic withdrawal secondary to increased pressure in the right atrium.[228]
iOH is not present on passive tilt table testing [229] which may be due to the lack of lower limb muscle contraction or that passive tilt testing change of body positioning is too slow to generate the initial drop. After the initial muscle contraction, the muscle fibres relax and there is rapid and proportional localised vasodilation. This decrease in lower limb total peripheral resistance (TPR) is thought to result in blood pooling and therefore a drop in overall blood pressure.[18, 225] The sympathetic withdrawal is related to the muscle contraction, the muscle contraction causes an increase in venous return to the heart. This increase in right atrial pressure activates the cardiopulmonary mechanical baroreceptors which, in turn, cause a sudden brief drop in TPR.[228] Both mechanisms are secondary and proportional to lower limb muscle contraction, which could explain why teenagers, young adults[225], and healthier older adults[230] are more likely to have iOH than frail older people [226]. Unlike cOH, there appears to be no diurnal variation in iOH, but it can be worsened by prolonged recumbency prior to standing.[231, 232] Since it is more prevalent in healthier populations and does not appear to correlate with underlying diseases, it has been argued that iOH is a normal but exaggerated physiological pattern caused by a mismatch between the drop in TPR and cardiac output (CO).

4.4 Initial Orthostatic Hypotension and Syncope
iOH is a common finding in teenagers and young adults who are presenting with near-syncope.[225] It was also identified as the cause of syncope in 11.2% of patients being investigated for unexplained syncope at a specialist syncope unit[233] and as the cause of syncope in 7% of patients presenting to the emergency department with presyncope/syncope.[234]

4.5 Initial Orthostatic Hypotension and Falls
iOH also appears to be associated with an increased risk of falls.[226] The magnitude of the initial drop appears to be related to a history of previous falls in nursing home residents.[227]

4.6 Initial Orthostatic Hypotension and Mortality
The initial drop within the first 15 seconds of standing does not appear to be associated with increased mortality risk but the recovery pattern afterwards may be associated with an increased mortality rate.[108]
4.7 Initial Orthostatic Hypotension and Frailty

There is conflicting evidence on the relationship between iOH and frailty. Two smaller studies have found a higher prevalence of frailty in people with iOH, one cohort was community based older adults[226] and the other were nursing home residents[227]. The Malaysian Elders Longitudinal Research (MELoR) study found that people with iOH had better physical performance, cognitive scores, and were less likely to be frail.[230] This is attributed to the reduced standing speed of the frail patient, which results in less dramatic initial haemodynamic challenges.[118]

4.8 Initial Orthostatic Hypotension Management

Two management strategies have been shown to improve iOH in patients: standing up more slowly and using PCMs after standing. Standing up slowly results in less intense and longer muscle activation which may result in less localised vasodilation.[118] PCMs are thought to work by quickly preventing excessive blood pooling in the lower limbs and helping the return of blood to the heart.[235]
SECTION 5: IMPAIRED STABILISATION OF BLOOD PRESSURE

5.1 Impaired stabilisation definition
There is no agreed or formal definition for impaired stabilisation of blood pressure during the active stand, but it has been described in the literature as a persistent blood pressure drop of 20/10mmHg at time points between the 30-60 seconds mark of the active stand.[108, 114, 236] From The Irish Longitudinal Study on Ageing (TILDA) sample, it was shown that non-recovery of BP by 40 seconds should be considered abnormal in the general population.[237] A separate prospective longitudinal study has found higher sensitivity (0.91) and specificity (0.88) for diagnosing OH using the impaired stabilisation definition (>30 seconds).[238]

5.2 Impaired stabilisation pathophysiology
Impaired stabilisation is thought to represent a subclinical pathological state that is the result of a combination of physiological impairments including increased arterial stiffness, impaired sympathetic control resulting in a reduced ability to vasoconstrict, and arterial baroreceptor dysfunction.[236, 239] It is also more common in those who have a diagnosis of atrial fibrillation, which is often reflective of underlying baroreflex dysfunction.[240] Impaired stabilisation is also associated with higher mortality rates at 5-year follow up when compared with patients who do not have OH, which may reflect underlying cardiovascular dysfunction.[108, 241]

5.3 Impaired stabilisation and OI
In the Technology Research for Independent Living (TRIL) study, impaired stabilisation at 30 seconds had a stronger association with OI than the total SBP drop or the depth of the SBP nadir. Participants in the study who managed to recover at least 80% of their baseline SBP at 30 seconds were very unlikely to report OI.[242]

5.4 Impaired stabilisation and Falls
Impaired stabilisation may be associated with falls because it represents a more prolonged period of central hypotension and therefore increases the likelihood of a person developing cerebral hypoperfusion. This reduced cerebral hypoperfusion can lead to lack of environmental awareness and balance instability, both of which contribute to an increased risk of falls.[39] This theory is supported by the findings that the strongest association was between OH and unexplained falls.[243] Similarly, prolonged hypotension at around the 50 second mark during an active stand was associated with the highest rates of falls.[238]
Additionally, impaired stabilisation is associated with impaired gait, and OH at 30 seconds was associated with slower gait speed and shorter step length.[244]

5.5 Impaired stabilisation and Syncope
Similarly, impaired stabilisation is thought to be a risk factor for syncope as a result of causing more prolonged cerebral hypoperfusion. Impaired stabilisation is an underrecognised cause for syncope in clinical practice, and one study found that '43% of the patients with delayed BP recovery were classified as unexplained syncope'.[234] In a study that took five automated readings during an active stand resulting in time points of 28, 52, 76, 100, and 116 seconds, OH identified at 28 seconds was been associated with the highest incidence of syncope (17.0 per 1000 person-years) longitudinally when compared to the other time points.[238]

5.6 Impaired stabilisation and Diabetes
Cross-sectionally, impaired stabilisation (OH at 30 seconds) is associated with people who have diabetes, independently of glycosylated haemoglobin (HbA1c) levels. In this subgroup, people with diabetes had a more prolonged impaired stabilisation when looking at DBP instead of SBP. There was a higher prevalence of a sustained DBP deficit at 60 seconds in people with diabetes.[245] It has been suggested that diabetes reduces the body’s ability to increase TPR in response to the stress of orthostasis.[246, 247]

5.7 Impaired stabilisation and Depression
Cross-sectionally, selective serotonin reuptake inhibitor (SSRI) usage is associated with impaired stabilisation (OH at 30 seconds)[78] and, longitudinally, symptomatic impaired stabilisation (OH at 30 seconds) is associated with an increased risk of developing late-life depression.[248]
SECTION 6: ORTHOSTATIC INTOLERANCE

6.1 Orthostatic Intolerance definition
Orthostatic intolerance (OI) is a syndrome characterised by a constellation of symptoms associated with cerebral hypoperfusion (e.g. dizziness, light-headedness, fatigue, blurred vision)[249] that occur in response to a person standing up. It is commonly divided into two groups, based on the haemodynamic changes that occur on standing: OH (if there is a blood pressure drop) and postural orthostatic tachycardia syndrome (POTS) (if there is a sustained tachycardia in the absence of blood pressure changes). In both syndromes, the symptoms are attributed to changes in cerebral blood flow, but the pathophysiology underlying each is thought to be quite different.

6.2 Cerebral perfusion
The maintenance of cerebral blood flow (CBF) is a complex task involving multiple interactive regulatory mechanisms that are influenced by factors both intracranially (cerebral metabolism, vascular smooth muscle dilatation/constriction) and extracranially (central blood pressure, partial pressure of carbon dioxide (pCO₂), the autonomic nervous system).[250] Functionally, the cerebral circulation is considered as relatively independent from the general circulation, where the former takes priority over the latter as impaired cerebral perfusion can lead to loss of consciousness, brain damage, and death. The two main physiological mechanisms involved in the preservation of CBF are cerebrovascular reactivity and cerebral autoregulation.

6.3 Cerebrovascular reactivity (CVR)
CVR is defined as the response of cerebral blood vessels to vasoactive substances.[251] CO₂ is the most common vasoactive substance involved in CVR and raised levels of pCO₂ act as a local cerebrovascular vasodilator resulting in increased CBF.[252] The brain is very sensitive to any changes in pCO₂ levels and there is an ‘approximate 3–6% increase and/or 1–3% decrease in flow per millimetre of mercury (mmHg) change in CO₂ above and below eupnoeic PaCO₂, respectively’. [253] Intact CVR is considered reflective of good cerebrovascular health and impaired CVR is an independent risk factor for ischaemic stroke.[254]
6.4 Cerebral autoregulation

Cerebral autoregulation is the buffering of CBF from fluctuations in the mean arterial blood pressure (MAP) by vasoconstricting or vasodilating the cerebral arteries[255] and is vital in protecting the brain from the harms of either hypo- and hyper- perfusion. Its mechanisms are traditionally conceptualised into two separate components: static and dynamic autoregulation. Static cerebral autoregulation is the ability of the body to adapt to long-term or chronic changes in MAP that results in a stable CBF. It was famously described by Lassen in 1959 when they plotted average BP vs total cerebral blood flow. From these plots, Lassen proposed a ‘plateau region’ where if MAP is within the range of 60-150 mmHg then CBF is constant due to static cerebral autoregulation.[256]

Dynamic cerebral autoregulation (dCA) is the ability of the body to acutely modify the CBF in response to a sudden change in MAP. This is a relatively new area of research as it requires more advanced measurement tools such as transcranial doppler and digital photoplethysmography. The ability of dynamic cerebral autoregulation to buffer the acute changes in MAP is not perfect and there can be a brief lag in CBF response and recovery.[257, 258]

While the static-dynamic classification is the most commonly used method of conceptualising how we maintain CBF while the MAP changes, there is a growing body of research that challenges this division.[253, 259] It is suggested that the ‘plateau’ range may be much narrower than previously thought and that cerebral autoregulation may be more effective at buffering against increases in perfusion pressure than decreases.[253]

6.5 Orthostatic Hypotension and Orthostatic Intolerance (OI)

When we discuss Orthostatic Intolerance (OI) in the context of OH, we refer to a failure of the dynamic cerebral perfusion to adequately maintain CBF in the context of an acute drop in MAP due to standing up. It is thought that while dynamic cerebral autoregulation can generally compensate for an initial drop in SBP, it is the failure to recover blood pressure that pushes dCA beyond its limits.[242] This theory is echoed by another study that showed that patients with both OH and OI on a HUT, had a characteristic cerebral tissue oxygenation pattern, as measured by near-infrared spectroscopy (NIRS), that demonstrated a persistent drop in cerebral oxygenation when tilted and that drop mirrored their SBP pattern.[260]

Cerebral autoregulation appears to be different in males and females, with females having better CBF regulation during orthostasis.[261, 262] It is thought that cerebral autoregulation does not get worse with ageing per se.[259, 263, 264]
SECTION 7: FALLS

7.1 Falls epidemiology
Falls are common in older people, with 30% of community dwelling older adults falling each year[265] and 50% of older adults in a nursing home setting falling annually.[266] There are significant public health concerns associated with falls including increased morbidity/mortality, institutionalisation, and healthcare costs.[267] It is estimated that healthcare spending on non-fatal and fatal falls is $23.3 billion annually in the United States of America (USA) and £1.2 billion in the United Kingdom (UK).[268]

7.2 Falls definition
The Prevention of Falls Network Europe (ProFANE) group define a fall as ‘an unexpected event in which participants come to rest on the ground, floor or lower level’ and this definition is the most commonly used definition in the literature today.[269] A fall can be with or without loss of consciousness. The mechanism of falls is extremely complex and falls are rarely caused by one factor but are generally due to an interaction of multiple risk factors, both intrinsic and extrinsic.[270]

7.3 Intrinsic risk factors for falls
Intrinsic risk factors encompass a wide range of factors specific to the person themselves including age, gender, gait, strength, vision, cognition, the vestibular system, chronic diseases, and medication usage.[271] The risk of falls increases as people age and female sex is associated with a higher prevalence of falls.[272, 273] Gait, vision, cognition and vestibular systems are key components of a complex system that provides the stability and balance required to walk safely and impairment in just one of these components can lead to an increased risk of falls.[274] Chronic diseases associated with falls include neurodegenerative disorders (Alzheimer’s disease, Parkinson’s disease), OH, atrial fibrillation and depression.[275] Medications associated with an increased risk of falls include polypharmacy (taking five or more medications), psychotropic medications (benzodiazepines, antidepressants, antipsychotics), antihypertensives, and diuretics.[276]
7.4 Extrinsic risk factors for falls
Extrinsic risk factors are generally thought of as the environmental hazards a person must navigate while walking. They cause ‘trips or slips’ and can include loose carpets, uneven or slippery walking surfaces, staircases or bathtubs without railings, poor lighting, environmental clutter including furniture, and ill-fitting shoes.[277] There is a growing body of evidence that occupational therapist-led home modifications can prevent future falls.[278-280]

7.5 Falls and Orthostatic Hypotension
A systematic review (63 studies included) and meta-analysis (50 studies totalling 49,164 individuals) studying the relationship between OH and falls found that ‘OH was positively associated with falls in older adults, independently of study population, study design, study quality, OH definition, and blood pressure measurement method’ with an odds ratio of 1.73 (95% CI 1.50 - 1.99).[281] A recent prospective study on the association between OH and falls found that by using beat-to-beat BP monitoring and the 2011 American Academy of Neurology (AAN) definition of OH, OH was an independent predictor of falls (OR 10.30, 95% CI 1.70–61.4) and time to first fall (hazard ratio 3.02, 1.29 - 7.05).[282]

7.6 Falls and Orthostatic Hypotension pathophysiology
OH is a recognised risk factor for falling and is thought to increase the risk of falling by temporarily dropping cerebral oxygenation leading to dizziness, blurred vision, and impaired concentration.[283] There is also a suggestion that OH may indirectly increase falls by increasing cerebral white matter hyperintensities,[284-286] which have been associated with subjective dizziness [287] and falls in older people.[288] However, there have been other studies showing no association between OH and white matter hyperintensity burden.[289, 290] Cognitive impairment is strongly associated with an increased risk of falls.[291] OH resulting in cognitive impairment via repeated episodes of cerebral hypoperfusion has also been hypothesised as a possible indirect link between OH and falls.[292]

7.7 Falls and the treatment of Orthostatic Hypotension
It is recommended to both screen for and treat OH in patients who are presenting with falls.[293, 294] However, there have not been any prospective trials showing that treating and improving OH prevents future falls.
SECTION 8: SYNCOPE

8.1 Syncope definition
The European Society of Cardiology defines syncope as a ‘total loss of consciousness (TLOC) due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery’ and defines TLOC as ‘a state of real or apparent LOC with loss of awareness, characterised by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration.’[128]

8.2 Syncope aetiology
Syncope is caused by a sudden drop in cerebral perfusion secondary to a drop in MAP. MAP is the product of TPR and CO so if there is a sudden drop in either, a person is at risk of having a syncopal event. The causes of syncope are classified into three groups: orthostatic hypotension, reflex (neurally mediated), and cardiac syncope. Reflex syncope includes vasodepressor/cardioinhibitory/mixed vasovagal syncope, situational syncope, and carotid sinus syndrome. Cardiac syncope typically involves an underlying cardiac arrhythmia that results in a sudden drop in cardiac output but it can also include rarer causes such as structural heart disease and pulmonary embolism.[128]

8.3 Syncope and OH epidemiology
Syncope is a common presentation and around 40% of people will have a syncopal episode in their lifetime.[295] Syncope has a bimodal distribution with a peak in young adults in their 20s and an exponential rise after the age 70.[296, 297] The overall incidence rate of a first-time episode of syncope is 17.2 per 1000 person-years but there is a sharp rise in incidence rates with age, with up to 81.2 per 1000 patient years greater than 80 years of age.[298] Neurally mediated syncope is the most common cause of syncope across all ages and sexes.[295] Syncope secondary to OH is not rare in patients over the age of 65 years, with an estimated prevalence of 4-24% in cases of syncope presenting to the emergency department.[299-302] OH was reported as being responsible for 45% of all syncope in adults aged over 65 years who were assessed in a specialist Falls and Syncope Clinic[303] and 50% of all syncope in the Syncope and Dementia (SYD) registry study.[304]
8.4 Syncope and OH pathophysiology

As explained previously, OH is a failure of the body to compensate for the haemodynamic changes induced by changing position from lying to standing. There are two proposed mechanisms for how OH can cause syncope by a sudden drop in cerebral perfusion and then TLOC:

1. The magnitude of the blood pressure changes exceeds the body’s compensatory mechanisms or the body’s usual response to orthostasis is impaired.
2. The cerebral autoregulation is impaired and therefore more susceptible to changes in SBP.

Older adults are thought to be at increased risk of syncope secondary to OH due to altered baroreceptor responsiveness, polypharmacy, and the increased risk of volume depletion.[305]

8.5 Syncope and OH treatment

The treatment for syncope secondary to OH is to address underlying OH and the most common interventions are to increase fluid intake and advise patients to stand up slowly. Polypharmacy has been identified as a significant predictor of future syncope and reduced medication burden should be considered as a low cost intervention to reduce OH and syncope.[306] The Screening Tool of Older Person’s Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) are tools developed to help identify potentially inappropriate prescribing (PIP) in older adults.[307] A Dutch retrospective study applied these tools to patients over the age of 65 years who were attending a specialist Falls and Syncope Clinic and found a PIP in approximately 80%. The classes of medications that were the biggest culprits were diuretics, vasodilators, and psychotropic drugs.[303]

8.6 Syncope and OH prognosis

There are no studies that specifically study the outcomes of patients diagnosed with syncope secondary to OH. There is conflicting evidence on whether having one or more syncopal events can predict future major adverse cardiovascular events (MACE) or death, but this may be a result of the time delay from syncope to adverse outcomes. In short term studies, there appears to be no link between noncardiac syncope and adverse events,[296, 308-310] and a systematic review and meta-analysis reassuringly found low rates of adverse events and mortality in the short term after a syncopal episode.[311] The Framingham Heart Study initially found no difference between those diagnosed with noncardiac syncope and healthy controls, but post-hoc analysis identified an increased mortality associated with a diagnosis of syncope.[312]
There are multiple studies that identified syncope as a possible early sign of subclinical cardiac disease in healthy patients presenting with syncope. Noncardiac syncope has been identified as a predictor of future MACE, stroke, and death.
SECTION 9: THE IRISH LONGITUDINAL STUDY ON AGEING (TILDA)

9.1 The Irish Longitudinal Study on Ageing (TILDA)

TILDA is a prospective nationally representative study of community dwelling adults in the Republic of Ireland aged 50 years and over.[316] TILDA participants were selected using multi-stage, stratified random sampling that identified 640 geographical areas, stratified by socio-economic characteristics, and selected 40 households within each area.[317] The Irish GeoDirectory listing of all residential addresses provided the sampling frame. Details of the sample maintenance strategies used by TILDA are available elsewhere.[318] The first Wave of data collection took place between the years 2009 – 2011 and fieldwork was completed in February 2011 when the target sample of more than 8000 participants had been achieve. The subsequent waves were collected biennially (Wave 2 in 2012, Wave 3 in 2014, etc.).[319] An initial multi-stage probability sample of addresses was chosen by means of the RANSAM sampling procedure, developed by the Economic and Social Research Institute.[320]

Addresses were selected by means of a three-stage process:

1. Selection of first stage units (clusters which are subdivisions of District Electoral Divisions comprising between 500 and 1180 addresses) using proportionate stratification by socio-economic status (per cent in professional/managerial occupations), age structure (per cent of population aged ≥50 years) and geographical location. Selection of first stage units was based on probability proportionate to size, the size measure used being the estimated number of addresses containing a person aged ≥50 years in the cluster.

2. Selection of a systematic random sample of fixed size (50 addresses) within each cluster. Each residential address in the country had an equal probability of selection. The selected addresses were randomly partitioned into two groups: an initial sample list of 25 600 addresses (40 addresses in each of the 640 clusters, Figure 1) for immediate issue and a reserve list of 6400 addresses (10 randomly selected from each of the 640 clusters). As the target sample size was achieved using the initial sample list, the reserve list was not utilized.
3. All household residents aged ≥50 years were eligible to participate in the study (primary respondent). The spouses/partners (of any age) of respondents were also invited to participate (secondary respondent). The sample was designed to give each household in the country an equal probability of selection and, since all members aged ≥50 years in each household were eligible, each person aged ≥50 years also had an equal probability of selection. The spouses aged <50 years were interviewed mainly to provide couple- or household-level data and will not in general be included in person-level analyses.

TILDA collects information on its participants in three separate ways: computer-assisted personal interviews (CAPI), self-completion questionnaires (SCQ), and a comprehensive health assessment by a trained nurse. The information collected by TILDA at each Wave covers a wide range of topics involving health, economic, social and family circumstances. The CAPI and SCQ are repeated at each Wave and the health assessments were repeated at Wave 3 and are planned again at Wave 6 in 2021.[321]

The CAPI was undertaken in the participants’ own homes by trained professional social interviewers using laptop computers. TILDA questionnaire includes detailed questions on socio-demographics, living standards, income and wealth, physical health, lifestyle and behaviour, social support and participation, use and perceived need for health and social care and attitudes to ageing. Following completion of the interview, participants were asked to complete a SCQ and were invited to participate in the physical assessment component of the study.

The physical assessments take place in one of the two dedicated clinical assessment centres in Dublin and Cork, which are staffed by a team of trained study nurses. Participants are reimbursed for the cost of attending the centres. The duration of the clinical assessment is ~150 min and includes—anthropometric measurements: height, weight and waist circumference; cardiovascular measurements: heart rate variability, blood pressure and pulse wave velocity; gait, balance and sensory measurements: timed up and go, gait assessment using a sensored mat, visual acuity and contrast sensitivity; bone and muscle strength: grip strength, heel ultrasound; cognitive measurements: global cognition, sustained attention, executive function, visual memory, speed of processing and assessment of macular degeneration: macular pigment optical density and retinal photograph. Respondents who are unable or refuse to attend a clinical assessment centre are given the option of a home visit by a study nurse for a subset of the clinic physical assessment.
9.2 Ethics
Ethical approval for each wave of TILDA is obtained from the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin. Participants are provided with enough information to make an informed decision about their participation including advance notice of the study. Written consent is obtained for separate components of the study (i.e. interview, health assessment, blood samples); participants may refuse to take part in or withdraw at any time without justification.
SECTION 10: MD Hypothesis

As I have discussed in the previous sections, measuring the body’s haemodynamic response to standing, and accurately identifying pathological states is a complex task that has been refined over 100 years. The introduction of FinAP technology was a great advance in this field but, unfortunately, we have not changed our approach in how we define a pathological state. OH is a pathological state in which a person’s compensatory mechanisms that reduce the haemodynamic effects of gravity are impaired. This impairment is generally the result of a combination of factors including those transient (dehydration, medications) and permanent (Parkinson’s disease, diabetes). This interaction of factors means that the body’s haemodynamic response to standing can be affected at different timepoints after standing.

Our current way of conceptualising OH reduces our ability to appreciate or assess this multifaceted complexity and, instead, is focused on definitions using a set cut-off value occurring at a single set timepoint. I believe that OH should be conceptualised as a ‘drop in BP followed by a recovery’, which is a more useful approach to studying the body’s response to orthostasis. I believe this because, as mentioned earlier, there is a large variety of factors that can affect the initial BP drop, the subsequent recovery pattern, or both.

The current approach may explain why there are conflicting prevalence and associations in the OH literature. For example, there is a wide range of reported OH prevalence and some medications have been associated with both an increased and a decreased risk of having OH, including ACEI and CCBs. This uncertainty in the OH literature may have an impact on the prescribing practices of clinicians and therefore impact upon patients.

In addition, we know that there are multiple factors that can influence a person’s haemodynamic response to standing and that the effects can occur at different timepoints during the stand. As a result, it would make intuitive sense that as a person accumulates these factors (medications, chronic conditions, physical health), it would result in worse haemodynamic patterns.

The primary hypothesis of this MD is that the accumulation of abnormal blood pressure responses during the active stand is associated with overall poorer health status and more adverse clinical outcomes such as higher risk of orthostatic intolerance, history of falls or syncope. As part of this hypothesis, I also wanted to explore whether it was useful to study the AS data as a times series (focusing on patterns of initial drops and subsequent recoveries) than the traditional method of conceptualising OH as a single threshold at a particular timepoint.
My secondary hypothesis was that using purely SBP or DBP criteria to define OH would result in identifying different populations with different underlying health deficits. This is based on the theory that SBP and DBP represent different aspects of the underlying cardiac physiology and should be treated differently.

Finally, I hypothesised that these manually clustered groupings would have different HR patterns during the AS that would contribute to the BP recovery patterns and be indicative of either underlying autonomic dysfunction or be a result of medications such as beta-blockers.
CHAPTER TWO: CLINICAL CLUSTERING OF EIGHT ORTHOSTATIC PATTERNS USING SYSTOLIC BLOOD PRESSURE
SECTION 10: INTRODUCTION

Orthostatic hypotension (OH) increases with age[16] and is associated with falls[281], cognitive decline[322] and death[323]. OH is traditionally defined as a reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing[18]. This definition is based on intermittent blood pressure (BP) measurements via sphygmomanometer during a 3-minute assessment.

Non-invasive continuous beat-to-beat hemodynamic monitoring during active stand (AS) testing provides a more detailed picture of a person’s early orthostatic BP behaviour[221] and generates data that is outside the scope of the traditional OH definition[324], requiring overall clinical interpretation.

Continuous orthostatic BP monitoring is not commonplace in most clinics, but research efforts have aimed at identifying single features of the continuous AS pattern that may be associated with increased clinical risk. Thus, there has been interest in the immediate BP drop (which takes place within the first 10-15 seconds post-stand and is not captured by the traditional sphygmomanometer assessment) [222, 325], and the early (i.e. within 30-40 seconds) BP recovery phase [114, 242], which is often missed by the traditional method. By 2-3 minutes post-stand, the ability of the sphygmomanometer method to detect a given BP drop is comparable to that of the AS method [220].

Continuous hemodynamic patterns following AS are morphologically heterogeneous [64, 236] and recognition of key AS features could help guide clinical risk assessment and treatments.

Chronological age alone is not very informative of a person’s health status and survival, as two individuals of the same chronological age can have drastically different health statuses.[326] The accumulation of health deficits is a framework that attempts to explain this increasing variance in health status seen within groups of same chronological age.[327] An interesting feature of this framework is that the cumulative number of deficits gives more information about an individual’s health status than which individual deficits the individual has acquired.[328] This also means that the framework can account for a wide range of clinical features and health disorders.

Accumulation of health deficits is associated with worse health outcomes [329] and I hypothesised that this principle may also apply to accumulation of adverse BP features during the AS. To test that hypothesis, I modelled AS patterns according to the presence/absence of immediate, early and late BP deficits, and explored their clinical associations in participants from Wave 1 TILDA. An additional aim was to gain clinical insights into the potential pathophysiology of different continuous BP patterns.
SECTION 11: METHODS

Sample
An analysis was conducted on data from the health assessment of TILDA Wave 1 (June 2009–June 2011). Full details of the study design, sampling and methodology have been described elsewhere [330, 331]. Participants who were unwilling/unable to provide informed consent or had inadequate AS data were not included.

Active stand protocol
Participants underwent an AS test with the Finometer MIDI device (Finapres Medical Systems BV, Amsterdam, The Netherlands), performed by trained research nurses and recorded at 200 Hz. Participants underwent the AS following approximately 10 minutes of supine rest. Baseline BP was calculated as the mean value between 60 and 30 seconds before stand. Data was downsampled to 1 Hz. Two smoothing filters were applied, a 10-point moving average filter and an 11-point median filter. Onset of the stand was detected via an algorithm using data from the Finometer height correction unit [224]. Here I utilised BP response data up to 120 seconds post-stand, at 10-second intervals.

Active stand features and groupings
The decision to focus on SBP features was based on a study by Fedorowski et al., which found that approximately 95% of patients with classical OH can be identified by SBP changes alone [332]. Eight mutually exclusive AS patterns were manually extracted based on three sequential binary SBP deficits previously utilised by our research group: SBP drop ≥40mmHg within 10 seconds post-stand (“immediate drop”: yes or no), failure to return to within 20mmHg of supine level at 40 seconds after standing (“stabilisation failure”: yes or no), and drop ≥20mmHg at any time between >40 and 120 seconds post-stand (“late deficit”: yes or no) (Figure 3).
Figure 3. Hypothesised eight mutually exclusive groups based on three sequential systolic blood pressure (SBP) features during the active stand. The column on the right shows the classification result (in brackets: number of participants in the group, percentage of the total sample).
Clinical characterisation variables

The following variables were used to characterise the eight AS patterns: age (years), sex, a binary Fried’s frailty phenotype category (non-frail vs. pre-frail/frail) [34], time taken to stand during the AS [333], cognition as per Mini-Mental State Examination (MMSE) score, multimorbidity (history of two or more self-reported diseases among the following: myocardial infarction, heart failure, angina, atrial fibrillation, hypertension, hypercholesterolemia, stroke, diabetes mellitus, chronic obstructive pulmonary disease, asthma, arthritis, osteoporosis, cancer, Parkinson’s disease, and hip fracture). I also characterised the groups according to usage of antihypertensive and psychotropic medications. Polypharmacy was defined as concomitant use of 5 or more regular medications.

Although there are many clinical variants of orthostatic intolerance (OI) [334], our study defined it as present if participants self-reported dizziness, light-headedness or unsteadiness during the AS. Participants were also asked about history of falls in the past 12 months (yes or no), and blackouts in the past 12 months (i.e. recent syncope: yes or no).

Statistical analyses

Statistical analyses were performed in Stata version 14.1 (Stata Corp., College Station, TX, USA). The graphical visualisation of the eight AS patterns was performed with IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA), using mean SBP for each group.

Descriptive statistics were given as mean with standard deviation (SD), median with interquartile range (IQR), or number (n) with percentage (%). Overall differences between the eight AS groups (as nominal variable) were assessed using analysis of variance (ANOVA) in the case of normally distributed continuous variables, or the Kruskal-Wallis test in the case of interval, non-normal variables; for categorical (e.g. dichotomous) variables, the Chi-squared test was used. Given the projected number of comparisons (36 in total), and considering an Alpha level of 0.05, a Bonferroni’s adjustment calculation recommended to lower p<0.05 to p<0.001 to detect statistical significance during the characterisation of the sample.
For the cross-sectional associations between the AS groups and OI, falls and syncope, three logistic regression models were fitted for each outcome:

- model A, a univariate model with AS groups as independent variable using the no deficits group as reference;
- model B, a multivariate model controlling for the fixed effects of age and sex;
- and model C, a multivariate model controlling for the fixed effects of age, sex, baseline SBP, time to stand, Fried’s frailty status, MMSE, multimorbidity, polypharmacy, and use of antihypertensive, antidepressant, benzodiazepine [24], and Z-drug medications.

In these models, the threshold for statistical significance was set at p<0.05.
SECTION 12: RESULTS

In total, 8174 participants over the age of 50 were recruited to wave 1 of the TILDA study, of whom 5034 attended the health assessment centre. There were 4905 participants with adequate active stand data for analysis, of whom 4899 had complete data for the generation of the eight AS groups using the decision tool in Figure 3. Overall, the mean age was 61, and 55% were female.

As Figure 3 shows, the largest group was the one with no deficits (68%), followed by immediate deficit only (13%), all three deficits (6%), and late deficit only (5%). The other groups contained fewer than 5% of participants each. The graphical visualisation of the groups (mean SBP) is presented in Figure 4.

The clinical characteristics of the total sample and the eight AS groups are summarised in Table 3. Overall, OI was reported by 38% of participants; 20% had history of falls, and 5% reported recent syncope.

Participants in the largest group with no deficits had the lowest baseline SBP and were among the youngest, least frail, least comorbid, and least medicated. They were also among the groups with lowest proportion of OI (Table 3).

The group with all three deficits was not among the oldest but seemed to have the highest use of beta-blockers, benzodiazepines, antidepressants, highest baseline SBP, highest proportion of falls and one of the highest proportions of OI (Table 3). Groups 2, 5 and 6 (older and with impaired stabilisation) had proportions of diabetes mellitus over 10%.

The results of the three logistic regression models for the prediction of OI, falls and syncope (Models C) are shown in Table 4; full information for Models A, B and C is available in the Appendix.

In models C (Table 4), there were statistically significant associations between OI and three groups with immediate deficit, with a seemingly incremental Odds Ratio (OR) according to the number of deficits: OR 1.42 (95% CI: 1.19-1.70, p<0.001) for immediate only; OR 1.60 (95% CI: 1.20-2.13, p=0.001) for immediate and late; and OR 1.83 (95% CI: 1.41-2.38, p<0.001) for immediate, stabilisation and late. There was also a statistically significant association between the group with all three deficits and falls (OR 1.54, 95% CI: 1.15-2.07, p=0.004).
Table 3. Characterisation of the overall sample and the eight active stand groups based on SBP features. SD: standard deviation; * Kruskal-Wallis test; # Chi-square test.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>4899 (100.0)</td>
<td>272 (5.6)</td>
<td>43 (0.9)</td>
<td>209 (4.3)</td>
<td>632 (12.9)</td>
<td>145 (3.0)</td>
<td>38 (0.8)</td>
<td>248 (5.1)</td>
<td>3312 (67.6)</td>
<td></td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>61.0 (8.8)</td>
<td>64.5 (9.3)</td>
<td>68.1 (10.5)</td>
<td>60.3 (7.7)</td>
<td>61.6 (8.6)</td>
<td>66.9 (9.2)</td>
<td>68.8 (9.5)</td>
<td>61.3 (9.2)</td>
<td>60.2 (8.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>2703 (55.2)</td>
<td>172 (63.2)</td>
<td>23 (53.5)</td>
<td>142 (67.9)</td>
<td>364 (57.6)</td>
<td>101 (69.7)</td>
<td>18 (47.4)</td>
<td>153 (61.7)</td>
<td>1730 (52.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Non-frail, n (%)</td>
<td>3471 (72.6)</td>
<td>174 (65.4)</td>
<td>31 (75.6)</td>
<td>155 (74.9)</td>
<td>448 (72.4)</td>
<td>80 (57.6)</td>
<td>24 (64.9)</td>
<td>156 (65.3)</td>
<td>2403 (74.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pre-frail or frail, n (%)</td>
<td>1313 (27.5)</td>
<td>92 (34.6)</td>
<td>10 (24.4)</td>
<td>52 (25.1)</td>
<td>171 (27.6)</td>
<td>59 (42.5)</td>
<td>13 (35.1)</td>
<td>83 (34.7)</td>
<td>833 (25.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean time to stand in seconds (SD)</td>
<td>7.6 (3.0)</td>
<td>7.9 (2.7)</td>
<td>8.3 (3.5)</td>
<td>7.3 (2.3)</td>
<td>7.5 (2.8)</td>
<td>9.7 (4.5)</td>
<td>9 (3.8)</td>
<td>8.1 (3.2)</td>
<td>7.5 (2.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median MMSE (IQR)</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>28 (3)</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Multimorbidity, n (%)</td>
<td>2236 (45.6)</td>
<td>132 (48.5)</td>
<td>22 (51.2)</td>
<td>85 (40.7)</td>
<td>303 (47.9)</td>
<td>92 (63.5)</td>
<td>27 (71.1)</td>
<td>113 (45.6)</td>
<td>1462 (44.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>109 (2.3)</td>
<td>7 (2.6)</td>
<td>2 (4.7)</td>
<td>2 (1.0)</td>
<td>16 (2.6)</td>
<td>3 (2.1)</td>
<td>4 (10.5)</td>
<td>3 (1.2)</td>
<td>72 (2.2)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Parkinson's disease, n (%)</td>
<td>15 (0.3)</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (2.1)</td>
<td>0 (0.0)</td>
<td>3 (1.2)</td>
<td>7 (0.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>300 (6.1)</td>
<td>17 (6.3)</td>
<td>5 (11.6)</td>
<td>7 (3.4)</td>
<td>35 (5.5)</td>
<td>15 (10.3)</td>
<td>5 (13.2)</td>
<td>14 (5.7)</td>
<td>202 (6.1)</td>
<td>0.065*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1934 (39.7)</td>
<td>119 (44.1)</td>
<td>24 (57.1)</td>
<td>98 (47.1)</td>
<td>294 (46.9)</td>
<td>63 (43.8)</td>
<td>16 (42.1)</td>
<td>108 (43.9)</td>
<td>1212 (36.7)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Polypharmacy, n (%)</td>
<td>830 (17.0)</td>
<td>68 (25.1)</td>
<td>13 (30.2)</td>
<td>25 (12.0)</td>
<td>98 (15.6)</td>
<td>46 (32.4)</td>
<td>9 (24.3)</td>
<td>55 (22.4)</td>
<td>516 (15.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Anti-hypertensive medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1553 (31.7)</td>
<td>99 (36.4)</td>
<td>16 (37.2)</td>
<td>60 (28.7)</td>
<td>211 (33.4)</td>
<td>67 (46.2)</td>
<td>19 (50.0)</td>
<td>77 (31.1)</td>
<td>1004 (30.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>563 (11.5)</td>
<td>55 (20.3)</td>
<td>7 (16.3)</td>
<td>28 (13.5)</td>
<td>81 (12.9)</td>
<td>27 (19.0)</td>
<td>3 (8.1)</td>
<td>26 (10.6)</td>
<td>336 (10.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diuretics</td>
<td>289 (5.9)</td>
<td>17 (6.3)</td>
<td>5 (11.6)</td>
<td>7 (3.4)</td>
<td>35 (5.0)</td>
<td>13 (9.2)</td>
<td>4 (10.8)</td>
<td>16 (6.5)</td>
<td>192 (5.8)</td>
<td>0.211*</td>
</tr>
<tr>
<td>ACE inhibitors/Angiotensin receptor blockers</td>
<td>1047 (21.5)</td>
<td>53 (19.6)</td>
<td>13 (30.2)</td>
<td>33 (15.9)</td>
<td>150 (23.9)</td>
<td>44 (31.0)</td>
<td>10 (27.0)</td>
<td>54 (22.0)</td>
<td>690 (20.9)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>402 (8.2)</td>
<td>23 (8.5)</td>
<td>6 (14.0)</td>
<td>11 (5.3)</td>
<td>38 (6.0)</td>
<td>19 (13.4)</td>
<td>11 (29.7)</td>
<td>22 (8.9)</td>
<td>272 (8.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>71 (1.5)</td>
<td>8 (3.0)</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
<td>9 (1.4)</td>
<td>6 (4.2)</td>
<td>0 (0)</td>
<td>6 (2.4)</td>
<td>41 (1.2)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Psychoactive medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>444 (9.1)</td>
<td>46 (16.9)</td>
<td>6 (14.0)</td>
<td>16 (7.7)</td>
<td>67 (10.6)</td>
<td>21 (14.5)</td>
<td>3 (7.9)</td>
<td>28 (11.3)</td>
<td>257 (7.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Z-drugs</td>
<td>109 (2.2)</td>
<td>12 (4.4)</td>
<td>2 (4.7)</td>
<td>3 (1.4)</td>
<td>14 (2.2)</td>
<td>11 (7.8)</td>
<td>1 (2.7)</td>
<td>5 (2.0)</td>
<td>61 (1.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>140 (2.9)</td>
<td>17 (6.3)</td>
<td>0 (0)</td>
<td>9 (4.3)</td>
<td>15 (2.4)</td>
<td>5 (3.5)</td>
<td>2 (5.4)</td>
<td>10 (4.1)</td>
<td>82 (2.5)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>281 (5.7)</td>
<td>35 (12.9)</td>
<td>4 (9.3)</td>
<td>9 (4.3)</td>
<td>47 (7.4)</td>
<td>12 (8.3)</td>
<td>1 (2.6)</td>
<td>15 (6.1)</td>
<td>158 (4.8)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>
Table 3 continued. Characterisation of the overall sample and the eight active stand groups based on SBP features. SD: standard deviation; * Kruskal-Wallis test; # Chi-square test.

<table>
<thead>
<tr>
<th>Characterisation</th>
<th>Overall</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic Intolerance during active stand, n (%)</td>
<td>1880 (38.4)</td>
<td>130 (47.8)</td>
<td>21 (48.8)</td>
<td>93 (44.5)</td>
<td>271 (42.9)</td>
<td>57 (39.3)</td>
<td>13 (34.2)</td>
<td>103 (41.7)</td>
<td>1192 (36.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>At least 1 fall in the past 12 months, n (%)</td>
<td>960 (19.6)</td>
<td>77 (28.3)</td>
<td>6 (14.0)</td>
<td>36 (17.3)</td>
<td>125 (19.8)</td>
<td>32 (22.1)</td>
<td>7 (18.4)</td>
<td>47 (19.0)</td>
<td>630 (19.0)</td>
<td>0.025*</td>
</tr>
<tr>
<td>At least 1 syncope in the past 12 months, n (%)</td>
<td>226 (4.62)</td>
<td>13 (4.8)</td>
<td>1 (2.3)</td>
<td>11 (5.3)</td>
<td>23 (3.7)</td>
<td>11 (7.8)</td>
<td>2 (5.3)</td>
<td>9 (3.6)</td>
<td>156 (4.7)</td>
<td>0.585*</td>
</tr>
<tr>
<td>Mean baseline SBP, mmHg (SD)</td>
<td>135.8 (22.3)</td>
<td>147.7 (24.9)</td>
<td>142.1 (27.9)</td>
<td>142.9 (25.0)</td>
<td>140.3 (23.0)</td>
<td>141.8 (19.1)</td>
<td>143.8 (24.3)</td>
<td>132.4 (20.6)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Mean baseline HR, beats per minute (SD)</td>
<td>65.0 (9.9)</td>
<td>61.9 (9.9)</td>
<td>63.5 (9.8)</td>
<td>61.2 (9.2)</td>
<td>63.1 (9.5)</td>
<td>67.1 (11.7)</td>
<td>69.9 (10.9)</td>
<td>65.0 (9.9)</td>
<td>65.7 (9.7)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Table 4. Results of the fully adjusted logistic regression models (Models C). Statistically significant results are highlighted in bold. OI: orthostatic intolerance; OR: odds ratio; CI: confidence interval.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>OI</td>
<td>1.83 (1.41, 2.38)</td>
<td>&lt;0.001</td>
<td>1.85 (0.98, 3.47)</td>
<td>0.05</td>
<td>1</td>
<td>1.60 (1.20, 2.13)</td>
<td>0.00</td>
<td>1</td>
</tr>
<tr>
<td>Recent Falls</td>
<td>1.54 (1.15, 2.07)</td>
<td>0.004</td>
<td>0.64 (0.27, 1.56)</td>
<td>0.32</td>
<td>6</td>
<td>0.86 (0.58, 1.26)</td>
<td>0.44</td>
<td>0</td>
</tr>
<tr>
<td>Recent syncope</td>
<td>0.91 (0.49, 1.66)</td>
<td>0.750</td>
<td>0.56 (0.05, 4.21)</td>
<td>0.65</td>
<td>8</td>
<td>1.27 (0.67, 2.41)</td>
<td>0.46</td>
<td>4</td>
</tr>
<tr>
<td>(Base)</td>
<td></td>
<td></td>
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</table>
**Figure 4.** Graphical visualisation of the eight active stand groups. SBP: Systolic Blood Pressure.
SECTION 13: DISCUSSION

In this large population-based study of Irish participants aged 50+ undergoing continuous orthostatic BP measurements, I showed eight different orthostatic BP patterns based on three sequential SBP deficits. I showed that the most common patterns were characterised by no deficits or an immediate deficit only. Groups with an immediate deficit had higher risk of OI, with a seemingly incremental OI risk as more deficits were present. The group with all three deficits was associated with recent falls. Our findings confirm and expand previous observations that hemodynamic AS patterns are heterogeneous [236], highlighting the need to take a nuanced approach to the interpretation of the AS that considers potentially different pathophysiological mechanisms and clinical associations.

Our results are consistent with the definition of initial OH in that the immediate SBP drop is associated with OI [222]; however, our results underscore the merit of considering the immediate BP drop and OI separately. Indeed, the fact that the strength of the association with OI seemed stronger as more deficits were seen in the AS pattern acknowledges the importance of not just the immediate BP change but also the recovery phase [324]. In addition, this finding is consistent with the theory of accumulation of health deficits [327, 329], which postulates that deficit accumulation may be a useful measure of biological age and thus of increased clinical risk [335]. Interestingly, the three-deficit pattern was not seen in the oldest group, perhaps in keeping with the principle that accumulation of health deficits is heterogeneous resulting in poor correlation with chronological age [327].

In terms of the pathophysiology behind the accumulation of deficits effect in association with OI, some studies have suggested that the presence of an isolated immediate BP deficit (without OI symptoms) may not be pathological and is often seen in young healthy people [228]. However, in older people who may be affected by comorbidities, initial orthostatic hypotension may be a risk factor for unexplained syncope [233]. Our study suggests that an isolated immediate BP deficit is common in a healthier group of older people, but it is seen with other deficits in less healthy groups. A possible explanation for the variable relationship between immediate SBP drops and health status is that the healthier the person is, the faster they are generally able to stand up [224]. This increased speed in changing from supine to standing gives the body less time to compensate for the stress of orthostasis and, as a result, there may be a greater immediate SBP drop. Therefore, the clinical significance of an immediate BP deficit needs to be assessed in the context of the subsequent SBP recovery.
Cooke et al. came to a similar conclusion in their study that attempted to classify OH into 3 different subtypes based on how the SBP responded to the initial SBP drop. They similarly found a wide range of SBP response patterns and felt that the recovery patterns may guide predicting future adverse outcomes in OH [336].

Looking at the groups with immediate deficit, 3 and 4 were younger and tended to stand quicker, which may explain their immediate drop; whilst 4 fully recovered, 3’s late deficit might be due to a marginally higher proportion of beta-blockers (lowest baseline heart rate) and benzodiazepines. Groups 1 and 2 were older, which is associated with impaired BP stabilisation [220, 243]. Group 1 is reminiscent of the syndrome of supine hypertension with OH, in which baseline hypertension is followed by a marked late deficit possibly due to pharmacological influences (e.g. beta blockers, antidepressants and benzodiazepines) [64, 88]; in group 2 (older than 1), late recovery seemed to occur in the context of a lower SBP baseline and less of the latter pharmacological influences (e.g. none on benzodiazepines).

Looking at the groups without an immediate deficit, 8 and 7 were younger and did not fail to stabilise, but 7’s late deficit was in the context of a higher proportion of benzodiazepines and antidepressants. Groups 5 and 6 (with stabilisation failure) were older and had proportions of diabetes mellitus (DM) over 10%. DM can cause orthostatic hypertension, which might appear as better late recoveries (this also applies to group 2) [337]. Again, a difference between 5 and 6 was that 5’s late deficit was seen with a higher burden of beta blockers and antidepressants.

**Conclusion**

The interpretation of AS patterns requires consideration of immediate, stabilisation and late deficits simultaneously. Older age was associated with stabilisation deficits and late deficits were seen with a higher burden of beta blockers and psychotropic medications. Whilst observations are not causal and longitudinal research is required, the recognition of continuous AS patterns could help personalise prescribing.
CHAPTER THREE: CLINICAL CLUSTERING OF EIGHT ORTHOSTATIC PATTERNS USING DIASTOLIC BLOOD PRESSURE
SECTION 14: INTRODUCTION

OH is traditionally defined by consensus statement as a reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes of standing.[18] As mentioned previously, Fedorowski et al found that approximately 95% of patients with traditionally defined OH can be identified by SBP changes alone using a passive head-up tilt method.[332] This focus on SBP over DBP measurements is not new and SBP has been the focus of attention of research since the Framingham Study showed that SBP hypertension was the best predictor of both all-cause and cardiovascular mortality, even among individuals with diastolic hypertension.[338] As a result, there are very few studies that analyse OH defined just by DBP criteria. The Malmo Preventive Project found a longitudinal association between diastolic OH in the middle age and developing dementia in later life.[339]

However, there is a growing body of evidence that demonstrates that SBP and DBP represent different aspects of the underlying cardiac physiology and should be treated differently.[340] High SBP is typically associated with increased arterial stiffness, whereas stiffening of large arteries can induce a decrease in DBP.[341] Both SBP and DBP have different pathological associations, SBP is associated with strokes and myocardial infarctions, while DBP is associated with reduced coronary blood flow, subclinical myocardial damage, and cardiovascular events as most coronary perfusion occurs during diastole.[49, 342, 343]

Considering there are differences between SBP and DBP, the clinical clustering was repeated using only the DBP OH criteria to explore the cross-sectional associations and outcomes.

SECTION 15: METHODS

Active stand features and groupings

Eight mutually exclusive AS patterns were manually extracted based on three sequential binary DBP deficits previously utilised by our research group: DBP drop ≥20mmHg within 10 seconds post-stand (“immediate drop”: yes or no), failure to return to within 10mmHg of supine level at 40 seconds after standing (“stabilisation failure”: yes or no), and drop ≥10mmHg at any time between >40 and 120 seconds post-stand (“late deficit”: yes or no) (Figure 5).
Figure 5. Hypothesised eight mutually exclusive groups based on three sequential diastolic blood pressure (DBP) features during the active stand. The column on the right shows the classification result (in brackets: number of participants in the group, percentage of the total sample).

<table>
<thead>
<tr>
<th>Is there an immediate orthostatic drop? (difference in DBP ≥ 20mmHg at 10 seconds)</th>
<th>Is there a failure to stabilise DBP at 40s? (difference in SBP ≥ 10mmHg of supine levels at 40 seconds)</th>
<th>Is there a late DBP deficit after 40s? (difference in DBP ≥ 10mmHg at any time between 50 and 120 seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>YES</td>
<td>Group 1 (272, 3.6%)</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
<td>Group 2 (43, 0.9%)</td>
</tr>
<tr>
<td>NO</td>
<td>YES</td>
<td>Group 3 (209, 4.3%)</td>
</tr>
<tr>
<td>NO</td>
<td>NO</td>
<td>Group 4 (632, 12.9%)</td>
</tr>
<tr>
<td>NO</td>
<td>YES</td>
<td>Group 5 (245, 3.0%)</td>
</tr>
<tr>
<td>NO</td>
<td>NO</td>
<td>Group 6 (38, 0.8%)</td>
</tr>
<tr>
<td>NO</td>
<td>YES</td>
<td>Group 7 (248, 5.1%)</td>
</tr>
<tr>
<td>NO</td>
<td>NO</td>
<td>Group 8 (3312, 67.8%)</td>
</tr>
</tbody>
</table>
SECTION 15: RESULTS

As Figure 5 shows, the largest group was the one with no deficits (49.4%), followed by immediate drop only (30.7%), immediate drop and late deficit (7.8%) and all three deficits (6.4%). The other groups contained fewer than 5% of participants each. The graphical visualisation of the groups (mean DBP) is presented in Figure 6.

The clinical characteristics of the total sample and the eight AS groups are summarised in Table 5. Overall, OI was reported by 38% of participants; 20% had history of falls, and 5% reported recent syncope.

The group with only an immediate drop (Group 4) was the youngest and healthiest group, with the fastest standing time, and lowest rates of frailty, co-morbidities, and polypharmacy. This group had the third highest rate of OI but the lowest rates of recent falls, and low rates of syncope.

Participants in the largest group with no deficits (Group 8) had the second lowest baseline DBP and were the second youngest and healthiest group with low levels of frailty, co-morbidities, and polypharmacy. They were also among the groups with lowest proportion of OI, recent falls, and recent syncope (Table 5).

The group with all three deficits (Group 1) has the highest use of benzodiazepines, antidepressants, highest baseline DBP, highest proportion of OI and the second highest proportions of falls (Table 5).

The group with only impaired stabilisation (Group 6) was the oldest and frailest group, with the highest rates of multimorbidity and atrial fibrillation. They had the lowest baseline DBP and the highest baseline SBP and the highest rates of usage for beta-blocker, diuretics, ACEI/ARB, and alpha-blockers.

Groups 2, 5 and 6 (older and with impaired stabilisation) had the highest proportions of diabetes mellitus, ranging from 10 – 19.2%.
The results of the three logistic regression models for the prediction of OI, falls and syncope (Models C) are shown in Table 6; full information for Models A, B and C is available in the Appendix.

In models C (Table 6), there were statistically significant associations between OI and three groups with immediate deficit: OR 1.49 (95% CI: 1.30-1.70, p<0.001) for immediate only; OR 1.42 (95% CI: 1.14-1.79, p=0.002) for immediate and late; and OR 1.77 (95% CI: 1.38-2.27, p<0.001) for immediate, stabilisation and late.

There was a statistically significant association between the group with all three deficits and recent falls (OR 1.56, 95% CI: 1.18-2.07, p=0.002).

There was also a statistically significant association between the group with impaired stabilisation and recent syncope (OR 3.61, 95% CI: 1.16-11.24, p=0.027).
Table 5. Characterisation of the overall sample and the eight active stand groups based on DBP features. SD: standard deviation; * Kruskal-Wallis test; # Chi-square test.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>4904</td>
<td>314 (6.4)</td>
<td>47 (1.0)</td>
<td>383 (7.8)</td>
<td>1505 (30.7)</td>
<td>78 (1.6)</td>
<td>27 (0.6)</td>
<td>127 (2.6)</td>
<td>2423 (49.4)</td>
<td></td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>61.03 (8.8)</td>
<td>65.87 (9.3)</td>
<td>68.94 (9.4)</td>
<td>61.09 (8.1)</td>
<td>60.12 (8.2)</td>
<td>68.97 (9.1)</td>
<td>71.07 (9.2)</td>
<td>63.72 (9.9)</td>
<td>60.29 (8.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>2706 (55.2)</td>
<td>170 (54.1)</td>
<td>25 (53.2)</td>
<td>204 (53.3)</td>
<td>791 (52.6)</td>
<td>51 (65.4)</td>
<td>13 (48.2)</td>
<td>75 (59.1)</td>
<td>1377 (56.8)</td>
<td>0.093*</td>
</tr>
<tr>
<td>Binary Fraility Category, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-frail/Frail</td>
<td>1315 (27.5)</td>
<td>96 (31.4)</td>
<td>18 (38.3)</td>
<td>94 (24.9)</td>
<td>354 (24.1)</td>
<td>40 (54.8)</td>
<td>16 (64.0)</td>
<td>54 (43.6)</td>
<td>643 (27.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean Time to stand (SD)</td>
<td>7.6 (3.0)</td>
<td>8.1 (2.9)</td>
<td>8.5 (2.8)</td>
<td>7.2 (2.3)</td>
<td>7.1 (2.2)</td>
<td>12.3 (5.1)</td>
<td>10.9 (4.2)</td>
<td>8.4 (4.1)</td>
<td>7.7 (3.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median gait velocity, cm/sec (IQR)</td>
<td>136.6 (20.3)</td>
<td>130.8 (20.3)</td>
<td>128.1 (20.3)</td>
<td>137.2 (18.6)</td>
<td>138.5 (17.8)</td>
<td>115.0 (26.3)</td>
<td>115.2 (24.2)</td>
<td>130.8 (23.3)</td>
<td>137.5 (20.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median MMSE (IQR)</td>
<td>29 (2.0)</td>
<td>29 (2.0)</td>
<td>29 (2.0)</td>
<td>29 (2.0)</td>
<td>29 (2.0)</td>
<td>29 (3.0)</td>
<td>29 (2.0)</td>
<td>29 (3.0)</td>
<td>29 (2.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Multimorbidity, n (%)</td>
<td>2240 (45.7)</td>
<td>161 (51.3)</td>
<td>23 (48.9)</td>
<td>173 (45.2)</td>
<td>655 (43.5)</td>
<td>59 (75.6)</td>
<td>22 (81.5)</td>
<td>60 (47.2)</td>
<td>1087 (44.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>38 (0.8)</td>
<td>3 (1.0)</td>
<td>0 (0)</td>
<td>3 (0.8)</td>
<td>10 (0.7)</td>
<td>1 (1.3)</td>
<td>1 (3.7)</td>
<td>2 (1.6)</td>
<td>18 (0.7)</td>
<td>0.648*</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>109 (2.3)</td>
<td>18 (5.9)</td>
<td>1 (2.2)</td>
<td>10 (2.6)</td>
<td>27 (1.8)</td>
<td>5 (6.7)</td>
<td>3 (11.5)</td>
<td>6 (4.7)</td>
<td>39 (1.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Parkinson’s disease, n (%)</td>
<td>15 (0.3)</td>
<td>2 (0.6)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>3 (0.2)</td>
<td>1 (1.3)</td>
<td>1 (3.7)</td>
<td>1 (0.8)</td>
<td>6 (0.3)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>301 (6.1)</td>
<td>22 (7.0)</td>
<td>5 (10.6)</td>
<td>19 (5.0)</td>
<td>73 (4.9)</td>
<td>15 (19.2)</td>
<td>5 (18.5)</td>
<td>11 (8.7)</td>
<td>151 (6.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1938 (39.7)</td>
<td>143 (45.8)</td>
<td>22 (46.8)</td>
<td>183 (48.2)</td>
<td>56 (37.5)</td>
<td>39 (50.7)</td>
<td>18 (69.2)</td>
<td>59 (47.2)</td>
<td>913 (37.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Polypharmacy, n (%)</td>
<td>832 (17.0)</td>
<td>73 (23.3)</td>
<td>13 (28.3)</td>
<td>53 (13.9)</td>
<td>203 (13.5)</td>
<td>36 (47.4)</td>
<td>10 (38.5)</td>
<td>34 (26.7)</td>
<td>410 (17.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1554 (31.7)</td>
<td>128 (40.8)</td>
<td>23 (48.9)</td>
<td>117 (30.6)</td>
<td>435 (28.9)</td>
<td>44 (56.4)</td>
<td>17 (63.0)</td>
<td>57 (44.9)</td>
<td>733 (30.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>564 (11.6)</td>
<td>64 (20.5)</td>
<td>7 (15.2)</td>
<td>56 (14.7)</td>
<td>168 (11.2)</td>
<td>12 (15.8)</td>
<td>9 (34.6)</td>
<td>21 (16.5)</td>
<td>227 (9.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diuretics</td>
<td>589 (5.9)</td>
<td>15 (4.8)</td>
<td>6 (13.0)</td>
<td>19 (5.0)</td>
<td>69 (4.6)</td>
<td>15 (19.7)</td>
<td>7 (26.9)</td>
<td>10 (7.9)</td>
<td>148 (6.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>1047 (21.5)</td>
<td>69 (22.0)</td>
<td>19 (41.3)</td>
<td>68 (17.9)</td>
<td>308 (20.5)</td>
<td>28 (36.8)</td>
<td>12 (46.2)</td>
<td>42 (33.1)</td>
<td>501 (20.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CCB</td>
<td>402 (8.2)</td>
<td>33 (10.5)</td>
<td>8 (17.4)</td>
<td>19 (5.0)</td>
<td>9 (6.5)</td>
<td>15 (19.7)</td>
<td>2 (7.7)</td>
<td>16 (12.6)</td>
<td>212 (8.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>71 (1.5)</td>
<td>11 (3.5)</td>
<td>1 (2.2)</td>
<td>2 (0.5)</td>
<td>15 (1.0)</td>
<td>6 (7.9)</td>
<td>5 (19.2)</td>
<td>2 (1.6)</td>
<td>29 (1.2)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>
Table 5 continued. Characterisation of the overall sample and the eight active stand groups based on DBP features. SD: standard deviation; * Kruskal-Wallis test; # Chi-square test.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychoactive medications, n (%)</td>
<td>Overall</td>
<td>444 (9.1)</td>
<td>50 (15.9)</td>
<td>4 (8.5)</td>
<td>26 (6.8)</td>
<td>131 (8.7)</td>
<td>13 (16.7)</td>
<td>3 (11.1)</td>
<td>20 (15.8)</td>
<td>197 (8.1)</td>
</tr>
<tr>
<td>Z-drugs</td>
<td>Overall</td>
<td>109 (2.2)</td>
<td>18 (5.8)</td>
<td>3 (6.5)</td>
<td>2 (0.5)</td>
<td>25 (1.7)</td>
<td>6 (7.9)</td>
<td>0 (0)</td>
<td>4 (3.2)</td>
<td>51 (2.1)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Overall</td>
<td>140 (2.9)</td>
<td>12 (3.8)</td>
<td>1 (2.2)</td>
<td>10 (2.6)</td>
<td>47 (3.1)</td>
<td>3 (4.0)</td>
<td>1 (3.9)</td>
<td>7 (5.5)</td>
<td>59 (2.5)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Overall</td>
<td>281 (5.7)</td>
<td>35 (11.2)</td>
<td>1 (2.1)</td>
<td>17 (4.4)</td>
<td>85 (5.7)</td>
<td>7 (9.0)</td>
<td>2 (7.4)</td>
<td>12 (9.5)</td>
<td>122 (5.0)</td>
</tr>
<tr>
<td>Orthostatic Intolerance during active stand, n (%)</td>
<td>Overall</td>
<td>1883 (38.4)</td>
<td>144 (45.9)</td>
<td>20 (42.6)</td>
<td>154 (41.2)</td>
<td>646 (43.0)</td>
<td>35 (44.9)</td>
<td>9 (33.3)</td>
<td>43 (33.9)</td>
<td>832 (34.4)</td>
</tr>
<tr>
<td>At least 1 fall in the past 12 months, n (%)</td>
<td>Overall</td>
<td>960 (19.6)</td>
<td>88 (28.0)</td>
<td>13 (27.7)</td>
<td>74 (19.4)</td>
<td>283 (18.8)</td>
<td>19 (24.4)</td>
<td>9 (33.3)</td>
<td>32 (25.2)</td>
<td>442 (18.2)</td>
</tr>
<tr>
<td>At least 1 blackout in the past 12 months, n (%)</td>
<td>Overall</td>
<td>226 (4.5)</td>
<td>12 (3.9)</td>
<td>2 (4.3)</td>
<td>20 (5.2)</td>
<td>65 (4.3)</td>
<td>10 (12.8)</td>
<td>5 (18.5)</td>
<td>8 (6.3)</td>
<td>104 (4.3)</td>
</tr>
<tr>
<td>Mean baseline DBP, mmHg (SD)</td>
<td>Overall</td>
<td>73.2 (11.2)</td>
<td>76.8 (12.4)</td>
<td>73.9 (12.3)</td>
<td>76.4 (12.2)</td>
<td>73.6 (10.5)</td>
<td>72.0 (13.7)</td>
<td>71.4 (14.9)</td>
<td>74.3 (13.3)</td>
<td>71.9 (10.9)</td>
</tr>
<tr>
<td>Mean baseline SBP, mmHg (SD)</td>
<td>Overall</td>
<td>135.8 (22.3)</td>
<td>141.9 (25.1)</td>
<td>141.8 (26.9)</td>
<td>141.7 (24.3)</td>
<td>135.3 (21.8)</td>
<td>141.3 (26.2)</td>
<td>143.0 (30.6)</td>
<td>141.1 (23.8)</td>
<td>133.8 (21.1)</td>
</tr>
<tr>
<td>Mean baseline HR, bpm (SD)</td>
<td>Overall</td>
<td>65.0 (9.9)</td>
<td>62.3 (9.8)</td>
<td>63.1 (10.6)</td>
<td>62.8 (9.3)</td>
<td>63.2 (9.3)</td>
<td>67.7 (12.2)</td>
<td>64.9 (13.8)</td>
<td>66.7 (11.1)</td>
<td>66.7 (9.8)</td>
</tr>
</tbody>
</table>
Table 6. Results of the fully adjusted logistic regression models (Models C). Statistically significant results are highlighted in bold. OI: orthostatic intolerance; OR: odds ratio; CI: confidence interval.

<table>
<thead>
<tr>
<th>Group</th>
<th>Group1 OR (95% CI)</th>
<th>p</th>
<th>Group2 OR (95% CI)</th>
<th>p</th>
<th>Group3 OR (95% CI)</th>
<th>p</th>
<th>Group4 OR (95% CI)</th>
<th>p</th>
<th>Group5 OR (95% CI)</th>
<th>p</th>
<th>Group6 OR (95% CI)</th>
<th>p</th>
<th>Group7 OR (95% CI)</th>
<th>p</th>
<th>Group8 OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OI</td>
<td>1.77 (1.38-2.27)</td>
<td>&lt;0.001</td>
<td>1.68 (0.92-2.07)</td>
<td>0.091</td>
<td>1.42 (1.14-1.79)</td>
<td>0.002</td>
<td>1.49 (1.30-1.70)</td>
<td>&lt;0.001</td>
<td>1.63 (0.99-2.68)</td>
<td>0.054</td>
<td>1.20 (0.52-2.80)</td>
<td>0.669</td>
<td>1.04 (0.71-1.53)</td>
<td>0.831</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent Falls</td>
<td>1.56 (1.18-2.07)</td>
<td>0.002</td>
<td>1.47 (0.75-2.89)</td>
<td>0.265</td>
<td>1.12 (0.84-1.48)</td>
<td>0.440</td>
<td>1.05 (0.89-1.25)</td>
<td>0.554</td>
<td>1.15 (0.65-2.03)</td>
<td>0.629</td>
<td>1.73 (0.72-4.13)</td>
<td>0.217</td>
<td>1.43 (0.93-2.19)</td>
<td>0.099</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent Syncope</td>
<td>0.89 (0.47-1.67)</td>
<td>0.711</td>
<td>1.02 (0.24-4.34)</td>
<td>0.981</td>
<td>1.42 (0.86-2.35)</td>
<td>0.175</td>
<td>1.08 (0.78-1.51)</td>
<td>0.648</td>
<td>2.19 (0.97-4.97)</td>
<td>0.067</td>
<td>3.61 (1.16-11.24)</td>
<td>0.027</td>
<td>1.41 (0.66-3.02)</td>
<td>0.374</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Base)
Figure 6. Graphical visualisation of the eight active stand groups. DBP: Diastolic Blood Pressure.
SECTION 16: DISCUSSION

In this section I explored eight different orthostatic BP patterns based on three sequential DBP deficits. I showed that the most common patterns were characterised by no deficits or an immediate deficit only. Groups with an immediate deficit had higher risk of OI, with a seemingly incremental OI risk as more deficits were present. The group with all three deficits was associated with recent falls.

The group with only impaired stabilisation is the oldest group and the unhealthiest. The higher rates of frailty and multimorbidity could be related to the higher age of the participants. A failure to stabilise one’s blood pressure within the first minute is thought to be a sign of poor cardiovascular health and can reflect underlying arterial stiffness and baroreflex dysfunction.

The high rate of atrial fibrillation in this group may be reflective of underlying baroreflex dysfunction. There are further hints of poor cardiovascular health in the medication usage and physical signs, despite there being no differences in self-reported heart failure between the groups. The high rates of ACEI/beta-blockers/diuretics/alpha-blockers, which are commonly used together in the treatment of heart failure, coupled with the widened pulse pressure would suggest that there may be an element of undiagnosed heart failure in this group.

This group is positively associated with episodes of syncope in the past year. This may be due to statistical underpowering given the small sample size (28), the dramatic change from Models A/B to Model C, and the wide confidence intervals for the OR. If I were to postulate a physiological link to explain the relationship, it could be a result of many pathologies including: cardiogenic syncope from arrhythmias (also has a highest rate of atrial fibrillation), an inability to mount an appropriate heart rate response, or an issue with a fixed cardiac output (from undiagnosed heart failure).

This is in keeping with the current literature on the association between the DBP response to orthostasis and cardiovascular outcomes. The Captopril Prevention Project found that DBP OH was a predictor of myocardial infarctions [342] and another study found that a diastolic drop that occurred in the first minute after standing was associated with an increased risk of cardiovascular disease at 11 years follow-up (median) [344], however it is difficult to say whether this represents an ‘immediate deficit’ or ‘impaired stabilisation’.

When comparing the group that has immediate drop and impaired stabilisation, the group with the immediate drop appears to be much healthier as they are less frail, have lower rates of polypharmacy, and have faster gait speed. This furthers the idea that an immediate drop is in
fact a marker of robust health as you need a level of fitness and muscle bulk to be able to generate a large drop. [333, 345]

When comparing the group with just the immediate drop to the group with no deficits, they appear very similar. However, the group with the immediate drop is slightly healthier across multiple categories such as time to stand, multimorbidity, diabetes and polypharmacy.

The group with all three deficits was associated with recent falls in the past year, which makes sense from a pathophysiological point of view. This group is spending a significant duration of time after standing in a state of central hypotension and possibly then cerebral hypoperfusion. Cerebral hypoperfusion is associated with impaired gait, reduced environmental awareness, and dizziness.

Psychotropic medications appear to be associated with late deficits of blood pressure as the Group 1, 5, and 7 all have late deficits are part of their definition and have the highest rates of psychotropic usage. The relationship between psychotropics and OH is well established.[78, 88]

**Conclusion**

By studying active stand patterns as a time series instead of a once off measurement, eight groups have been identified that appear to be different in both clinical characteristics and outcomes. This enables a physician to tailor interventions in a more meaningful manner to try and improve OH.
CHAPTER FOUR: COMPARISON OF EIGHT CLINICALLY CLUSTERED ORTHOSTATIC PATTERNS USING SYSTOLIC AND DIASTOLIC BLOOD PRESSURE
SECTION 18: INTRODUCTION

I the above I report how I manually clustered eight orthostatic patterns according to either the SBP or the DBP diagnostic criteria. As explained in the last section, there are distinct differences between the physiology and clinical associations of OH secondary to SBP versus DBP. This section aims to descriptively analyse the groups from both clustering efforts, to see if there are meaningful differences in utilising the SBP and DBP definitions separately in identifying clinically relevant associations and outcomes.

SECTION 18: RESULTS

The group with no deficits (Group 8) is very similar when defined by either SBP or DBP criteria, the main difference is that Group 8 defined by SBP presents a much larger proportion of the study population (67.6 vs 49.4%) (Table 7).

The group with only the immediate drop (Group 4) is also very similar when defined by either the SBP or DBP criteria, except that, when defined by DBP criteria, there is a much higher prevalence of people with an immediate deficit. If defined by SBP, there are higher rates of hypertension and this group also have a higher baseline SBP (140.3 vs 135.3mmHg) (Table 7).

While there appears to be minor differences if you define Groups 4 and 8 by either SBP or DBP, there are much starker contrasts when looking at Groups 5 (impaired stabilisation, late deficit) and 6 (impaired stabilisation).

Group 5 when defined by the DBP criteria has much higher rates of prefrail/frailty, multimorbidity, and atrial fibrillation. They also had higher rates of self-reported hypertension but a similar baseline SBP when compared to Group 5 defined by SBP criteria. They had higher rates of overall anti-hypertensives usage but also specifically diuretics, CCB, and alpha-blockers. There was also a much higher prevalence of past/current smokers in the Group 5 defined by DBP (73.1 vs 56.6%) (Table 7).

The differences between Group 6 when defined by SBP and DBP criteria are similar to those of Group 5, Group 6 when defined by DBP have higher rates of prefrail/frailty, multimorbidity, and atrial fibrillation. They also had higher rates of overall anti-hypertensives usage and much higher rates of each class of anti-hypertensive usage with the exception being CCBs (Group 6 defined by SBP had much higher rates of use: 29.7% vs 7.7%).
With regards outcomes, Group 6 defined by DBP has higher rates of recent falls and syncope. Group 6 defined by SBP had a higher baseline DBP (75.9 vs 71.4 mmHg) and a higher baseline HR (69.9 vs 64.9 bpm) (Table 7).

When comparing the associations from the logistic regression models, Groups 1, 3 and 4 all have similar associations and OR for those cross-sectional outcomes. The differences are that Group 6 (impaired stabilisation only) when defined by DBP is strongly associated with recent syncope (OR 3.61, 1.16-11.24) and that Group 7 (late deficit only) when defined by SBP is associated with OI (OR 1.32, 1.00-1.74). These OR are represented graphically in the forest plots in Figures 7-9.
<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>4904</td>
<td>272</td>
<td>314</td>
<td>43 (0.9)</td>
<td>47 (1.0)</td>
<td>209</td>
<td>383</td>
<td>1505</td>
<td>78 (1.6)</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>61.03</td>
<td>64.5</td>
<td>65.87</td>
<td>68.1</td>
<td>68.94</td>
<td>60.3</td>
<td>61.09</td>
<td>60.12</td>
<td>66.9</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>2706</td>
<td>172</td>
<td>170</td>
<td>23</td>
<td>25</td>
<td>142</td>
<td>204</td>
<td>170</td>
<td>18</td>
</tr>
<tr>
<td>Pre-frail/Frail, n (%)</td>
<td>1315</td>
<td>92</td>
<td>96</td>
<td>10</td>
<td>18</td>
<td>52</td>
<td>94</td>
<td>171</td>
<td>354</td>
</tr>
<tr>
<td>Mean Time to stand (SD)</td>
<td>7.64</td>
<td>7.9</td>
<td>8.12</td>
<td>8.3</td>
<td>8.47</td>
<td>7.3</td>
<td>7.2</td>
<td>7.4</td>
<td>7.5</td>
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<td>Median MMSE (IQR)</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>28 (3)</td>
<td>29 (2.0)</td>
<td>29 (2)</td>
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<td>Multimorbidity, n (%)</td>
<td>2240</td>
<td>142</td>
<td>161</td>
<td>22</td>
<td>23</td>
<td>85</td>
<td>173</td>
<td>303</td>
<td>92</td>
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<td>Atrial Fibrillation, n</td>
<td>109</td>
<td>7.2</td>
<td>18.5</td>
<td>2.4</td>
<td>2.1</td>
<td>1.0</td>
<td>2.1</td>
<td>2.6</td>
<td>2.1</td>
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<tr>
<td>Parkinson's disease, n</td>
<td>15 (0.3)</td>
<td>2.0</td>
<td>2.6</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.0</td>
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<td>Diabetes Mellitus, n (%)</td>
<td>301</td>
<td>17.0</td>
<td>17.0</td>
<td>17.0</td>
<td>17.0</td>
<td>17.0</td>
<td>17.0</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>138</td>
<td>143</td>
<td>143</td>
<td>24</td>
<td>22</td>
<td>183</td>
<td>294</td>
<td>63</td>
<td>39</td>
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<td>Polypharmacy, n (%)</td>
<td>832</td>
<td>68</td>
<td>73</td>
<td>13</td>
<td>13</td>
<td>25</td>
<td>53</td>
<td>98</td>
<td>203</td>
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<td>Anti-hypertensives</td>
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<td></td>
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<td></td>
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<tr>
<td>Overall</td>
<td>1554</td>
<td>99</td>
<td>128</td>
<td>44</td>
<td>60</td>
<td>117</td>
<td>211</td>
<td>435</td>
<td>67</td>
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<td>Beta-blockers</td>
<td>564</td>
<td>55</td>
<td>64</td>
<td>23</td>
<td>28</td>
<td>56</td>
<td>81</td>
<td>168</td>
<td>27</td>
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<td>Diuretics</td>
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<td>64</td>
<td>13</td>
<td>19</td>
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<td>35</td>
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<td>ACEI/ARB</td>
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<td>53</td>
<td>69</td>
<td>13</td>
<td>19</td>
<td>33</td>
<td>150</td>
<td>308</td>
<td>44</td>
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<tr>
<td>CCB</td>
<td>402</td>
<td>23</td>
<td>33</td>
<td>6</td>
<td>11</td>
<td>36</td>
<td>38</td>
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<td>Alpha-blockers</td>
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<td>1</td>
<td>9</td>
<td>15</td>
<td>2</td>
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</table>
Table 7 continued. Comparison of the eight active stand groups when defined by SBP or DBP criteria. SD: standard deviation.

<table>
<thead>
<tr>
<th>Overall</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>DBP</td>
<td>SBP</td>
<td>DBP</td>
<td>SBP</td>
<td>DBP</td>
<td>SBP</td>
<td>DBP</td>
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<tr>
<td>Psychoactive medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>444 (9.1)</td>
<td>46 (16.9)</td>
<td>50 (15.9)</td>
<td>6 (14.0)</td>
<td>4 (8.5)</td>
<td>16 (7.7)</td>
<td>26 (6.8)</td>
<td>67 (10.6)</td>
</tr>
<tr>
<td>Z-drugs</td>
<td>109 (2.2)</td>
<td>12 (4.4)</td>
<td>18 (5.8)</td>
<td>2 (4.7)</td>
<td>3 (6.5)</td>
<td>3 (1.4)</td>
<td>2 (0.5)</td>
<td>14 (2.2)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>140 (2.9)</td>
<td>17 (6.3)</td>
<td>12 (3.8)</td>
<td>0 (0.0)</td>
<td>1 (2.2)</td>
<td>9 (4.3)</td>
<td>10 (2.6)</td>
<td>15 (2.4)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>281 (5.7)</td>
<td>35 (12.9)</td>
<td>35 (11.2)</td>
<td>4 (9.3)</td>
<td>1 (2.1)</td>
<td>9 (4.3)</td>
<td>17 (4.4)</td>
<td>47 (7.4)</td>
</tr>
<tr>
<td>Orthostatic Intolerance during active stand, n (%)</td>
<td>1883 (38.4)</td>
<td>130 (47.8)</td>
<td>144 (45.9)</td>
<td>21 (48.8)</td>
<td>20 (42.6)</td>
<td>93 (44.5)</td>
<td>154 (41.2)</td>
<td>271 (42.9)</td>
</tr>
<tr>
<td>At least 1 fall in the past 12 months, n (%)</td>
<td>960 (19.6)</td>
<td>77 (28.3)</td>
<td>88 (28.0)</td>
<td>6 (14.0)</td>
<td>13 (27.7)</td>
<td>36 (17.3)</td>
<td>74 (19.4)</td>
<td>125 (19.8)</td>
</tr>
<tr>
<td>At least 1 blackout in the past 12 months, n (%)</td>
<td>226 (4.5)</td>
<td>13 (4.8)</td>
<td>12 (3.9)</td>
<td>1 (2.3)</td>
<td>2 (4.3)</td>
<td>11 (5.3)</td>
<td>20 (5.2)</td>
<td>23 (3.7)</td>
</tr>
<tr>
<td>Mean baseline DBP, mmHg (SD)</td>
<td>73.15 (11.2)</td>
<td>76.81 (12.8)</td>
<td>76.75 (12.4)</td>
<td>75.00 (14.3)</td>
<td>73.90 (12.3)</td>
<td>76.70 (13.8)</td>
<td>76.36 (12.2)</td>
<td>75.06 (11.3)</td>
</tr>
<tr>
<td>Mean baseline SBP, mmHg (SD)</td>
<td>135.81 (22.3)</td>
<td>147.7 (24.9)</td>
<td>141.91 (25.1)</td>
<td>142.1 (27.9)</td>
<td>141.83 (26.9)</td>
<td>142.9 (25.0)</td>
<td>141.67 (24.3)</td>
<td>140.3 (23.0)</td>
</tr>
<tr>
<td>Mean baseline HR, bpm (SD)</td>
<td>64.95 (9.9)</td>
<td>61.9 (9.9)</td>
<td>62.3 (9.8)</td>
<td>63.5 (9.8)</td>
<td>63.09 (10.6)</td>
<td>61.2 (9.2)</td>
<td>62.81 (9.3)</td>
<td>63.1 (9.3)</td>
</tr>
<tr>
<td>Angina</td>
<td>208 (4.3)</td>
<td>15 (5.5)</td>
<td>18 (5.7)</td>
<td>2 (4.6)</td>
<td>1 (2.1)</td>
<td>10 (4.8)</td>
<td>23 (6.0)</td>
<td>33 (5.2)</td>
</tr>
<tr>
<td>Heart attack</td>
<td>189 (3.86)</td>
<td>6 (2.2)</td>
<td>14 (4.5)</td>
<td>1 (2.3)</td>
<td>4 (8.5)</td>
<td>9 (4.3)</td>
<td>16 (4.2)</td>
<td>27 (4.3)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1967 (40.15)</td>
<td>109 (40.1)</td>
<td>125 (39.8)</td>
<td>16 (37.2)</td>
<td>22 (46.8)</td>
<td>80 (38.3)</td>
<td>144 (37.6)</td>
<td>245 (38.8)</td>
</tr>
<tr>
<td>Past/current smokers</td>
<td>2653 (54.16)</td>
<td>144 (52.9)</td>
<td>174 (55.4)</td>
<td>26 (60.5)</td>
<td>24 (51.1)</td>
<td>112 (53.6)</td>
<td>213 (55.6)</td>
<td>318 (50.3)</td>
</tr>
</tbody>
</table>
Figure 7. Forest Plot comparing the OR for orthostatic intolerance of the eight groups when defined by SBP or DBP.
Figure 8. Forest Plot comparing the OR for Recent Falls of the eight groups when defined by SBP or DBP.
Figure 9. Forest Plot comparing the OR for Recent Syncope of the eight groups when defined by SBP or DBP.
SECTION 19: DISCUSSION

One major difference between clustering the groups using purely SBP or DBP criteria is the proportions of the study population in Group 8, which is the completely ‘normal’ active stand grouping (SBP: 67.6% vs DBP: 49.4%). This finding is in keeping with a previous study of older adult who were inpatients in Italian hospitals that found diastolic OH was more prevalent than systolic OH when taking intermittent blood pressure measurements during AS. [346]

When comparing according to either SBP or DBP definition, both definitions are in keeping with the accumulation of health deficits theory and the groups with more AS deficits have a greater number of clinical deficits despite not being the oldest. There is an interesting trend when looking at the patterns of deficit accumulation between the SBP and DBP groups because the DBP groups have higher rates of cardiovascular risk factors and cardiovascular disease. There appears to be a higher prevalence of past/current smokers, atrial fibrillation, previous heart attacks, and anti-hypertensive usage (especially diuretics) in the DBP groups.

The association between cardiovascular disease and DBP OH is reflected in a previous study that demonstrated that patients who had DBP OH had significantly higher intima-media thickness (IMT) ($p = 0.010$) than patients with a normal AS. [347] IMT is a commonly used surrogate marker for early atherosclerosis and is associated with cardiovascular risk factors such as: SBP hypertension, smoking and hypercholesterolaemia. [348]

The relationship between OI and the groups with immediate drop in their definition (Groups 1,3,4) furthers the idea the OI is related to the immediate drop but also that the recovery after the drop is as important for developing OI. While there is not as clear a gradient of OR for the DBP criteria, Group 1 has a higher OR for having OI when defined by either SBP or DBP.

One interesting divergence in the OR for OI is that when Group 7 was defined by SBP criteria, there is an increased likelihood of having OI. This may be a result of the larger effect SBP changes can have on pulse pressure and therefore cerebral hypoperfusion.

I found no differences in the rates of falls and whether I clustered the groups using purely SBP or DBP criteria. However, there has been some research that has found that there is an association between DBP OH and the fear of falling (FOF), which was not found in patients with SBP OH and that the greater the DBP drop, the greater the likelihood of having FOF was. [349] FOF is a recognised risk factor for falls [350], however, as mentioned previously, falls are complex multifactorial outcome that are rarely attributed to one thing.
Conclusion

The current definition of OH using both SBP and DBP criteria may be capturing groups with different underlying pathology and clinical associations. Using purely the DBP definition, there was a higher proportion of participants with cardiovascular disease and risk factors associated with DBP deficits. The finding that a greater proportion of people would have a ‘normal’ active stand when using only the SBP definition is interesting and suggests that focusing purely on SBP criteria may mean missing a diagnosis of OH.
CHAPTER FIVE: HEART RATE ANALYSIS OF EIGHT CLINICALLY CLUSTERED ORTHOSTATIC PATTERNS
SECTION 21: INTRODUCTION

Resting heart rate (RHR) is a sensitive marker of ANS health and a raised RHR is associated with an increased risk of heart failure, atrial fibrillation, stroke, cancer, and all-cause mortality.[351] Similarly, the mean orthostatic HR between 30-60s mark of an active stand (meanHR) has been found to be an independent predictor of mortality at 2-year follow-up.[352]

In response to the haemodynamic stress of standing up, there is a sudden ‘vagal withdrawal’ resulting in a rapid increase in heart rate. This increase in heart rate is sustained over the next 5-10 seconds of the stand is due to a combination of the vagal inhibition and the increase in sympathetic action from the medulla.[23, 353] Once this raised heart rate has achieved an adequate SBP recovery, there is a rapid decline in heart rate back to its baseline, known as heart rate recovery (HRR), which is driven by parasympathetic reactivation and sympathetic withdrawal.[353] The ability to raise a heart rate response and then be able to quickly return to baseline is a well-recognised marker of autonomic function and control. In neurogenic OH, there is frequently a blunted or absent heart rate raise in response to orthostasis.[18, 354] HRR is typically studied as a measure of autonomic control in the context of after exercise and is a common non-invasive measurement in cardiology research[355] and, in patients with underlying coronary artery disease, delayed HRR is significantly associated with all-cause mortality[356] and development of diabetes.[357] The speed of HRR between the 10-20second mark of an active stand has been identified as a predictor of increased mortality at 4 years.[358]

Considering the effect that the heart rate response has on blood pressure in the active stand, I wanted to study the heart rate patterns of the eight orthostatic groups.

SECTION 22: METHODS

Statistical analyses were performed in Stata version 14.1 (Stata Corp., College Station, TX, USA).

RHR was calculated as the mean value between 60 and 30s before stand.

meanHR was calculated as the mean of the HR between 30 and 60s post-stand.

MaxHR was the highest HR achieved during the active stand.

DeltaHR is the difference between the baselineHR and the MaxHR

HRR10_20 the the speed of heart rate recovery between the 10 and 20s mark and is calculated by subtracting the difference from baseline value of HR at 10s from the value at 20s.

\[
\text{Speed of HRR}_{10s|20s} = (\Delta HR_{20s} - \Delta HR_{10s})
\]

I compared these variables using the eight groups defined by both SBP and DBP separately.
SECTION 23: RESULTS

When looking at RHR, Groups 1 and 3 had the lowest RHR (61.9/62.3bpm, 61.2/62.8 bpm) when defined by either SBP or DBP criteria. Groups 5 and 6 had the highest RHR (67.1, 69.9bpm) when defined by SBP, and Groups 5,7,8 had the highest RHR (67.7, 66.7, 66.7bpm) when defined by DBP criteria. A similar pattern is found when looking at meanHR.

Groups 1 and 3 had the lowest maxHR (77.7/76.4bpm, 77.6/79.1bpm) when defined by either SBP or DBP criteria. Group 6 and 8 had the highest maxHR (87.2, 83.2bpm) when defined by SBP and Groups 5,7,8 had the highest maxHR 82.2, 83.0, 84.6bpm) when defined by DBP. Group 8 had the greatest deltaHR (17.6/18.0bpm) and Groups 1 and 5 (15.8/14.0bpm, 15.4/14.5bpm) had the lowest for both SBP and DBP definitions.

Group 8 had the quickest HRR10_20 recovery for both SBP and DBP definitions (-6.7, -6.8) and Group 6 had the slowest (1.6) when defined by SBP. Groups 5 and 6 were the slowest (0.9, 0.3) when defined by DBP.
<table>
<thead>
<tr>
<th></th>
<th>RHR</th>
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<th>deltaHR</th>
<th>HRR10_20</th>
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<tr>
<td></td>
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<td>DBP</td>
<td>SBP</td>
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<td>63.1</td>
<td>74.1</td>
<td>72.8</td>
<td>79.9</td>
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<tr>
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<td>62.8</td>
<td>68.1</td>
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<td>77.6</td>
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<tr>
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<td>79.9</td>
</tr>
<tr>
<td>Group5</td>
<td>67.1</td>
<td>67.7</td>
<td>76.4</td>
<td>74.1</td>
<td>82.8</td>
</tr>
<tr>
<td>Group6</td>
<td>69.9</td>
<td>64.9</td>
<td>81.1</td>
<td>73.3</td>
<td>87.2</td>
</tr>
<tr>
<td>Group7</td>
<td>65.0</td>
<td>66.7</td>
<td>73.4</td>
<td>72.7</td>
<td>81.7</td>
</tr>
<tr>
<td>Group8</td>
<td>65.7</td>
<td>66.7</td>
<td>73.5</td>
<td>74.9</td>
<td>83.2</td>
</tr>
</tbody>
</table>

Table 8. Characterisation of the heart rate features of each of the eight groups.
SECTION 24: DISCUSSION

The groups who are the most comorbid and frail have the highest RHR which might reflect poor physical fitness, poor levels of health, or underlying autonomic dysfunction. Group 6 also had high rates of atrial fibrillation, which if not well controlled can lead to a higher RHR or it may be evidence of underlying baroreflex dysfunction. Group 8, the group with no deficits, had a normal RHR of 65bpm but did not have the lowest RHR overall. Groups 1 and 3 had the lowest RHR (61.9/62.3bpm, 61.2/62.8bpm), it is important to note that Group 1 had the highest rates of beta-blocker usage (20%) so this may be iatrogenic. Previous research by Cooke et al found that a higher RHR was associated with OH in community-dwelling older adults (71.3 vs 68.1bpm) but they do not comment on rates of beta-blocker prescription or atrial fibrillation in their study.

The relationship between RHR and cardiovascular disease/risk factors is bidirectional. RHR is influenced by cardiovascular disease and risk factors as they can lead to state of subclinical dysautonomia (increased sympathetic activity or reduced vagal tone) which results in a higher RHR. On the other hand, a higher RHR increases the oxygen demands of the cardiac cells and it is a recognised risk factor for the future development of cardiovascular ischaemia, arrhythmias, heart failure, and death.

When comparing RHR and the eight groups based on either the SBP or DBP criteria, there were similar RHR for most of the groups. The major difference is when comparing the RHR of Group 6 based on SBP and DBP (69.9 vs 64.9bpm) but there was a large difference in beta-blocker usage between them (8.1 vs 34.6%) that may explain the difference.

meanHR followed a similar pattern to RHR, with a similar difference in meanHR between Group 6 when defined by SBP or DBP.

The main finding from maxHR is that it appears that the groups who start on a higher baseline reach a higher maxHR. This coupled with the fact that most groups had a very similar deltaHR would suggest that the maxHR might be more influenced by the RHR than the deltaHR. There is no differences in deltaHR between the groups depending on whether they are defined by SBP or DBP. Group 8 had the greatest range of HR during the active stand (17.6/18.0) which would suggest a healthy baroreflex sensitivity. Group 5 had the narrowest range of HR during the active stand (15.4/14.5), which could be related to the older age and high rates of prefrail/frailty in this group.
The most striking difference in HRR10_20 is the differences between Group 6 (1.6/0.3) and Group 8 (-6.7/-6.8). Group 8 had the greatest slope for the HRR10_20 which is evidence of a healthy and intact autonomic nervous system, whereas the impaired HRR in Group 6 is indicative of parasympathetic/sympathetic imbalance and dysfunction.[364] While there are very few papers studying the HRR after an AS, there have been some studies that have looked at the HRR immediately after exercise on a treadmill, which is a similar but more intense stimulus. The speed of HRR after exercise has been found to be a prognostic indicator in patients without confirmed underlying cardiovascular disease, who have been referred for a screening exercise stress test. [365, 366]

Conclusion
There appear to be differences in baseline heart rate and max heart rate achieved by each of the eight groups but there does not appear to be major differences if you decide to define them by SBP or DBP. The differences in HRR reflects underlying autonomic control and it is not surprising that the healthiest group appears to have the most responsive and tightest controlled HRR.
CHAPTER SIX: CONCLUSION
SECTION 25: CONCLUSION

I was interested in undertaking this research as I felt that there was a gap between our current OH definition framework and the technology available to assess OH. From my clinical work in the Falls and Syncope Unit, I had noticed that there was a large amount of heterogeneity in the people we were diagnosing with OH and I wanted to attempt to apply a different framework that both utilised more of the data available to us from FinAP technology and applied the concept of OH being a drop followed by a recovery. As discussed in the earlier chapters, AS patterns are the result of complex interactions of underlying physiology, pathology, and medications and, as a result, abnormal AS responses are frequently multifactorial.

In the past few years, the literature has been exploring possible subtypes of OH that may have different values (greater drop for iOH 40/20mmHg) or that occur at different timepoints (iOH and ‘impaired stabilisation’). Considering there are different compensatory mechanisms occurring at different times during an AS, it is plausible to think that different pathologies/medications could impair different compensatory mechanisms and therefore affect the AS pattern at different timepoints.

I have attempted in this study to combine these proposed variants of OH to explore whether there is value in considering the AS a timeseries and to explore whether AS patterns are analogous to the accumulation of health deficits theory. In this study we have found that similar to the accumulation of health deficits theory, the accumulation of AS deficits was reflective of a frailer and more multimorbid population. However, the immediate drop after standing appears to be a marker of good physical health and robustness, even when associated with other orthostatic deficits. This study suggests that one should consider OH not as a single timepoint but as a timeseries of haemodynamic changes and demonstrates that the recovery pattern after the drop is as important, if not more, than the initial BP drop.

The current practice of using SBP or DBP to identify OH may result in two OH populations with different underlying pathophysiology being grouped together. This grouping could result in clinical associations being obscured and less personalised interventions being offered. There also appears to be differences in heart rate measures between the groups which could be contributory to the blood pressure patterns seen. These variations in heart rate may reflect underlying autonomic dysfunction or be a result of medications such as beta-blockers.
To my knowledge, this is the largest study to date and may serve as a population-wide reference to help clinicians identify normal and abnormal AS responses, inform their bedside interpretation, and potentially lead to more personalised medical care. I believe that this study serves as a proof of concept that we should be thinking of OH as a timeseries instead of once off measurements and it also raises questions over using a combined SBP/DBP definition. I hope that this contributes to the scientific process of improving our interpretation of the wealth of information available to us from FinAP technology.

This study has limitations. Firstly, it is of cross-sectional nature and observations do not imply causality. As regards clinical outcomes, our definitions of falls and syncope are limited by recall bias. In addition, our binary OI variable is limited in that not all the features of OI were asked during the AS and also postural dizziness is very common in older people and is often multifactorial [334]. Finally, the method of classifying individuals is open to bias as this was done manually without blinding. However, our classification method is not intended to represent a gold standard as some of the resulting groups were small and there may have been some clinical overlap between them. In practice, some individuals may fit into more than one category, or there may be a spectrum of risk rather than discrete categories. Our data invite hypotheses but cannot answer them.

SECTION 26: IMPLICATIONS FOR FUTURE RESEARCH

We should consider doing further research into defining OH via purely SBP or DBP criteria because when analysing them separately in this study, they appear to identify different populations. It is unclear as to whether this is generalisable outside of the TILDA population so it would be important for it to be repeated in other datasets. There have been no other large-scale studies that have compared groupings defined on SBP vs DBP criteria to assess whether a combined SBP/DBP OH definition is appropriate or accurate.

Further study of the longitudinal implications of these orthostatic grouping is warranted, both to assess the reproducibility of the patterns and to assess whether they can predict future outcomes such as falls/syncope or incident disease. It would be interesting to explore the long-term reproducibility or persistence of AS patterns as we know that there is poor reproducibility in AS that are repeated at 6-8 weeks. It is likely that most participants would switch between the eight orthostatic groupings if followed up long term (greater than 2 years) due to the
multifactorial nature of haemodynamic responses. However, if there was a long-term persistence of AS patterns then this could be a sign of underlying serious pathology. This may be explained by the fact that people who demonstrate persistence in the AS pattern could have a higher burden of disease/dysfunction resulting in reduced compensatory ability. This would mean that their bodies are not capable of the same degree of variability in haemodynamic response to standing that the general healthy population has.

Another interesting aspect would be to explore whether AS patterns would be longitudinally associated with incident diagnosed disease, objective disability, or mortality. It is possible that some AS patterns may be reflective of subtle dysautonomia that are early signs of diseases such as Parkinson’s Disease and Diabetes Mellitus.

Finally, the manual clustering introduces bias into how these groups are formed and further research will apply artificial intelligence techniques, which I hope will more efficiently divide the sample into a smaller number of more different groups. Automatic clustering approaches could be compared with manual approaches in their ability to predict outcomes.


319. TILDA. *TILDA: Where are we now? 2020* [cited 2020 15/09/2020]; Available from: https://tilda.tcd.ie/about/where-are-we-now/.


APPENDIX
**Supplementary Table 1. Results of the logistic regression models for SBP Groups (Models A, B and C).**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Orthostatic intolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model A</td>
<td>1.63 (1.27, 2.08)</td>
<td>&lt;0.00</td>
<td>1</td>
<td>1.7 (0.93, 3.10)</td>
<td>0.08</td>
<td>6</td>
<td>1.42 (1.07, 1.89)</td>
</tr>
<tr>
<td>Model B</td>
<td>1.73 (1.35, 2.23)</td>
<td>&lt;0.00</td>
<td>1</td>
<td>1.85 (1.01, 3.39)</td>
<td>0.04</td>
<td>6</td>
<td>1.46 (1.10, 1.94)</td>
</tr>
<tr>
<td>Model C</td>
<td>1.83 (1.41, 2.38)</td>
<td>&lt;0.00</td>
<td>1</td>
<td>1.85 (0.98, 3.47)</td>
<td>0.05</td>
<td>6</td>
<td>1.60 (1.20, 2.13)</td>
</tr>
</tbody>
</table>

| Falls in the past year | | | | | | | |
| Model A | 1.34 (1.12, 2.12) | 0.003 | 0.50 (0.21, 1.56) | 0.34 | 5 | 0.87 (0.41, 1.24) | 0.64 | 3 | 1.01 (0.32, 1.45) | 0.864 | 1 | 1.01 (0.34, 1.87) | 0.96 | 5 | 0.78 (0.23, 1.98) | 0.75 | 4 | 0.87 (0.45, 1.67) | 0.87 | 5 | (Base) |
| Model B | 1.53 (1.15, 2.03) | 0.003 | 0.58 (0.24, 1.40) | 0.22 | 6 | 0.88 (0.61, 1.28) | 0.50 | 3 | 1.02 (0.82, 1.26) | 0.875 | 1 | 1.04 (0.69, 1.56) | 0.85 | 7 | 0.81 (0.35, 1.85) | 0.61 | 1 | 0.96 (0.69, 1.34) | 0.83 | 1 | (Base) |
| Model C | 1.54 (1.15, 2.07) | 0.004 | 0.64 (0.27, 1.56) | 0.32 | 6 | 0.86 (0.58, 1.26) | 0.44 | 0 | 1.00 (0.80, 1.26) | 0.957 | 1 | 0.90 (0.58, 1.40) | 0.64 | 1 | 0.91 (0.39, 2.22) | 0.82 | 4 | 0.94 (0.67, 1.33) | 0.73 | 2 | (Base) |

| Syncope in the past year | | | | | | | |
| Model A | 1.02 (0.57, 1.82) | 0.949 | 0.48 (0.07, 3.52) | 0.47 | 2 | 1.12 (0.60, 2.13) | 0.71 | 6 | 0.77 (0.49, 1.20) | 0.240 | 1 | 1.66 (0.88, 3.13) | 0.11 | 8 | 1.12 (0.27, 4.71) | 0.87 | 3 | 0.76 (0.39, 1.52) | 0.44 | 3 | (Base) |
| Model B | 0.98 (0.55, 1.76) | 0.943 | 0.45 (0.06, 3.29) | 0.43 | 0 | 1.12 (0.60, 2.10) | 0.72 | 2 | 0.75 (0.48, 1.18) | 0.217 | 1 | 1.56 (0.82, 2.98) | 0.17 | 7 | 1.04 (0.25, 4.39) | 0.95 | 7 | 0.76 (0.38, 1.50) | 0.42 | 3 | (Base) |
| Model C | 0.91 (0.49, 1.66) | 0.750 | 0.56 (0.05, 4.21) | 0.65 | 8 | 1.27 (0.67, 2.41) | 0.46 | 4 | 0.72 (0.45, 1.16) | 0.180 | 1 | 1.29 (0.64, 2.58) | 0.47 | 8 | 0.60 (0.80, 4.47) | 0.61 | 6 | 0.74 (0.37, 1.50) | 0.40 | 9 | (Base) |
### Supplementary Table 2. Results of the logistic regression models for DBP Groups (Models A, B and C).

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
<th>Group 8</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
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<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Orthostatic intolerance</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model A</td>
<td>1.62 (1.28, 2.05)</td>
<td>&lt;0.00 ** 1</td>
<td>1.42 (0.79, 2.54)</td>
<td>0.24 4</td>
<td>1.29 (1.03, 1.60)</td>
<td>0.02 6</td>
<td>1.44 (1.26, 1.65)</td>
<td>&lt;0.00 ** 1</td>
</tr>
<tr>
<td>Model B</td>
<td>1.71 (1.34, 2.18)</td>
<td>&lt;0.00 ** 1</td>
<td>1.54 (0.86, 2.78)</td>
<td>0.14 9</td>
<td>1.29 (1.04, 1.61)</td>
<td>0.02 3</td>
<td>1.43 (1.56, 1.64)</td>
<td>&lt;0.00 ** 1</td>
</tr>
<tr>
<td>Model C</td>
<td>1.77 (1.38-2.27)</td>
<td>&lt;0.00 ** 1</td>
<td>1.68 (0.92-3.05)</td>
<td>0.09 1</td>
<td>1.42 (1.14-1.79)</td>
<td>0.00 2</td>
<td>1.49 (1.30-1.70)</td>
<td>&lt;0.00 ** 1</td>
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<tr>
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<td>1.75 (1.34, 2.28)</td>
<td>&lt;0.00 ** 1</td>
<td>1.71 (0.90, 3.27)</td>
<td>0.10 3</td>
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<td>1.48 (0.77, 2.84)</td>
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<td>1.07 (0.81, 1.40)</td>
<td>0.64 8</td>
<td>1.05 (0.89, 1.23)</td>
<td>0.594</td>
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<tr>
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<td>1.47 (0.75-2.89)</td>
<td>0.26 5</td>
<td>1.12 (0.84-1.48)</td>
<td>0.44 4</td>
<td>1.05 (0.89-1.25)</td>
<td>0.554</td>
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<td>Syncope in the past year</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Model A</td>
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<td>0.99 (0.24, 4.14)</td>
<td>0.99 0</td>
<td>1.23 (0.75, 2.01)</td>
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<td>1.01 (0.73, 1.38)</td>
<td>0.965</td>
</tr>
<tr>
<td>Model B</td>
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<td>0.662</td>
<td>0.96 (0.23, 4.02)</td>
<td>0.95 2</td>
<td>1.23 (0.75, 2.01)</td>
<td>0.41 3</td>
<td>1.01 (0.73, 1.38)</td>
<td>0.961</td>
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<tr>
<td>Model C</td>
<td>0.89 (0.47-1.67)</td>
<td>0.711</td>
<td>1.02 (0.24-4.34)</td>
<td>0.98 1</td>
<td>1.42 (0.86-2.35)</td>
<td>0.17 5</td>
<td>1.08 (0.78-1.51)</td>
<td>0.648</td>
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