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Orthostatic Hypertension: The Contribution of Cardiovascular Risk Factors and Body Composition

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Sara Solis

April 2025

To my family and their unconditional support

Summary

Orthostatic hypertension is an emerging clinical entity characterised by an exaggerated increase in blood pressure upon standing. Although its recognition has grown in recent years, the historical heterogeneity in diagnostic definitions and methodologies has complicated comparisons across studies and delayed standardised clinical understanding. In response to these challenges, a recent consensus definition has been proposed, providing a unified framework for research and clinical practice.

This thesis aims to investigate the prevalence and clinical associations of exaggerated orthostatic pressor response (EOPR) and orthostatic hypertension (OHT), as defined by the recent consensus criteria, in older adults. Furthermore, it explores the contribution of body composition parameters, to these blood pressure phenotypes. Given the physiological influence of body composition parameters understanding their potential role offers novel insights into the potential underlying mechanisms of OHT.

Using data from two independent cohorts—the Technology Research for Independent Living (TRIL) Clinic and the FRAILMatics Clinical Study—this research determined the prevalence of EOPR and OHT, examined their associations with cardiovascular conditions and metabolic markers, and explored the relationships between body composition and orthostatic blood pressure changes. Orthostatic BP responses were assessed at multiple time stamps (including 60-, 90-, 120- and 180-seconds post-stand), allowing for a more nuanced characterisation of haemodynamic patterns.

The prevalence of EOPR ranged from 7.0% to 24.3%, while that of OHT ranged from 7.0% to 21.5% across both cohorts. Notably, EOPR and OHT were significantly associated with female sex ($p = 0.031$, OR = 3.36, 95% CI: 1.1–10.0), heart failure ($p = 0.019$, OR = 2.5, 95% CI: 1.1–5.4), higher haemoglobin levels ($p = 0.050$, OR = 1.4, 95% CI: 1.0–2.0), and lower serum albumin, which appeared to have a protective effect ($p = 0.041$, OR = 0.85, 95% CI: 0.7–0.9). Variations in body composition also emerged as relevant factors, with associations observed for body mass index (BMI) ($p = 0.033$, OR = 1.0, 95% CI: 1.0–1.1), greater adiposity ($p = 0.026$, OR = 1.1, 95% CI: 1.0–1.3), and reduced muscle mass ($p = 0.036$, OR = 0.8, 95% CI: 0.7–0.9). These findings suggest that alterations in body composition may contribute to the pathophysiological mechanisms linking orthostatic blood pressure responses to increased cardiometabolic risk in older adults.

By applying recent consensus definitions and evaluating body composition in this context, this study advances current understanding of OHT and its clinical significance, underscoring the need for further research to confirm causal pathways and develop targeted intervention strategies.

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List of abbreviations

ABPM	Ambulatory Blood Pressure Monitor
ALB	Albumin
Alb: Cr	Albumin: Creatinine ratio
ANS	Autonomic Nervous System
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BNP	B-type natriuretic peptide
BNP: ANP	B-type natriuretic peptide: Atrial natriuretic peptide ratio
BP	Blood Pressure
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CKD	Chronic Kidney Disease
CO	Cardiac Output
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM2	Type 2 Diabetes Mellitus
EOPR	Exaggerated Orthostatic Pressor Response
Epi: Cr	Epinephrine: Creatinine ratio
HbA1c	Haemoglobin A1C
HF	Heart Failure
HGS	Hand Grip Strength

HR	Heart Rate
HTN	Hypertension
HUT	Head-up tilting test
MACE	Mayor Adverse Cardiovascular Events
MAP	Mean Arterial Pressure
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NE	Norepinephrine
NO	Nitic Oxide
OH	Orthostatic Hypotension
OHT	Orthostatic Hypertension
OR	Odds ratio
PAD	Peripheral Arterial Disease
PNS	Parasympathetic Nervous System
RAAS	Renin-Angiotensin-Aldosterone System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SHEP	Systolic Hypertension in the Elderly Program
SMP	Skeletal Muscle Pump
SNS	Sympathetic Nervous system
SPRINT	Systolic Blood Pressure Intervention Trial
TIA	Transient Ischemic Attack.
TRIL	Technology Research for Independent Living

Chapter 1: Introduction

Orthostasis and blood pressure response

Transitioning to an upright position demands rapid and coordinated physiological adjustments to counteract the effects of gravity and maintain adequate blood flow to vital organs (1). Gravity poses a significant challenge for the human body, since all intravascular pressures have a gravity dependent component. Consequently, it requires multiple control mechanisms to preserve optimal tissue perfusion when the magnitude or direction of the gravitational field changes relative to the body (2). This process, known as orthostasis, highlights the body's ability to maintain haemodynamic stability through intricate regulatory mechanisms.

Upon standing, blood is redistributed due to a venous pooling that shifts away blood from the thorax to the highly compliant venous capacitance vessels located below the diaphragm. This redistribution creates a transient drop in blood pressure (BP) and in consequence the venous return and cardiac preload, leading to a transient decline in stroke volume and mean arterial blood pressure (3). The decrease in BP subsequently reduces both peripheral and cerebral perfusion pressures (4), that without a counter-regulatory response, a precipitous fall in BP would occur, and cerebral hypoperfusion and loss of consciousness would follow (5).

The neuronal pathways of the autonomic nervous system (ANS) are the initial hemodynamic responses, this occurs trough the baroreceptors which are mechanosensitive afferent nerve endings that are interspersed in the arterial elastic layers (6). Baroreflexes are the principal counter regulators of short-term adjustments in systolic blood pressure (SBP), as their role is to “buffer” changes in BP by the level of sympathetic nervous system (SNS) outflow (7). When standing, the transient drop in BP is sensed by the baroreceptors which detect mechanical

deformation of the vessel wall. This triggers a decrease in the activity of the parasympathetic nervous system (PNS) and an increase in the SNS outflow via the vagus nerve (6).

Consequently, heart rate (HR) and cardiac contractility increase, as illustrated in Figure 1-1. Additionally, the heightened activity of the SNS promotes peripheral and splanchnic vasoconstriction (4, 8), ultimately enhancing cardiac output (CO) (9). Although, peripheral vasoconstriction may not significantly contribute BP recovery and maintenance, contractions of the lower limb muscles, denominated as skeletal muscle pump (SMP), appear to play a more prominent role by reducing venous pooling and actively pumping venous blood back to the heart (5). In health, the work in tandem of these systems restores BP within 30 seconds (10).

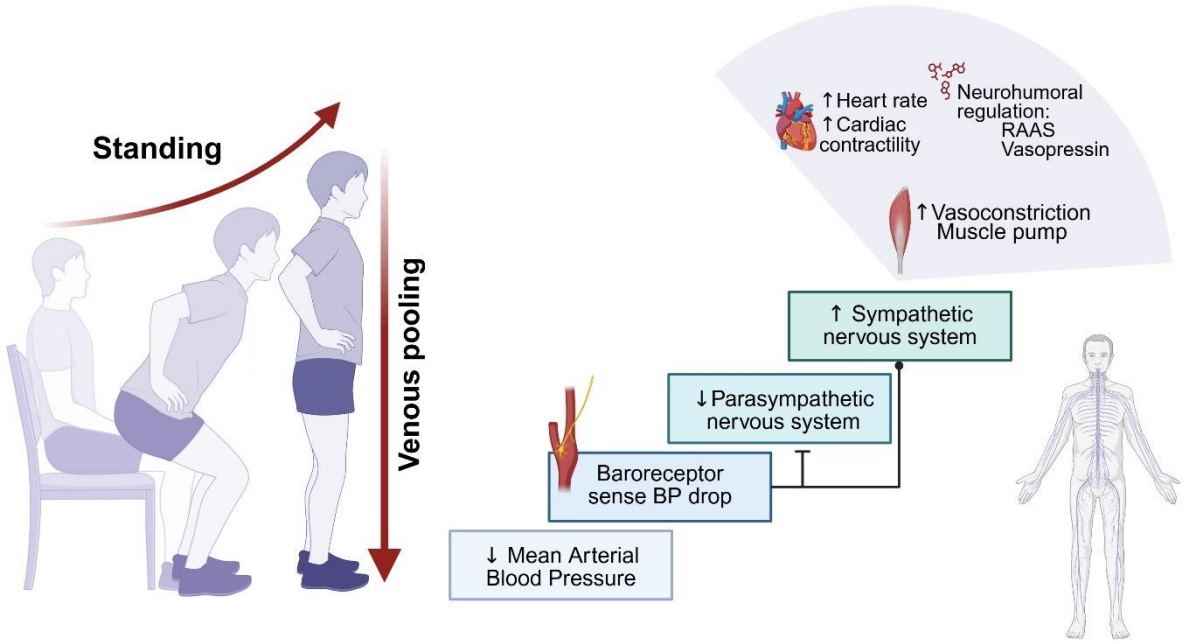

Figure 1-1. Adaptative cardiovascular mechanisms upon standing.

While HR and vasoconstriction help to recover BP extremely fast, maintaining BP and ensuring long-term cardiovascular stability requires both short-term (vasoregulatory) and long-term (natriuretic and diuretic) mechanism to support cardiopulmonary homeostasis (7). Baroreflexes also contribute to these processes by activating neurohumoral pathways, such as the renin-angiotensin-aldosterone system (RAAS) and vasopressin, which are essential for sustaining vascular tone and fluid balance, particularly during prolonged orthostasis (11, 12). Therefore, proper baroreceptor function is crucial for both immediate BP adjustments and long-term regulation.

Phenotypes of blood pressure response

The variability in BP upon standing gives rise to different phenotypes, which originate from inadequate coordination of ANS responses (13). These responses can manifest as an excessive drop on BP upon standing, as observed in orthostatic hypotension (OH), or conversely, as an exaggerated increase in BP, characteristic of orthostatic hypertension (OHT) (14, 15). Although OH was not formally defined until 1996—when a consensus statement was published by the American Autonomic Society and the American Academy of Neurology—it remains the most common and extensively studied disorder related to orthostasis (16).

The prevalence of OH varies widely depending on the study setting and population characteristics, such as age and comorbidities. In community-dwelling older adults, prevalence estimates range from 5% to 30%, with higher rates observed with increasing age (17-20). This BP phenotype can be asymptomatic or present with symptoms of orthostatic intolerance, such

as light-headedness and pre-syncope. Its clinical significance lies in its strong association with both syncopal and non-syncopal falls (21, 22). The aetiology of OH can be divided in non-neurogenic and neurogenic. Non-neurogenic causes of OH include hypovolaemia, medications, heart failure or valvular heart disease (23). In contrast, neurogenic OH results from damage caused to the central or peripheral baroreceptor and ANS pathways by either deposition of α-synuclein in primary autonomic failure or small fibre peripheral neuropathies in secondary autonomic failure (5, 24).

As mentioned before, the proper functioning of baroreceptors, plays a significant role in the maintaining BP and enabling a proper response to stand. However, impairment of the baroreflex system is not limited to neurodegenerative conditions (25). Other chronic pathophysiological and structural changes tend to diminish the baroreceptor capacity, primarily at the level of mechanosensory transduction. This includes direct damage to mechanosensitive baroreceptors, a disruption of the coupling between vascular wall stretch and receptor activation, and increased vascular stiffness, which leads to reduced distensibility (6). The diminished baroreflex sensitivity results in impaired autonomic regulation which favours an exaggerated sympathetic outflow (26). This heightened sympathetic activity has been associated to reduced cardiac performance and may be the aetiology of another BP phenotype: orthostatic hypertension (27, 28).

Orthostatic hypertension

OHT refers to an exaggerated increase in BP on standing. Although it has been infrequently reported in the literature (29), there is a growing recognition of its clinical significance (30). To understand the clinical relevance of OHT, it is necessary to examine how its definition has evolved over time.

Historical definitions and diagnostic approaches

Initially, an orthostatic increase of BP was described in 1922 by Schneider and Truesdell, whose study of apparently healthy aviators revealed that some individuals exhibited an average orthostatic increase in SBP by 2.3 mmHg with a maximal change reaching up to 40 mmHg (31). Subsequently, in 1940, the term of "orthostatic hypertension" was introduced by McCann and Romansky, who reported several cases of women with renal ptosis. They termed OHT as an increase in diastolic blood pressure (DBP) of 20 mmHg or more upon assuming an upright posture (32).

Over time, numerous research groups have proposed a definition for OHT. None of them based on normative data or cardiovascular risk estimates (33). Some definitions have focused solely on SBP, considering an increase of ≥10 or 20 mmHg as diagnostic (34). Others included the absolute difference in both SBP and DBP, with some proposing a threshold of ≥20 mmHg of SBP and ≥10 mmHg of DBP (35). Certain groups also have emphasised the transition from a normotensive supine BP to hypertensive levels (defined as ≥140/90 mmHg) upon standing as

indicative of OHT (36). Nevertheless, a standardised definition was not established until recent years, as discussed in subsequent sections

In addition to the definition variability, different diagnostic protocols have been employed to diagnose OHT and studies vary in their use of SBP and/or DBP, diagnostic cut-offs, and timings of BP measurements. While some studies have utilised passive head-up tilt testing (37), others have relied on active stand tests, using either manual or beat-to-beat BP measurements (38). This distinction is important, as the active stand test has shown to produce a marked transient BP reduction during the initial phase, likely reflecting systemic vasodilatation mediated by cardiopulmonary baroreflex activation (39). As summarised in Table 1, previous studies have employed heterogeneous definitions, varied diagnostic thresholds, and different measurement protocols. These methodological inconsistencies complicate the comparability of findings and have delayed the development of standardised clinical guidelines.

Table 1. Previous studies investigating OHT

Year	Author	Definition of OHT	Method of detection	Sample	Design	Observed clinical associations
1998	Kario et. al.(34)	ΔSBP ≥10 mmHg in the average of 6-10 min after standing	HUT test 24-h ABPM	Individuals with HTN aged ≥60	Cross sectional	• Nocturnal dipping
2000	Alagiakrishnan et. al. (38)	ΔSBP or DBP ≥10 mmHg at 3 min after standing	Active stand test	Individuals aged ≥65	Cohort	• Hypertension • BMI
2001	Yoshinari et. al. (36)	Conversion in SBP to ≥140 mmHg and DBP to ≥ 90 mmHg at 1 min after standing	Active stand test	Males with and without DM2	Cross sectional	• Diminished vibration sensation • Hypertriglyceridemia
2002	Kario et. al. (37)	ΔSBP ≥20 mmHg in the average of 6-10 min after standing	HUT MRI	Individuals with HTN aged ≥60	Cross sectional	• Silent cerebrovascular disease

2004	Eguchi et. al. (40)	ΔSBP ≥10 mmHg in the average of 2-9 min after standing	HUT ABPM MRI	Individuals with and without HTN	Cross sectional	• Silent cerebral infarct • Higher BNP:ANP ratio
2008	Hoshide et. al. (41)	Change of SBP divided by deciles	ABPM	Individuals with HTN	RCT	• Higher BNP level • Higher urinary Alb:Cr ratio
2010	Fan et. al.(42)	ΔSBP ≥20 mmHg after 3 min standing	Active stand test	Individuals with and without HTN aged ≥45	Cross sectional	• PAD • Stroke
2011	Yatsuya et. al. (43)	ΔSBP >20 mmHg categorized in 5 categories by cutoff points	Active stand test	Individuals aged 45-64	Cohort	• Lacunar stroke
2015	Veronese et. al. (44)	ΔSBP >20 mmHg after 1 and 3 min standing	Active stand test	Individuals aged ≥65	Cohort	• All-cause mortality • CVD mortality

2016	Agnoletti et. al. (45)	ΔSBP >20 mmHg after 1 and 3 min standing	Active stand test	Individuals aged ≥80 and living in a nursing home	Cohort	• CVD mortality • All-cause mortality
2016	Bursztyn et. al. (46)	ΔSBP >20 mmHg after 1 min standing	Active stand test	Individuals aged ≥85 years	Cohort	• Higher BMI • Anaemia
2016	Townsend et. al. (35)	ΔSBP ≥20 mmHg or ΔDBP ≥10 mmHg after 1 min standing	Active stand test	Individuals with HTN aged ≥50	Cross sectional	• High glucose • High weight • High sodium
2017	Velilla-Zancada et. al. (47)	ΔSBP ≥20 mmHg or ΔDBP ≥10 mmHg at 1 and/or 3 min after standing	Active stand test	Individuals aged ≥18	Cross sectional	• All-cause mortality
2018	Bhuachalla et. al.(48)	ΔSBP ≥20 mmHg or ΔDBP ≥10 mmHg at	Active stand test	Individuals aged ≥50	Cohort	• Age-related macular degeneration

		time 30s – 110 s after standing				
2019	Kostis et. al. (49)	ΔSBP ≥15 mmHg after 1min standing	Active stand test	Individuals with HTN aged ≥60	RCT	• All-cause mortality
2021	Rouabhi et. al. (50)	ΔSBP >20 mmHg from seated to standing	Active stand test	Individuals aged 21 - 74 years with mild to moderate CKD	Cohort	• Higher BMI • Higher risk of kidney outcomes or mortality
2022	Palatini et. al. (51)	Increments of SBP and DBP divided by deciles	Active stand test ABPM	Individuals with HTN aged ≥18	Cohort	• Smoking • Higher Epi:Cr ratio • MACE • Renal events
2022	Barzkar et. al. (52)	ΔSBP ≥20 mmHg or ΔDBP ≥10 mmHg at 3 min after standing	Active stand test	Individuals with history of TIA or minor stroke	Retrospective	• Lower incidence of TIA

2022	Strumia et. al. (53)	ΔSBP ≥20 mmHg or ΔDBP ≥10 mmHg at 3 min after standing	Active stand test Cognitive test	Individuals aged ≥65	Cohort	• Cognition (MMSE 0.52 points lower)
2023	Palatini et. al. (54)	ΔSBP >20 mmHg when standing	Active stand test ABPM	Individuals with HTN aged ≥18	Cohort	• Lower supine SBP
2024	Ma et. al. (55)	Change of SBP divided in 5 categories	Active stand test	Individuals aged 45-64	Cohort	• Dementia
2024	Choi et. al. (56)	ΔSBP >20 mmHg within 3 min standing and upright SBP ≥140mmHg	Active stand test	Individuals aged ≥65 years with HTN	RCT	• Physical frailty • Cognitive impairment

ABPM: ambulatory blood pressure monitor**; Alb: Cr:** Albumin: Creatinine ratio**; BNP:ANP:** B-type natriuretic peptide: Atrial natriuretic peptide ratio**; BMI:** body mass index**; CKD:** chronic kidney Disease**; CVD:** cardiovascular disease**; DBP:** diastolic blood pressure**; DM2:** type 2 diabetes mellitus**; Epi:Cr:** Epinephrine: Creatinine ratio**; HTN:** hypertension**; HUT:** Head-up tilting test**; MACE:** mayor adverse cardiovascular events**; MMSE:** Mini-Mental State Examination**; MRI:** magnetic resonance imaging**; PAD:** peripheral arterial disease**; SBP:** systolic blood pressure**; TIA**: transient ischemic attack**.**

Consensus definition of OHT

In 2023, OHT was recognized in the European Society of Hypertension (ESH) guidelines as a "Specific Hypertension Phenotype," emphasizing the ongoing lack of a universally accepted definition (57). To address this gap, the American Autonomic Society and the Japanese Society of Hypertension jointly proposed a consensus definition in 2023, aiming at establishing a pragmatic framework suitable for use in research and epidemiological studies (58). This consensus recognized that the increase in BP upon standing can manifest with and without increasing the absolute BP value, therefore they introduced the term Exaggerated Orthostatic Pressor Response (EOPR) and established a diagnostic criteria for OHT that included the increase of the absolute BP value.

This proposal was grounded by evidence from large population-bases studies, such as the Malmö Preventive Project, which included 33,346 individuals aged 45.7 ± 7.4 years, reported a mean increase in SBP upon standing of 1.2 mmHg with a standard deviation (SD) of 8.8 mmHg. Similarly, the Malmö Offspring Study demonstrated that, among 4,019 individuals, SBP increased by 1.4 ± 8.6 mmHg after three min of standing (59, 60). Based on these findings, a sustained SBP increase of at least 20 mmHg, corresponding to two standard deviations above the population mean, was proposed as diagnostic threshold for EOPR (58), recognising that this elevation can lead to either normal (normotensive) or high (hypertensive) BP levels while upright. The rationale for this threshold was to avoid excluding BP elevations that might have negative influences on the cardiovascular system, while remaining within the normotensive range (58). Furthermore, the diagnostic threshold for OHT included individuals

who met this criterion and exhibited an absolute standing SBP reaching hypertensive levels of ≥140 mmHg, (13, 58).

Therefore, the consensus definition (58) was established as follows:

- An **exaggerated orthostatic pressor response (EOPR)** is a sustained increase in systolic blood pressure by at least 20mmHg when changing from the supine to the standing position regardless of absolute blood pressure while standing.

- **Orthostatic hypertension (OHT)** is defined as an exaggerated orthostatic pressor response associated with a systolic blood pressure of at least 140 mmHg while standing.

A notable distinguishing feature of the consensus definition was the exclusion of DBP measurements as diagnostic criteria. This decision was based on the observation that, under normal physiological conditions, DBP typically increases by approximately 10 mmHg upon standing due to early stabilisation mechanisms (9), thereby complicating the interpretation of DBP changes in the context of OHT (9, 58). Furthermore, although the definition provides clear diagnostic cutoff values, it does not specify a timeframe for what constitutes a "sustained" increase, nor does it outline the criteria required to confirm the persistence of BP elevation. The timing of measurement remains a subject of ongoing debate. While some studies advocate for assessing blood pressure at 1- and 3-minutes post-standing, others recommend using the mean of measurements taken between 1 and 3 minutes (54). The authors of the consensus definition suggest measuring the standing BP at 1, 3, and 5 min after-standing, to confirm the sustained character of the orthostatic pressor response (58).

Epidemiology

The epidemiology of OHT varies substantially based on diagnostic criteria and population characteristics, with a higher prevalence among females and older individuals (33). In using a definition based on an increase in SBP ≥20 mmHg and/or DBP ≥10 mmHg upon 1 min standing, such as the study by Townsend et al., which aimed to characterise patterns of orthostatic SBP changes among participants in the Systolic Blood Pressure Intervention Trial (SPRINT), a prevalence of OHT of 5% was reported (35). Other studies, which have adopted definitions more closely aligned with the proposed criteria for EOPR, have reported prevalence rate ranging from 5% to 30% (44-46). The differences on the studied population may partly explain this variation. For instance, the study by Agnoletti et. al., which reported a prevalence of 28%, focused on a very old, institutionalised cohort (45). In contrast, Bursztyn's study, conducted among community-dwelling older adults, found a prevalence of only 5% (46). Variations in measurement protocols, including the timing of BP assessments and differences between methodologies, likely contribute to the substantial variability observed on prevalence estimates. This is particularly relevant given that the timing of BP measurement has been shown to influence diagnostic yield; for example, studies averaging BP values between one and three minutes of standing have reported much lower prevalence rates, as low as 0.6% (54).

Aetiology

The aetiology of OHT is unclear; however, it is considered a manifestation of an overactivity of the SNS, accompanied by a reduced PNS activity (61, 62). Early hypothesis suggested that this overresponse resulted from an excessive pooling to compliant veins upon standing. This pooling was thought to reduce the venous return and decreased the cardiac volume, thereby triggering a compensatory sympathetic overactivity that caused vasoconstriction and a rise on BP (63). Notably, these early observations relied on diagnostic criteria solely focused on the increase of DBP, without accounting for SBP changes.

Subsequent findings, particularly those by Lee et. al., challenged this theory. They demonstrated that individuals with OHT did not exhibit significant differences in CO and stroke volume, thereby refuting the idea that excessive pooling was the primary mechanism (64). Moreover, the immediate rise in BP suggests a primary increase in systemic vascular resistance rather a compensatory response to CO (65). Based on these findings, the authors hypothesized that vascular adrenergic hyperactivity was a more plausible explanation for the increase in total peripheral resistance (64). This hypothesis is further supported by studies demonstrating elevated levels of norepinephrine (NE) and vasopressin after standing in groups of individuals with OHT, compared to those with a normal orthostatic BP response (37).

It has been proposed that cardiopulmonary and/or arterial baroreceptor reflex hyperreactivity, as well as α-adrenergic hyper-reactive vascular function, may be responsible to this sympathetic overactivity (48). However, these mechanisms may differ across age groups. In

younger individuals a baroreflex hypersensitivity with sympathetic overactivation is likely to be the predominant mechanism (66). In contrast, in older adults, increased in vascular resistance and central sympathetic activation, due to comorbidities and age-related changes in vascular function, may impair baroreceptor sensitivity, facilitating a sustained BP elevation upon standing (13, 67). In both cases, individuals with OHT appear to exhibit an exaggerated baroreceptor-mediated sympathetic response to the transient drop in BP that occurs with orthostasis, likely due to an impaired regulation of the baroreceptors, with elevated plasma catecholamine level (18, 64).

Potential link between body composition and OHT

OHT has been associated with multiple cardiovascular conditions and metabolic risk factors, including hypertension (38), obesity (50) and hypertriglyceridemia (36), as it will be discussed later in this chapter. Owing to the overlap in risk profiles, these associations suggest that the pathophysiology of OHT may be influenced by underlying systemic factors. They raise the possibility of a pathophysiological link between OHT and body composition. However, while these associations are biologically plausible, direct empirical evidence specifically linking body composition components to orthostatic hypertension remains limited.

Body composition is known to be associated with several cardiovascular and metabolic conditions (68). Among its various components, fat mass and lean muscle mass have emerged as particularly significant determinants of cardiovascular health, primarily due to their substantial variability both between individuals and within individuals over time (69).

Historically, OHT has only been linked with elevated BMI (38, 46). However, BMI is a limited measure and fails to distinguish between fat and lean muscle mass (70). This limitation is particularly significant given the potentially physiological effects of these tissue compartments on orthostatic BP regulation.

Theoretically, the action of fat mass increasing the activity of the SNS (71), reducing the vagal tone (72) and increasing the activity of the SNS and the RAAS (73), may contribute to an exaggerated hypertensive response upon standing. These variations can increase vascular resistance and cardiac output, thereby elevating and facilitating a sustained BP elevation with orthostasis. Muscle mass, on the other hand, plays an important role in maintaining vascular function through its association with arterial elasticity, a key factor facilitating a rapid detection of BP variability during postural changes (74). Furthermore, both fat and muscle compartments modulate baroreflex sensitivity, partly via their impact on arterial distensibility and stiffness (75, 76). Together, these components of body composition may contribute to the underlying pathophysiological mechanisms of OHT.

Clinical associations

The clinical associations of OHT have been demonstrated across different populations, as illustrated in Table 1. A 2023 systematic review and meta-analysis (77), that included studies with orthostatic systolic and/or diastolic hypertension, found that systolic OHT was associated with a 21% greater risk of all-cause mortality (HR: 1.21, 1.05–1.40), a 39% increased risk of CVD mortality (HR: 1.39, 1.05–1.84), and near double odd of stroke/cerebrovascular disease (OR: 1.94, 1.52–2.48). Similarly, Kostis et. al (49). reported that OHT was associated with higher all-cause mortality at 4.5 (HR 1.87, 95% CI 1.30–2.69, p = 0.0007) and 17 years (HR1.40, 95% CI 1.17–1.68, p = 0.0003), in individuals aged ≥60 years at the Systolic Hypertension in the Elderly Program (SHEP).

OHT is associated with cardiovascular comorbidities, including hypertension (38) and peripheral arterial disease (42). In a study including individuals with and without hypertension, Eguchi et. al. (40), demonstrated that OHT, defined as an increase in SBP of ≥10 mmHg, was associated with greater cardiac burden as measured by the BNP/ANP ratio (5.1±3.9 vs. 2.4±1.5, $p < 0.01$) and higher number of silent cerebral infracts. Complementing these findings, Kario et. al. (34) observed that OHT was associated abnormal BP variations, particularly extreme nocturnal dipping in individuals with hypertension aged ≥60 years. The clinical significance of OHT extends to younger demographics as well; data from the Coronary Artery Risk Development in Young Adults study demonstrated that normotensive adults with an increase in BP upon standing showed an increased incidence of arterial hypertension during the follow-up period (66).

Notably, OHT also demonstrate significant correlations with metabolic risk factors, such as higher BMI (35) and elevated blood glucose levels (46). In a study with individuals with type 2 diabetes mellitus, Yoshinari et. al. (36) found that OHT, defined as an increase in SBP/DBP over ≥140/≥90 mmHg, was associated with vibration sensation and hypertriglyceridemia. Additionally, results from SPRINT study, identified other metabolic risk factors associated with OHT such as higher BMI, higher blood levels of glucose and sodium, in individuals with hypertension aged ≥50 years (35).

MD hypothesis and aims

Overall, OHT has been investigated across a range of studies. However, the existing literature is marked by considerable heterogeneity in terms of study populations, methodologies, research objectives, and the underlying mechanisms explored. As mentioned before, the lack of a unified definition has further complicated comparisons between studies and limited the generalisability of findings. The recent development of a consensus definition (58) represents a crucial step toward the understanding of the condition and ensuring more consistent research and clinical practice. Nevertheless, relatively few studies to date have adopted this definition. Moreover, the potential pathophysiological relationship between OHT and body composition has been hinted at but remains unconfirmed. These gaps highlight the need for studies applying the consensus definitions to investigate the clinical and metabolic correlates of OHT more precisely.

This study is motivated by the high prevalence of OHT in the older population alongside persistent gaps in understanding its clinical associations and underlying physiological mechanisms.

Hypothesis

My hypothesis is that an EOPR and OHT, as defined by recent consensus criteria, are associated with a higher prevalence of cardiovascular conditions and metabolic risk factors in older adults. According to these criteria (58), EOPR is characterised by a ≥20 mmHg increase in SBP, with OHT additionally requiring an absolute SBP ≥140 mmHg upon standing. Furthermore, these associations are hypothesised to be mediated, at least in part, by individual differences in body composition, reflecting the influence of adipose and muscle mass on autonomic function and blood pressure regulation

Research question

In line with this hypothesis, the following research question was formulated:

What are the associations between orthostatic hypertension (OHT) and cardiovascular and metabolic conditions in older adults, and how does body composition contribute to these associations?

This hypothesis was tested on data from the Technology Research for Independent Living (TRIL) Clinic and the FRAILMatics Clinical Cohort. Both studies collected information on community-dwelling older adults and including active stand tests and relevant clinical variables. Both were convenience samples, and whilst TRIL was one more representative of healthy volunteers, FRAILMatics was composed by attendees of a hospital-based falls clinic. The inclusion of two distinct cohorts allows for the examination of findings across populations with different health profiles, enhancing the generalisability of the results. The description of the populations utilized in this research will be fully detailed in the methods section, together with the design rationale for each aim. To address the research question, the study was structured around the following specific aims:

1. Determine the prevalence of EOPR and OHT, in two independent populations using the most recent consensus definition.
2. Examine the association between EOPR and OHT and cardiovascular and metabolic conditions.
3. Explore the relationship between body composition parameters and the presence of EOPR and OHT, and investigate their potential contribution to the underlying pathophysiology

Chapter 2: Research Settings and Study Populations

This project encompassed two cross-sectional studies, each utilizing secondary data analysis to explore key physiological patterns with the current definition of EOPR and OHT in two different convenience samples. The first study employed historic data from the Technology Research for Independent Living (TRIL) study. The second study analysed a contemporary dataset from the FRAILMatics clinical sample, providing a more current perspective. I personally carried out all statistical analyses, ensuring a rigorous and comprehensive approach to data interpretation.

Technology Research for Independent Living (TRIL)

The Technology Research for Independent Living (TRIL) was a clinical research platform designed to test and guide the development of new technologies aimed at maintaining and enhancing the independent living of older adults. TRIL was established in 2007 as a partnership between the TRIL Centre and the Mercer's Institute for Successful Ageing at St James's Hospital, Dublin, and funded by Intel Corporation. As well as aiming to guide the growth of new technologies, TRIL also offered a free outpatient clinical service to community-dwelling odder adults aged 60 and over, providing a comprehensive geriatric assessment (CGA) (78) with the goal of creating an efficient, patient-centred service that provided a detailed one-stop multidisciplinary assessment in multiple domains, this through the use of both existing an experimental technologies.

Participant selection

The recruitment of this study occurred trough the referrals from health professionals that considered individuals “at risk” and with the need of a CGA, and self-referrals from persons who learned about the clinic through leaflets, the TRIL website, or media articles. The inclusion criteria were as follows:

- Aged 60 and over
- Not medically unwell
- Able to walk independently (including with a stick or frame)
- Able to provide informed consent for research

Data Collection

The data from TRIL participants was collected between August 2007 and May 2009. Each evaluation included data collection across the following sections:

- Medical assessments
- Active stand test

The medical assessment included an evaluation of anthropometric data, questionnaire of past medical history and use of medications, physical exam, electrocardiogram and blood test.

For the active stand test, individuals underwent a lying-to-standing orthostatic test with non-invasive beat-to-beat blood pressure monitoring by the Finometer Pro device (Finapres Medical Systems BV, Amsterdam, The Netherlands), de detailed description of its calibration and use is described in detail by Romero-Ortuno et. al.(20). The standing process was aimed to be completed within three seconds, and after standing the BP was monitored for three minutes with subjects standing motionless and the monitored arm resting extended by the side (79). Immediately after the test, subjects were asked to report whether they had felt dizziness, faintness or light-headedness.

Measurements

During the TRIL the following individual measurements were considered for analysis.

Anthropometric data

This included measurements of height, weight, and body mass index (BMI), which provide an overall assessment of body composition.

Questionnaire on past medical history

A structured questionnaire was used to collect participants medical histories, including diagnosis of hypertension (history of high BP diagnosed by a physician), heart failure (previous medical diagnosis of heart failure), ischemic heart conditions (history of coronary artery disease, myocardial infarction, or angina), atrial fibrillation (history of diagnosis or

electrocardiographic evidence of atrial fibrillation), and stroke (history of cerebrovascular events, including ischemic or haemorrhagic stroke).

Medication use

Participants provided information on current medication use, including both prescription and over-the-counter drugs. Particular attention was given to medications with potential impact over cardiovascular function during orthostasis, such as beta-blockers, diuretics, alpha blockers and the regular use of nitrates.

Blood tests

Venous blood samples were obtained for the analysis of haemoglobin, albumin, B-type natriuretic peptide (BNP), and osmolality.

Characteristics of the TRIL sample

Between August 2007 and May 2009, a total of 624 community-dwelling older adults aged 60 years and over were recruited from two primary sources: self-referrals (n = 417, 67%) and health professional referrals (n = 207, 33%). Participants referred by health professionals were drawn from a range of allied health services, including the emergency department, the Falls and Blackout Unit at St. James's Hospital, general practitioners, and other clinical settings. Notably, the health profiles of these two groups differed, with self-referred participants exhibiting clinical characteristics consistent with the healthy volunteer effect.

Of the 624 subjects recruited, 16 were unable to complete the active stand test, 10 had an active stand data that could not be saved, and 11 had missing data, resulting in a sample of 587 participants available for analysis. To maximize the reliability of self-reported parameters, participants who scored below 23 on the Mini-Mental State Examination (MMSE) were excluded, as this threshold has been shown to be optimal for dementia screening in Irish community settings (80). Additionally, to reduce confounding conditions with overlapping physiological profiles, participants with diabetes, Parkinson's disease, severe chronic kidney disease, pacemakers, or deficiencies in vitamin B12 and folate were also excluded. These exclusion criteria resulted in the removal of 112 participants, yielding a final analytical sample of 442 individuals. This has been described by Romero-Ortuno (20) and is represented in Figure 2-1.

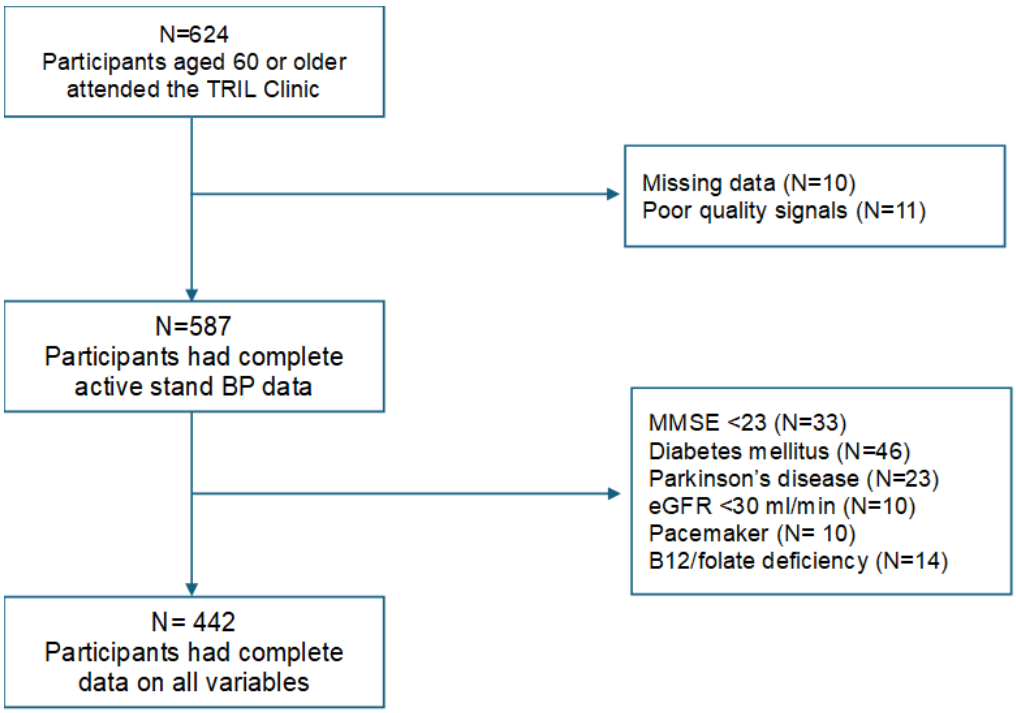

Figure 2-1. Flowchart of participants on TRIL study.

Ethical approval

This study received ethical approval from the St. James's Hospital and Adelaide and Meath hospital inc. National Children's Hospital (SJH/AMNCH) Research Ethics Committee (approval reference number: 2007/06/13). It complied with the Declaration of Helsinki, and all participants provided written informed consent.

FRAILMatics clinical sample

The FRAILMatics clinical sample is a study designed to research and develop advanced frailty identification tools that automatically detect subtle, dysregulated responses to stressors across physiological systems, without requiring expert interpretation. FRAILMatics is a Science Foundation Ireland-funded research programme (18/FRL/6188). The FRAILMatics Clinical sample was established in 2019 at the outpatient Falls and Syncope Unit (FASU) at the Mercer's Institute for Successful Ageing in St James's Hospital, Dublin. The FASU is a specialized outpatient clinic that employs non-invasive neuro-cardiovascular technologies to offer expert evaluations for adult patients referred for dizziness, pre-syncope, syncope, or fall (81).

Participant selection

The recruitment of this study occurred prospectively with the recruitment of one physician (5) in FASU clinic on average 2 mornings per week.

The inclusion criteria were as follows:

- Aged 50 and over
- Able to mobilise independently (including with a stick or frame)
- Able to provide informed consent for research
- Able to transfer independently or with minimal assistance

The exclusion criteria were the following:

- History of confirmed or presumed neurogenic OH
- Contraindication to bioelectrical impedance analysis (BIA)

Data Collection

The data of participants in FRAILMatics was collected between November 2021 and March 2022. Each evaluation included data collection across the following sections:

- Medical history
- Active stand test
- Hand grip strength (HGS)
- Bioelectrical impedance analysis (BIA)

The medical assessment included an evaluation of past medical history and use of medications, through self-report, electronic health record review and General Practitioner correspondence. For the active stand test, individuals underwent a lying-to-standing orthostatic test with non-invasive beat-to-beat blood pressure monitoring by the Finometer Pro device (Finapres Medical Systems BV, Amsterdam, The Netherlands). The standing process was aimed to be completed within three seconds, and after standing the BP was monitored for three minutes with subjects standing motionless and the monitored arm resting extended by the side

HGS was assessed using a Jamar Hydraulic Hand Dynamometer (Performance Health, Wisconsin, USA). The highest value from two consecutive seated measurements taken on the left and right hands was used. Values were rounded to the nearest 2 kg, in accordance with the device's precision. The anthropometric data was measured with a Seca 222 Stadiometer (Seca Ltd, Birmingham, UK) to the nearest 0.01m, and the bioelectrical impedance analysis was performed with the TANITA® DC-430 MAP Body Composition Analyzer (Tanita Europe, Amsterdam, The Netherlands). Participants stood barefoot on the scale, which measured weight to the nearest 0.01 kg.

Measurements

During the FRAILMatics study the following individual measurements were considered for analysis.

Anthropometric data

This included measurements of height, weight, body mass index (BMI), and the BIA was conducted to assess body composition, including fat mass, muscle mass, and percentage of total body water.

Questionnaire on past medical history

A structured questionnaire was used to collect participants medical histories, including diagnosis of hypertension (history of high BP diagnosed by a physician), heart failure (previous medical diagnosis of heart failure), and ischemic heart conditions (history of coronary artery disease, myocardial infarction, or angina).

Medication use

Participants provided information on current medication use, including both prescription and over-the-counter drugs. Particular attention was given to medications with potential impact over cardiovascular function during orthostasis, such as beta-blockers, and diuretics.

Characteristics of the FRAILMatics sample

Between November 2021 and March 2022, a total of 123 community-dwelling adults aged 50 years and over were recruited at the Falls and Syncope Unit at St. James's Hospital, creating a profile of participants that were already seeking medical attention. Of these, five had a contraindication to or declined BIA, seven had probable or confirmed neurogenic OH, and in two there was no active stand test, or the active stand signal was of poor quality. Thus, the included sample size was 109 participants. This has been described by Duggan (5) and is outlined in Figure 3.

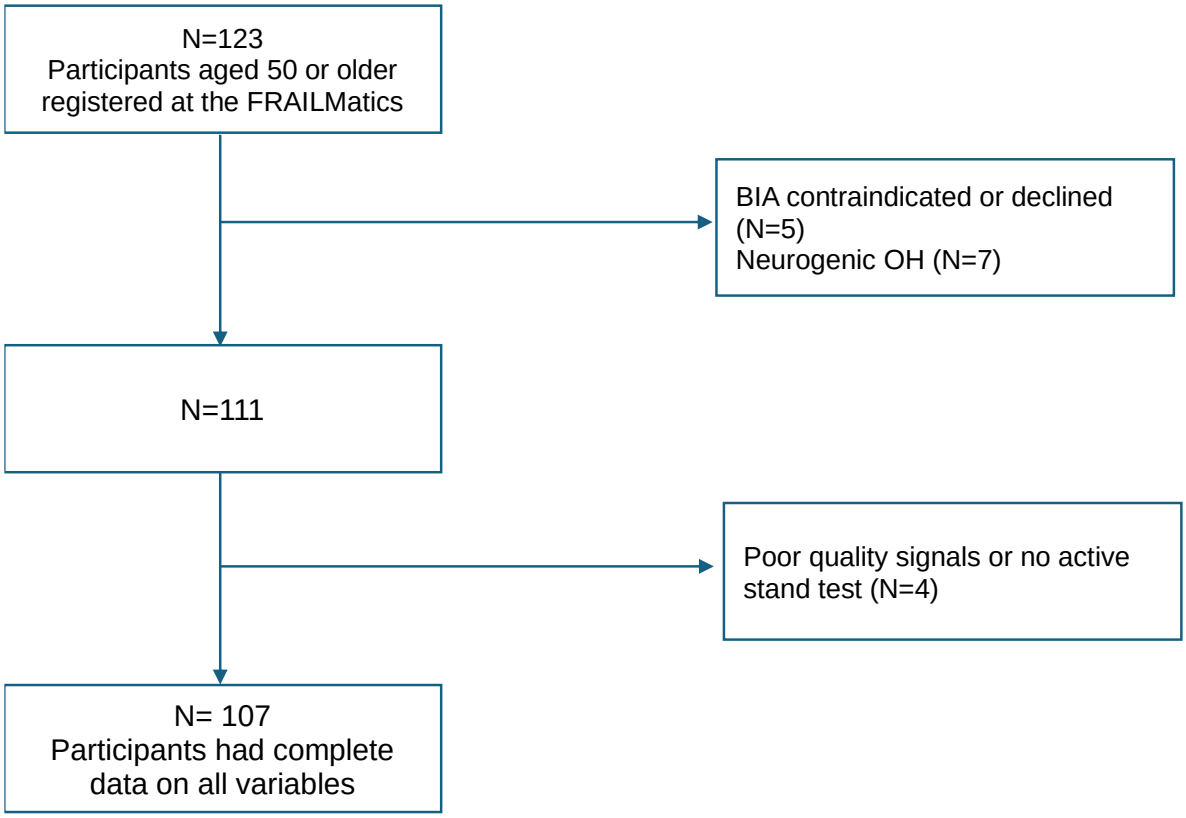

Figure 2- 2. Flowchart of participants on FRAILMatics study

Ethical approval

This study received ethical approval as an amendment to the original FRAILMatics study from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (Project ID: 0221; approved on 2 August 2022). It complied with the Declaration of Helsinki, and all participants provided written informed consent.

Orthostatic Hypertension

The proposed definitions by the American Autonomic Society and the Japanese Society of Hypertension in 2023 (58), were used to diagnose OHT. This definition was chosen because it is the only widely recognized consensus definition of OHT currently available. As previously described, the proposed criteria are based on the change (Δ) in SBP, calculated between baseline SBP the average of measurements obtained prior to standing) and the zenith (highest SBP point reached within 60, 90 and 120 seconds following active stand), as well as the time elapsed since standing. In the TRIL study the time recorded was of 120 seconds and in the FRAILMatics study was of 180 seconds.

The consensus definition of OHT and EOPR do not specify a precise timeframe for the concept of "sustained" elevation. Therefore, for the goals of this study, the term "sustained" was established as an increment of SBP lasting for more than 30 seconds after standing. EOPR was defined as a sustained increase in SBP of at least 20 mmHg upon standing, irrespective of the absolute standing SBP. OHT was defined as the combination of a sustained EOPR and an absolute standing SBP of ≥140 mmHg.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 26.0, Armonk, NY: IBM Corp.). Statistical significance was defined as $P < 0.05$ throughout.

For the demographic characteristics of both cohorts, continuous variables with a normal distribution were summarised using the mean and standard deviation (SD), while non-normally distributed continuous variables were described using the median and interquartile range. Categorical variables were presented as counts (n) and percentages (%). Depending on variable type, the chi-square test was used for categorical variables, and the Student's t-test was used for continuous variables.

Changes in SBP, stratified by orthostatic response status, were represented graphically from the point of standing up to 120 or 180 seconds, depending on data availability for each cohort. Mean SBP changes and standard errors of the mean (SEM) were plotted for the EOPR and OHT groups at each recorded time point.

Logistic regression models were employed to assess the predictive value of relevant covariates on the presence of EOPR and OHT across different time points. Statistical significance was determined using 95% confidence intervals (CI) and a P-value < 0.05. Multicollinearity among independent variables was assessed through correlation analysis; variables demonstrating strong correlations (defined as $r > 0.6$) were excluded from the regression models.

Chapter 3: Results

Technology Research for Independent Living (TRIL)

Introduction

This study explores the factors associated with OHT, using the currently established consensus definition proposed by the American Autonomic Society and the Japanese Society of Hypertension (58). Prior studies utilising alternative definitions of OHT have reported associations with elevated body mass index (BMI) (38), cardiovascular conditions(42) and other metabolic disorders (36), suggesting a potential link between OHT and cardiometabolic risk factors. However, these studies lack a unified definition of OHT, and considerable variability exists in the methodologies used for blood pressure assessment, thereby limiting the comparability and generalisability of their findings.

Considering these methodological inconsistencies, the present study aims to examine EOPR and OHT, along with their clinical and biochemical correlates, using data from the TRIL study. This dataset provides high-resolution measurements through continuous beat-to-beat BP monitoring during an active stand test, complemented by a detailed medical evaluation.

Demographics

A total of 624 community-dwelling older adults aged 60 years and over were registered to be part of the TRIL Clinic. Of those, participants with missing or poor quality data on the active stand test and with conditions that could diminish the reliability of self-reported symptoms (82) or increase the presence of autonomic disorders were excluded. The final analytical sample was 442 and the reasons and number of participants excluded has been described in the methodology section and by Romero-Ortuno (20).

The baseline characteristics of this study have been described in Table 2. The mean age of the sample was 72.1 years (SD = 7.1), 71.7% (n= 317) were female and the mean BMI was of 26.6 (SD 4.5). The prevalence of hypertension was 42.3% (n= 187), heart failure 28.7% (n= 127), ischemic heart conditions 14.7% (n= 65), 4.1% (n=18) had atrial fibrillation, and 3.2% (n = 14) had history of stroke. In relation to the use of drugs with cardiovascular effects 19.5% (n=86) of participants reported regular use of beta blockers, 19.2% (n= 85) used diuretics, 3.2% (n= 14) used alpha blockers, and 2.7% (n= 12) reported regular use of nitrates. Among the blood test, the mean haemoglobin was 13.5 g/dL (SD 1.3), albumin 41.7 g/dL (SD 2.9), B-type natriuretic peptide 263.2 pg/mL (SD 475.3) and osmolality of 295.5 mOsm/Kg (SD 6.5).

Table 2. Baseline characteristics of the TRIL study

Characteristics	Values
Age, years (mean SD)	72.1 (7.1)
Female (n %)	317 (71.7)
BMI (mean SD)	26.6 (4.5)
Hypertension (n %)	187 (42.3)
Heart failure (n %)	127 (28.7)
Ischemic heart conditions (n %)	65 (14.7)
Atrial fibrillation (n %)	18 (4.1)
Stroke (n %)	14 (3.2)
Haemoglobin (mean SD)	13.5 (1.3)
Albumin (mean SD)	41.7 (2.9)
BNP (mean SD)	263.2 (475.3)
Osmolality (mean SD)	295.5 (6.5)
Beta blockers (n %)	86 (19.5)
Diuretics (n %)	85 (19.2)
Alpha blockers (n %)	14 (3.2)
Nitrate (n %)	12 (2.7)

BMI: Body mass index; BNP: B-type natriuretic peptide; SD: Standard deviation; TRIL: Technology Research for Independent Living.

Bivariate visualisation

To examine the unadjusted differences in the BP response upon standing and to visualize the sustained increase lasting more than 30 seconds, graphical representations of the BP changes were created. Figure 3-1 displays the unadjusted mean change in SBP, along with 95% confidence intervals, for participants who met the criteria for EOPR at 60 and 90 seconds, respectively. Figure 3-2 illustrate the corresponding data for those meeting the criteria at 120 seconds. While the same representation corresponding unadjusted mean changes in SBP for individuals meeting the criteria for OHT at the same time points, is shown in the Figures 3-3 and 3-4. Visual inspection of the graphs indicates a lack of overlap in the 95% confidence intervals, suggesting a significant difference between individuals classified as having EOPR or OHT at each time point. Moreover, the sustained increase in blood pressure beyond 30 seconds is clearly evident in both groups.

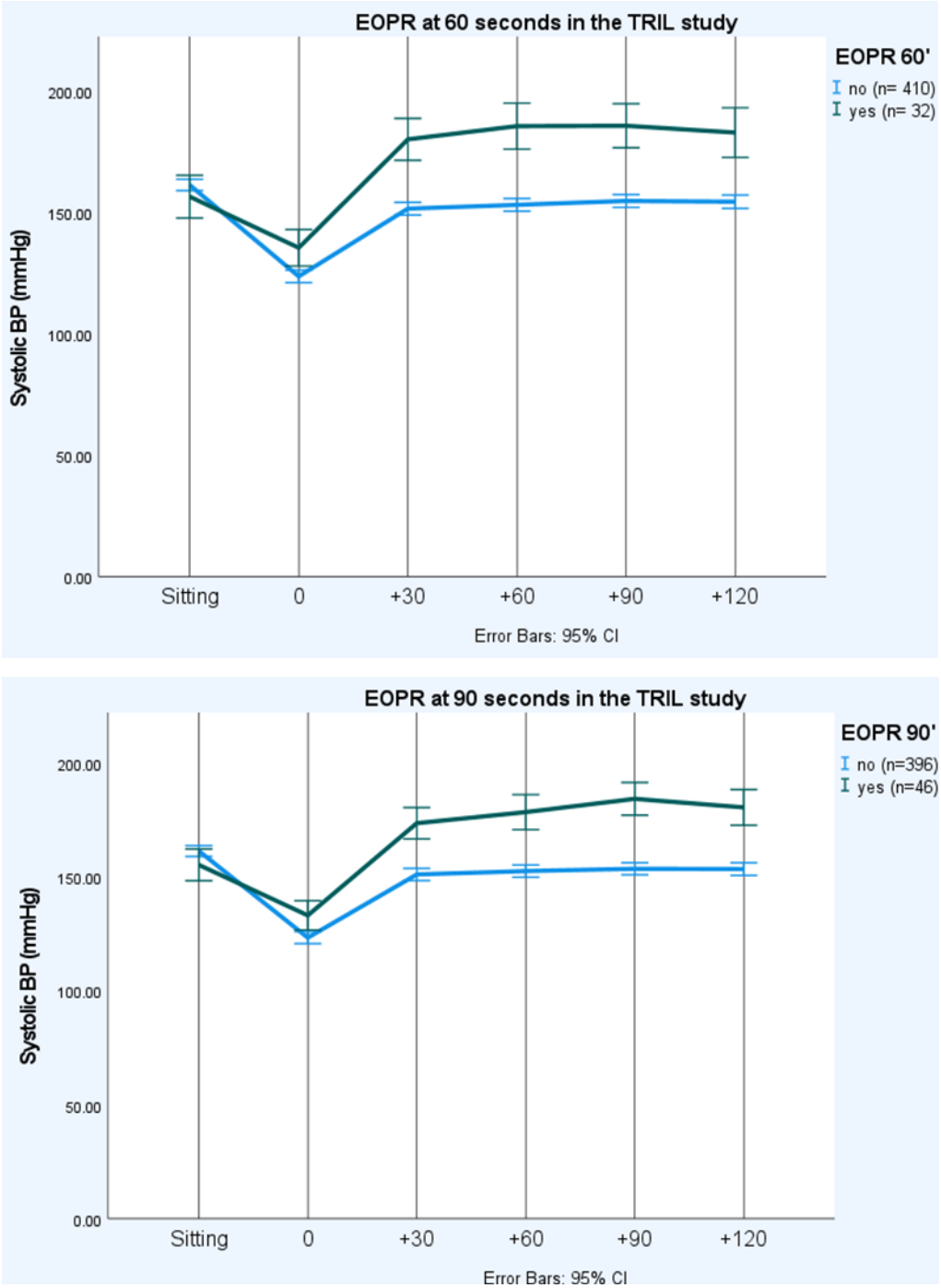

Figure 3-1. Mean change in SBP after standing grouped by EOPR cut-off at 60 and 90 seconds in the TRIL study.

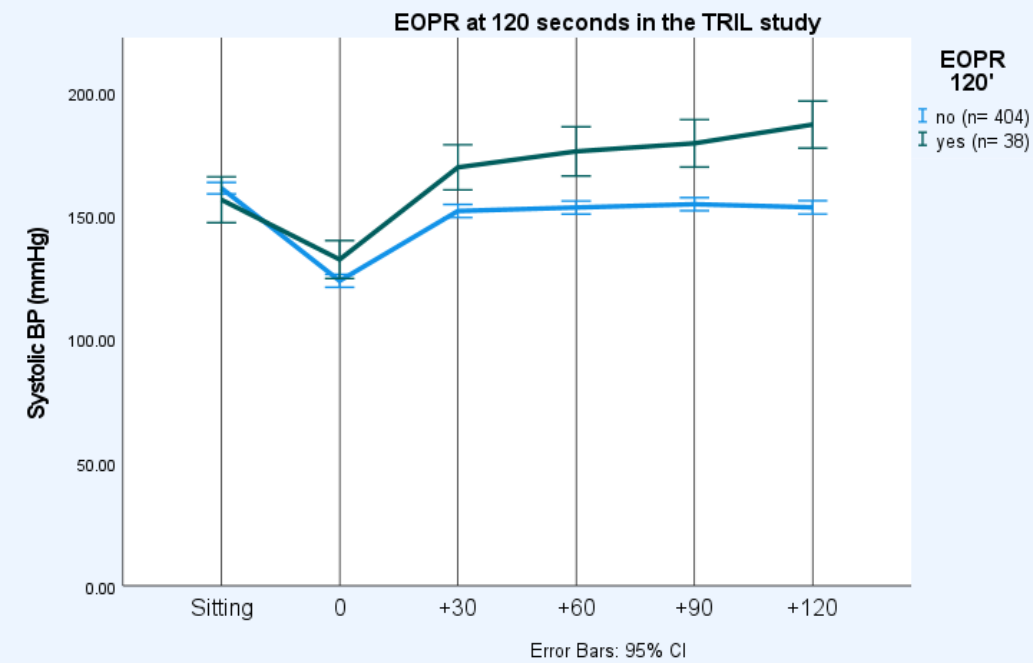

Figure 3-2. Mean change in SBP after standing grouped by EOPR cut-off at 120 seconds in the TRIL study.

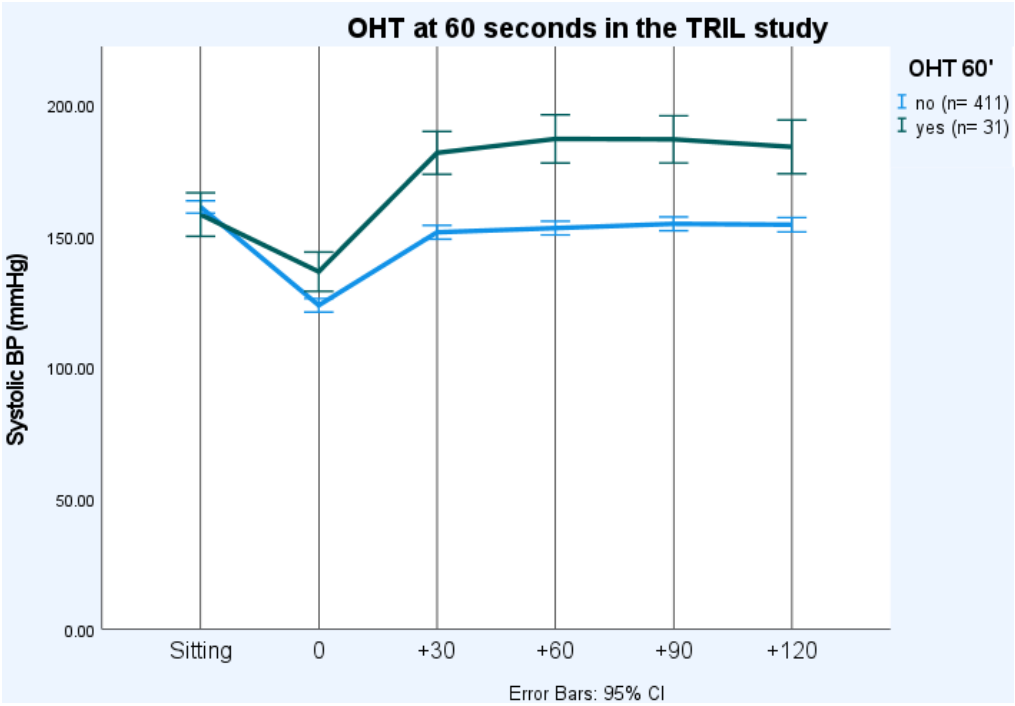

Figure 3-3. Mean change in SBP after standing grouped by OHT cut-off at 60 seconds in the TRIL study.

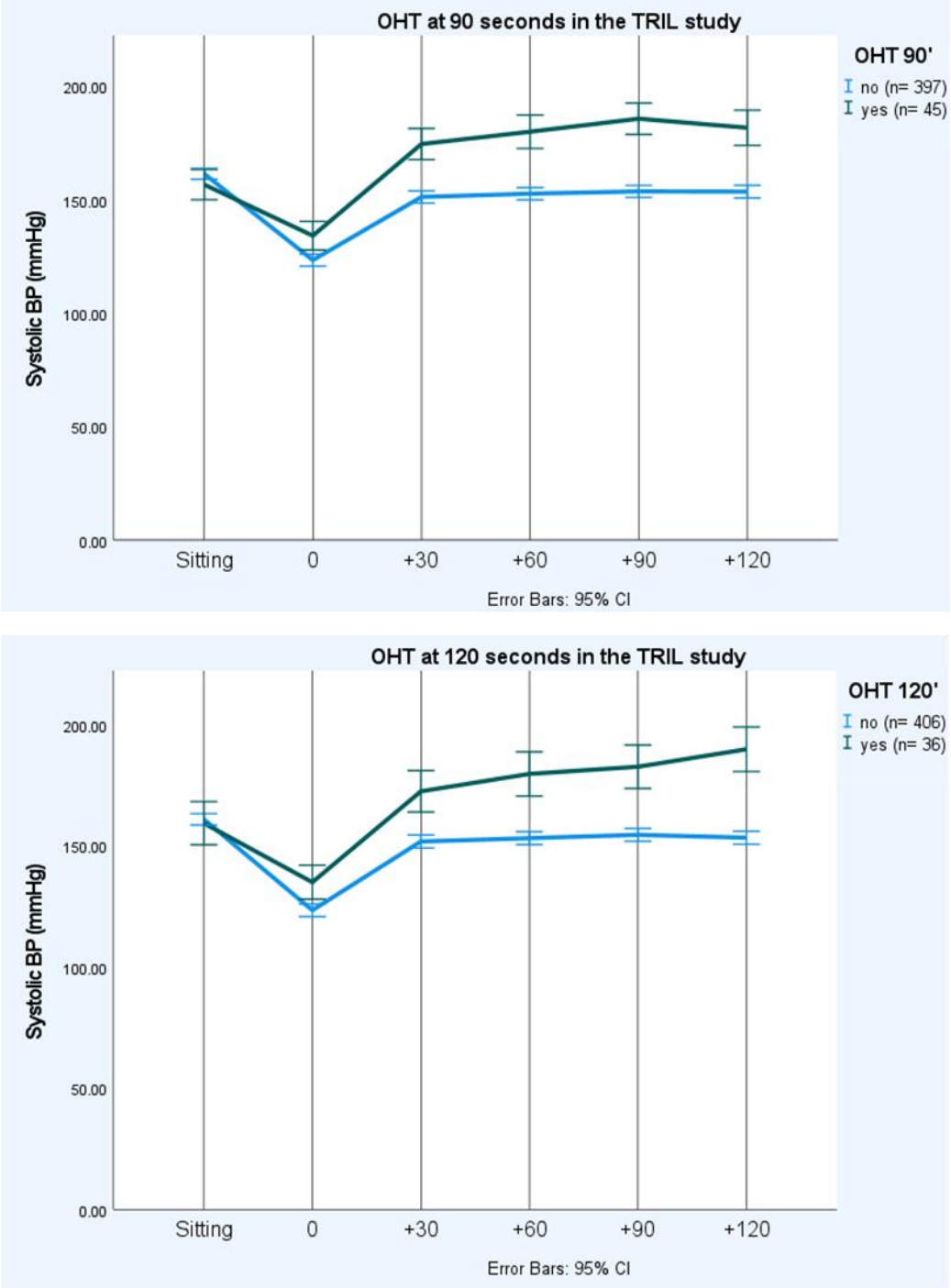

Figure 3- 4. Mean change in SBP after standing grouped by the criteria for OHT at 90 and 120 seconds in the TRIL study.

Demographics by orthostatic response status

The sample was stratified according to the presence or absence of exaggerated orthostatic pressor response (EOPR) at 60-, 90-, and 120-seconds post-standing. Characteristics of the study participants across these time points are presented in Tables 3-1 to 3-3. Differences between groups were assessed using independent t-tests for continuous variables and chi-squared tests for categorical variables. The prevalence of EOPR varied by the timing of measurement, with the lowest proportion observed at 60 seconds (7.2%) and the highest at 90 seconds (10.4%). A high proportion of females was observed across all time points, particularly at 90 seconds, where 82.6% of those with EOPR were women.

At 60 seconds, no statistically significant differences were observed between groups in terms of demographic, clinical, or biochemical variables. However, at 90 seconds, heart failure was significantly more prevalent in participants with EOPR compared to those with a normal response (41.3% vs. 27.3%, $p < 0.05$). This association was not sustained at 120 seconds. Nevertheless, at the 120-second time point, participants with EOPR were significantly older (mean 74.5 vs. 71.7 years, $p < 0.05$), though no other comorbidities reached statistical significance.

Regarding laboratory markers, serum albumin levels were consistently lower in the EOPR group at both 90 seconds ($p = 0.016$) and 120 seconds ($p = 0.023$). In addition, BNP levels were significantly higher in individuals with EOPR at 90 seconds (mean 390.4 vs. 250.6 pg/mL, $p = 0.007$) and at 120 seconds (345.0 vs. 256.4 pg/mL, $p = 0.043$).

Table 3-1. Clinical characteristics of participants with and without EOPR at 60 seconds in the TRIL study.

EOPR at 60 seconds in the TRIL study			
	No EOPR	**EOPR**	**P**
N (n %)	410 (92.8)	32 (7.2)	
Age, years (mean SD)	72.0 (7.1)	72.3 (7.6)	0.994
Female (n %)	294 (71.7)	23 (71.9)	0.984
BMI (mean SD)	26.4 (4.2)	28.2 (7.6)	0.597
Hypertension (n %)	173 (42.2)	14 (43.8)	0.864
Heart failure (n %)	114 (27.8)	13 (40.6)	0.123
Ischemic heart conditions (n %)	60 (14.6)	5 (15.6)	0.879
Atrial fibrillation (n %)	16 (3.9)	2 (6.3)	0.520
Stroke (n %)	13 (3.2)	1 (3.1)	0.989
Haemoglobin (mean SD)	13.5 (1.3)	13.6 (0.82)	0.713
Albumin (mean SD)	41.8 (2.9)	41.1 (2.8)	0.176
BNP (mean SD)	253.2 (480.1)	424.4 (513.3)	0.077
Osmolality (mean SD)	295.5 (6.4)	295.4 (7.3)	0.931
Beta blockers (n %)	76 (18.5)	10 (31.3)	0.080
Diuretics (n %)	76 (18.5)	9 (28.1)	0.185
Alpha blockers (n %)	13 (3.2)	1 (3.1)	0.989
Nitrates (n %)	12 (2.9)	0 (0.0)	0.327

*****Statistically significant difference ($P < 0.05$); EOPR: Exaggerated orthostatic pressor response; BMI: Body mass index; BNP: B-type natriuretic peptide; SD: Standard deviation; TRIL: Technology Research for Independent Living.

Table 3-2. Clinical characteristics of participants with and without EOPR at 90 seconds in the TRIL study.

EOPR at 90 seconds in the TRIL study			
	No EOPR	**EOPR**	**P**
N (n %)	396 (89.6)	46 (10.4)	
Age, years (mean SD)	71.7 (7.1)	74.2 (7.4)	0.078
Female (n %)	279 (70.5)	38 (82.6)	0.083
BMI (mean SD)	26.4 (4.3)	27.8 (6.2)	0.299
Hypertension (n %)	166 (41.9)	21 (45.7)	0.628
Heart failure (n %)	108 (27.3)	19 (41.3)	**0.047***
Ischemic heart conditions (n %)	57 (14.4)	8 (17.4)	0.587
Atrial fibrillation (n %)	15 (3.8)	3 (6.5)	0.377
Stroke (n %)	13 (3.3)	1 (2.2)	0.684
Haemoglobin (mean SD)	13.5 (1.2)	13.5 (1.1)	0.741
Albumin (mean SD)	41.9 (2.9)	40.7 (3.0)	**0.016***
BNP (mean SD)	250.6 (485.0)	390.4 (456.3)	**0.007***
Osmolality (mean SD)	295.5 (6.4)	296.1 (6.9)	0.480
Beta blockers (n %)	73 (18.4)	13 (28.3)	0.111
Diuretics (n %)	73 (18.4)	12 (26.1)	0.213
Alpha blocker (n %)	13 (3.3)	1 (2.2)	0.684
Nitrate (n %)	11 (2.8)	1 (2.2)	0.811

***Statistically significant difference ($P < 0.05$); EOPR: Exaggerated orthostatic pressor response; BMI: Body mass index; BNP: B-type natriuretic peptide; SD: Standard deviation; TRIL: Technology Research for Independent Living.

Table 3-3. Clinical characteristics of participants with and without EOPR at 120 seconds in the TRIL study

EOPR at 120 seconds in the TRIL study			
	No EOPR	**EOPR**	**P**
N (n %)	404 (91.4)	38 (8.6)	
Age, years (mean SD)	71.7 (7.1)	74.5 (7.1)	**0.012***
Female (n %)	287 (71.0)	30 (78.9)	0.301
BMI (mean SD)	26.4 (4.3)	27.9 (6.3)	0.315
Hypertension (n %)	168 (41.6)	19 (50.0)	0.315
Heart failure (n %)	112 (27.7)	15 (39.5)	0.126
Ischemic heart conditions (n %)	58 (14.4)	7 (18.4)	0.499
Atrial fibrillation (n %)	16 (4.0)	2 (5.3)	0.700
Stroke (n %)	13 (3.2)	1 (2.6)	0.844
Haemoglobin (mean SD)	13.5 (1.2)	13.4 (1.0)	0.462
Albumin (mean SD)	41.9 (2.9)	40.7 (2.6)	**0.023***
BNP (mean SD)	256.4 (485.4)	345.0 (458.2)	**0.043***
Osmolality (mean SD)	295.6 (6.3)	294.5 (7.6)	0.568
Beta blockers (n %)	75 (18.6)	11 (28.9)	0.122
Diuretics (n %)	73 (18.1)	12 (31.6)	**0.043***
Alpha blocker (n %)	13 (3.2)	1 (2.6)	0.844
Nitrate (n %)	11 (2.7)	1 (2.6)	0.974

***Statistically significant difference ($P < 0.05$); EOPR: Exaggerated orthostatic pressor response; BMI: Body mass index; BNP: B-type natriuretic peptide; SD: Standard deviation; TRIL: Technology Research for Independent Living.

Those meeting the criteria for OHT followed a similar trend to the EOPR group, with the lowest prevalence observed at 60 seconds (7.0%) and the highest at 90 seconds (10.2%). Characteristics of the study sample, stratified by OHT status, are presented in Tables 3-4, 3-5, and 3-6, corresponding to the 60-, 90-, and 120-second time points, respectively.

At 90 seconds, heart failure was significantly more prevalent among participants with OHT (42.2%) compared to those with a normal response (27.2%, $p < 0.05$). This association, however, did not remain statistically significant at 120 seconds. As shown in Table 3-6, older age was also significantly associated with OHT at 120 seconds (mean 74.3 years, $p < 0.05$), mirroring the pattern observed among those who met the criteria for EOPR. Regarding laboratory markers, serum albumin levels were significantly lower in participants with OHT at both 90 and 120 seconds ($p < 0.05$), and elevated BNP levels were also significantly associated with OHT at 90 seconds ($p < 0.01$) and 120 seconds ($p < 0.05$).

These findings suggest consistent associations between both EOPR and OHT, and markers of cardiovascular strain, particularly at later measurement points.

Table 3-4. Clinical characteristics of participants with and without OHT at 60 seconds in the TRIL study.

	OHT at 60 seconds in the TRIL study		
	No OHT	**OHT**	**P**
N (n %)	411 (93.0)	31 (7.0)	
Age, years (mean SD)	72.0 (7.1)	71.6 (7.1)	0.754
Female (n %)	295 (71.8)	22 (71.0)	0.923
BMI (mean SD)	26.4 (4.2)	28.4 (7.7)	0.459
Hypertension (n %)	173 (42.1)	14 (45.2)	0.739
Heart failure (n %)	115 (28.0)	12 (38.7)	0.203
Ischemic heart conditions (n %)	60 (14.6)	5 (16.1)	0.817
Atrial fibrillation (n %)	16 (3.9)	2 (11.1)	0.489
Stroke (n %)	13 (3.2)	1 (3.2)	0.985
Haemoglobin (mean SD)	13.5 (1.2)	13.6 (0.8)	0.658
Albumin (mean SD)	41.8 (2.9)	41.4 (2.5)	0.292
BNP (mean SD)	253.2 (479.4)	431.8 (524.1)	0.107
Osmolality (mean SD)	295.6 (6.4)	295.0 (7.1)	0.676
Beta blockers (n %)	76 (18.5)	10 (32.3)	0.062
Diuretics (n %)	77 (18.7)	8 (25.8)	0.335
Alpha blocker (n %)	13 (3.2)	1 (3.2)	0.985
Nitrate (n %)	12 (2.9)	0 (0.0)	0.335

*****Statistically significant difference ($P < 0.05$); OHT: orthostatic hypertension; BMI: Body mass index; BNP: B-type natriuretic peptide; SD: Standard deviation; TRIL: Technology Research for Independent Living.

Table 3-5. Clinical characteristics of participants with and without OHT at 90 seconds in the TRIL study.

	OHT at 90 seconds in the TRIL study		
	No OHT	**OHT**	**P**
N (n %)	397 (89.8)	45 (10.2)	
Age, years (mean SD)	71.7 (7.1)	74.2 (7.4)	0.092
Female (n %)	280 (70.5)	37 (82.2)	0.99
BMI (mean SD)	26.4 (4.3)	27.8 (6.2)	0.202
Hypertension (n %)	167 (42.1)	20 (44.4)	0.760
Heart failure (n %)	108 (27.2))	19 (42.2)	**0.035***
Ischemic heart conditions (n %)	57 (14.4)	8 (17.8)	0.539
Atrial fibrillation (n %)	15 (3.8)	3 (6.7)	0.355
Stroke (n %)	13 (3.3)	1 (2.2)	0.702
Haemoglobin (mean SD)	13.5 (1.2)	13.5 (1.1)	0.741
Albumin (mean SD)	41.9 (2.9)	40.7 (3.0)	**0.017***
BNP (mean SD)	250.6 (485.0)	390.4 (453.3)	**0.005***
Osmolality (mean SD)	295.5 (6.4)	296.1 (6.9)	0.502
Beta blockers (n %)	73 (18.4)	13 (28.9)	0.092
Diuretics (n %)	74 (18.6)	11 (24.4)	0.349
Alpha blocker (n %)	13 (3.3)	1 (2.2)	0.702
Nitrate (n %)	11 (2.8)	1 (2.2)	0.830

***Statistically significant difference ($P < 0.05$); OHT: orthostatic hypertension; BMI: Body mass index; BNP: B-type natriuretic peptide; SD: Standard deviation; TRIL: Technology Research for Independent Living.

Table 3-6. Clinical characteristics of participants with and without OHT at 120 seconds in the TRIL study.

	OHT at 120 seconds in the TRIL study		
	No OHT	**OHT**	**P**
N (n %)	406 (91.9)	36 (8.1)	
Age, years (mean SD)	71.8 (7.1)	74.3 (7.1)	**0.024***
Female (n %)	289 (71.2)	28 (77.8)	0.400
BMI (mean SD)	26.4 (4.3)	28.0 (6.4)	0.192
Hypertension (n %)	169 (41.6)	18 (50.0)	0.330
Heart failure (n %)	112 (27.6)	15 (41.7)	0.074
Ischemic heart conditions (n %)	58 (14.3)	7 (19.4)	0.402
Atrial fibrillation (n %)	16 (4.0)	2 (5.6)	0.641
Stroke (n %)	13 (3.2)	1 (2.8)	0.889
Haemoglobin (mean SD)	13.5 (1.3)	13.5 (0.96)	0.648
Albumin (mean SD)	41.9 (2.9)	40.7 (2.6)	**0.021***
BNP (mean SD)	255.7 (484.9)	355.7 (462.1)	**0.015***
Osmolality (mean SD)	295.6 (6.3)	294.5 (7.7)	0.638
Beta blockers (n %)	75 (18.5)	11 (30.6)	0.079
Diuretics (n %)	74 (18.2)	11 (30.6)	0.072
Alpha blocker (n %)	13 (3.2)	1 (2.8)	0.889
Nitrate (n %)	11 (2.7)	1 (2.8)	0.981

***Statistically significant difference ($P < 0.05$); OHT: orthostatic hypertension; BMI: Body mass index; BNP: B-type natriuretic peptide; SD: Standard deviation; TRIL: Technology Research for Independent Living.

Multivariate Logistic Regression

After conducting the univariate analysis to identify variables associated with EOPR and OHT, multivariate logistic regression was conducted independently at each time point to identify potential predictors, adjust for confounding factors, and assess the independent effects of each variable on that time point. Due to the absence of statistically significant associations at the 60 seconds time point, multivariate analysis was limited to the 90- and 120-seconds mark. To determine the variables included in the models, multicollinearity was assessed through correlation analysis among predictor variables and no strong correlations were identified (defined as $r > 0.6$), allowing for their inclusion in the regression models. The inclusion of pharmacological treatments in the models was not feasible, as the number of participants using certain medications was too small to support stable or reliable statistical estimates, thereby limiting the explanatory power of the models.

Meeting the criteria for EOPR at 90 seconds (Table 3-7), was significantly associated with female sex, with increased odds of developing an exaggerated response, with an odds ratio of 5.82 ($p=0.003$). Heart failure was also a strong predictor, showing an odds ratio of 2.50 ($p=0.019$). Higher haemoglobin levels were significantly associated with an increased likelihood of EOPR (OR: 1.47, $p=0.031$), while higher albumin levels were inversely associated with the response, indicating a protective effect (OR: 0.84, $p=0.022$). In contrast, age, BMI, hypertension, and osmolality did not reach statistical significance in predicting EOPR at this time point.

As detailed in Table 3-8, at 120 seconds, female sex remained a significant predictor for EOPR, though with a lower odds ratio of 3.18 (p=0.037). BMI, which was not significant at 90 seconds, emerged as a significant factor at this later time point, with an odds ratio of 1.10 (p=0.025). In contrast to the 90 seconds, heart failure was no longer a significant predictor (p=0.272). Albumin levels, which were significantly protective at 90 seconds, showed a borderline effect at 120 seconds (p=0.071), while age, hypertension, and osmolality remained non-significant.

Table 3-7. Multivariate logistic regression for EOPR at 90 seconds in the TRIL study.

EOPR 90 seconds	Odds ratio	95% Conf Interval		P
Age	1.03	0.98	1.09	0.272
Female	5.82	1.79	18.94	**0.003***
BMI	1.07	0.99	1.15	0.089
Hypertension	1.12	0.53	2.37	0.765
Heart failure	2.50	1.16	5.40	**0.019***
Haemoglobin	1.47	1.04	2.08	**0.031***
Albumin	0.84	0.73	0.98	**0.022***
Osmolality	1.01	0.95	1.07	0.803

*Statistically significant result ($P < 0.05$); EOPR: exaggerated orthostatic pressor response; BMI: body mass index; TRIL: Technology Research for Independent Living.

Table 3-8. Multivariate logistic regression for EOPR at 120 seconds in the TRIL study.

EOPR 120 seconds	Odds ratio	95% Conf Interval		P
Age	1.05	0.99	1.11	0.118
Female	3.18	1.08	9.39	**0.037***
BMI	1.10	1.01	1.19	**0.025***
Hypertension	1.03	0.47	2.26	0.941
Heart failure	1.58	0.70	3.57	0.272
Haemoglobin	1.31	0.93	1.84	0.127
Albumin	0.87	0.75	1.01	0.071
Osmolality	0.96	0.91	1.02	0.173

*Statistically significant result ($P < 0.05$); EOPR: exaggerated orthostatic pressor response; BMI: body mass index; TRIL: Technology Research for Independent Living.

For those participants meeting the criteria for OHT, a similar analysis was performed, with results presented in Tables 3-9 and 3-10. Once more, due to the absence of statistically significant associations at the 60 seconds time point, multivariate analysis was limited to the 90- and 120-seconds mark and the inclusion of variables was guided by an assessment of multicollinearity where no strong correlations were identified (defined as $r > 0.6$).

As shown in Table 3-9, at 90 seconds female sex was again a strong predictor of OHT, with an odds ratio of 5.82 ($p=0.003$), while heart failure was also significantly associated with increased odds (OR: 2.50, $p=0.019$). Higher haemoglobin levels were a significant predictor (OR: 1.47, $p=0.031$), whereas albumin levels showed a protective effect (OR: 0.84, $p=0.022$). Similarly, at 120 seconds (Table 3-10), female sex continued to be significantly associated with OHT, though with a lower odds ratio of 3.36 ($p=0.031$). BMI once more became significant at this time point, with an odds ratio of 1.09 ($p=0.033$). Unlike in EOPR, haemoglobin remained a significant predictor at 120 seconds, although with borderline significance (OR: 1.43, $p=0.050$). Albumin continued to be protective (OR: 0.85, $p=0.041$), while heart failure was no longer a significant predictor ($p=0.192$). Similar to the results obtained in the EOPR analysis, age, hypertension, and osmolality did not reach statistical significance.

Table 3-9. Multivariate logistic regression for OHT at 90 seconds in the TRIL study.

OHT 90 seconds	Odds ratio	95% Conf Interval		P
Age	1.03	0.98	1.09	0.272
Female	5.82	1.79	18.94	**0.003***
BMI	1.07	0.99	1.15	0.089
Hypertension	1.12	0.05	2.37	0.765
Heart failure	2.50	1.16	5.40	**0.019***
Haemoglobin	1.47	1.04	2.08	**0.031***
Albumin	0.84	0.73	0.98	**0.022***
Osmolality	1.01	0.95	1.07	0.803

*Statistically significant result (P < 0.05); OHT: orthostatic hypertension; BMI: body mass index; TRIL: Technology Research for Independent Living.

Table 3-10. Multivariate logistic regression for OHT at 120 seconds in the TRIL study.

OHT 120 seconds	Odds ratio	95% Conf Interval		P
Age	1.04	0.98	1.10	0.201
Female	3.36	1.12	10.06	**0.031***
BMI	1.09	1.01	1.18	**0.033***
Hypertension	1.15	0.52	2.56	0.727
Heart failure	1.74	0.76	3.91	0.192
Haemoglobin	1.43	1.00	2.04	**0.050***
Albumin	0.85	0.73	0.99	**0.041***
Osmolality	0.96	0.91	1.02	0.207

*Statistically significant result (P < 0.05); OHT: orthostatic hypertension; BMI: body mass index; TRIL: Technology Research for Independent Living.

Overall, in the TRIL study, female sex seemed to be the most consistent predictor for both EOPR and OHT across different time points. While heart failure, haemoglobin and BMI showed a variable significance, with each being significant at either 90 or 120 seconds, respectively. Albumin appeared to have a protective effect against both EOPR and OHT, particularly at 90 seconds, although its impact at 120 seconds was less robust, yet but still statistically significant.

FRAILMatics clinical sample

Introduction

In the previous study, the presence of an exaggerated orthostatic pressor response (EOPR) and orthostatic hypertension (OHT) had observed associations with sex, BMI, heart failure, haemoglobin and albumin. As mentioned in the introduction of the TRIL study, prior research has demonstrated an association of OHT with higher BMI (38), cardiovascular conditions such as hypertension and heart failure (34, 38) and interestingly, with greater Albumin: Creatinine ratio in patients with renal conditions (41), but this has been found without a unified definition and with different methodologies. Some studies defined OHT based on quintiles of SBP increase, while others included the measurement of DBP or considered all measurements taken after standing without a clear determination of when this phenomenon was most frequent. In some cases, the definitions used aligned more closely with EOPR rather than OHT. Consequently, while the findings are comparable to those of previous reports, direct comparisons remain challenging due to methodological differences.

Given these limitations and the observed associations, past and present, with haemoglobin, albumin, and BMI, further investigation into the potential role of nutritional status and body composition in orthostatic responses is warranted. To address this, the FRAILMatics clinical sample was analysed. In this study participants underwent an active stand test with beat-to-beat blood pressure monitoring alongside BIA to assess body composition.

Demographics

A total of 123 individuals were enrolled in the FRAILMatics clinical sample. As mentioned in the methodology section, some participants either had contraindications to or declined the BIA, had probable or confirmed neurogenic orthostatic hypotension, and either did not undergo an active stand test or had poor-quality active stand signals. Consequently, the final sample included 109 participants, this has been described in the methodology section and by Duggan (5).

Of the 107 included participants, the mean age of the sample was 69.8 years (SD = 10.4)), 57.0% (n= 61) were female. The prevalence of hypertension was 47.7% (n= 51), heart failure 13.1% (n= 14) and ischemic heart conditions 11.2% (n= 12). In relation to the use of drugs with cardiovascular effects only 18.7% (n=20) of participants reported regular use of beta blockers, and 8.4% (n= 9) used diuretics. Regarding the body composition, the mean height was 1.67 m (SD 0.08), weight 74.3 kg (SD 15.8), BMI was 26.4 (SD 4.6), muscle mass 47.8 kg (SD 10.4), total percentage of body water 46.7% (SD 5.8) and fat mass 24.0 kg (SD 9.0).

Table 3. Baseline characteristics of the FRAILMatics Cohort

Characteristics	**Values**
Age, years (mean SD)	69.8 (10.4)
Female (n %)	61 (57.0)
Hypertension (n %)	51 (47.7)
Heart failure (n %)	14 (13.1)
Ischemic heart conditions (n %)	12 (11.2)
Height (mean SD)	1.67 (0.08)
Weight (mean SD)	74.3 (15.8)
BMI (mean SD)	26.4 (4.6)
Muscle mass (mean SD)	47.8 (10.3)
Percentage of body water, % (mean SD)	46.7 (5.8)
Fat mass, kg (mean SD)	24.0 (9.0)
Betablockers (n %)	20 (18.7)
Diuretics (n%)	9 (8.4)

BMI: Body mass index; SD: Standard deviation.

Bivariate visualisation

To explore the unadjusted differences in the BP response upon standing and to visualize the sustained increase lasting more than 30 seconds, graphical representations of the BP changes were created. Figure 3-5 displays the unadjusted mean SBP, along with along with 95% confidence intervals, for participants who met the criteria for EOPR at 60 and 90 seconds. Figure 3-6 illustrate the corresponding data for those meeting the criteria at 120 and 180 seconds.

Likewise, Figures 3-7 and 3-8 show the corresponding unadjusted mean changes in SBP for individuals meeting the criteria for OHT at the same time points, accordingly. Visual inspection of these figures indicates a lack of overlap in the 95% confidence intervals, suggesting a significant difference between individuals classified as having EOPR or OHT at each time point, and the sustained increase in blood pressure beyond 30 seconds is clearly evident in the both groups. Moreover, those with EOPR show a steady and prolonged increase in BP, and individuals with OHT experience a more pronounced and rapid rise in blood pressure, often peaking around 90 to 120 seconds, followed by minor fluctuations.

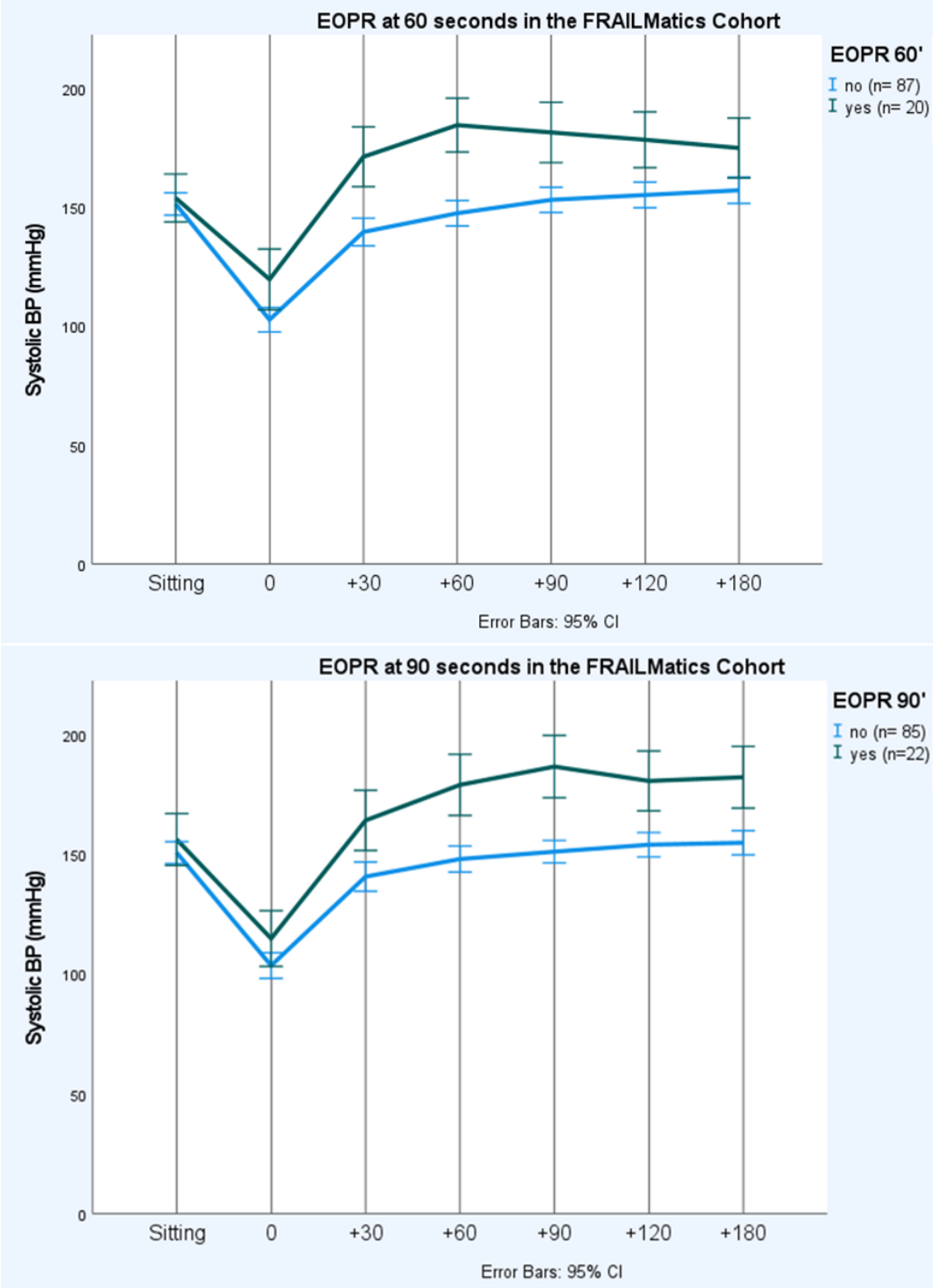

Figure 3-5. Mean change in SBP after standing grouped by EOPR at 60 and 90 seconds in the FRAILMatics Cohort.

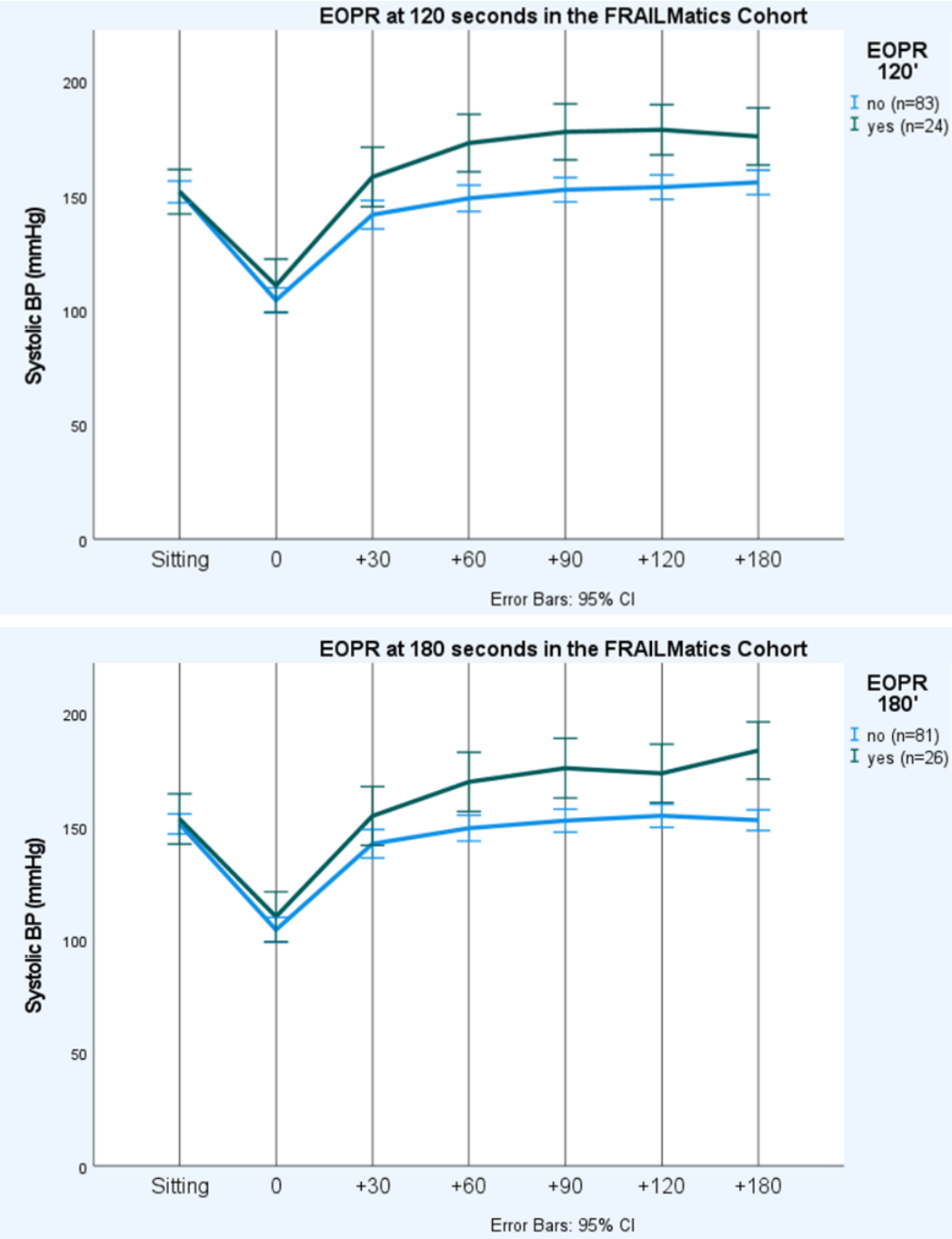

Figure 3-6. Mean change in SBP after standing grouped by EOPR at 120 and 180 seconds in the FRAILMatics Cohort.

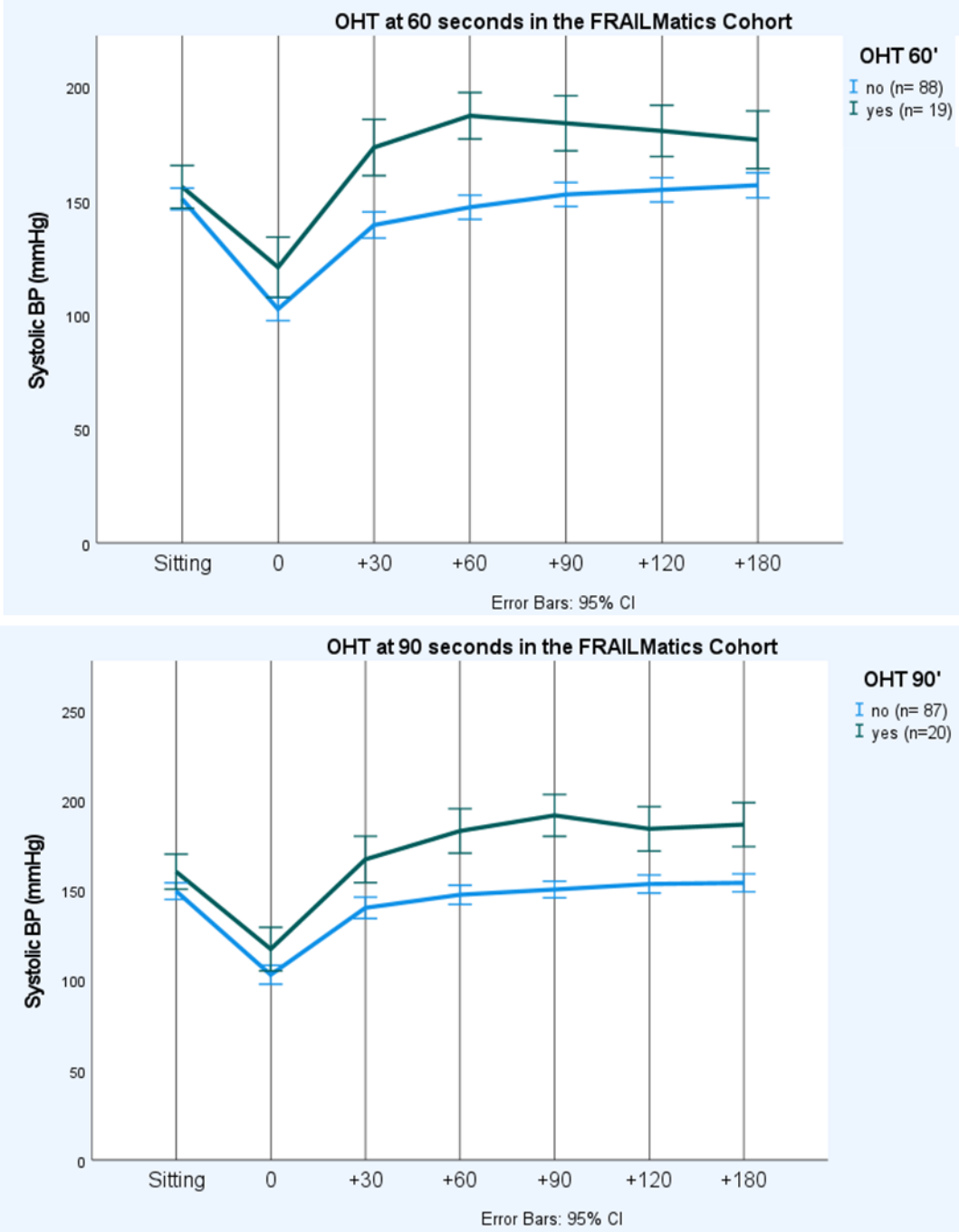

Figure 3-7. Mean change in SBP after standing grouped by OHT at 60 and 90 seconds in the FRAILMatics Cohort.

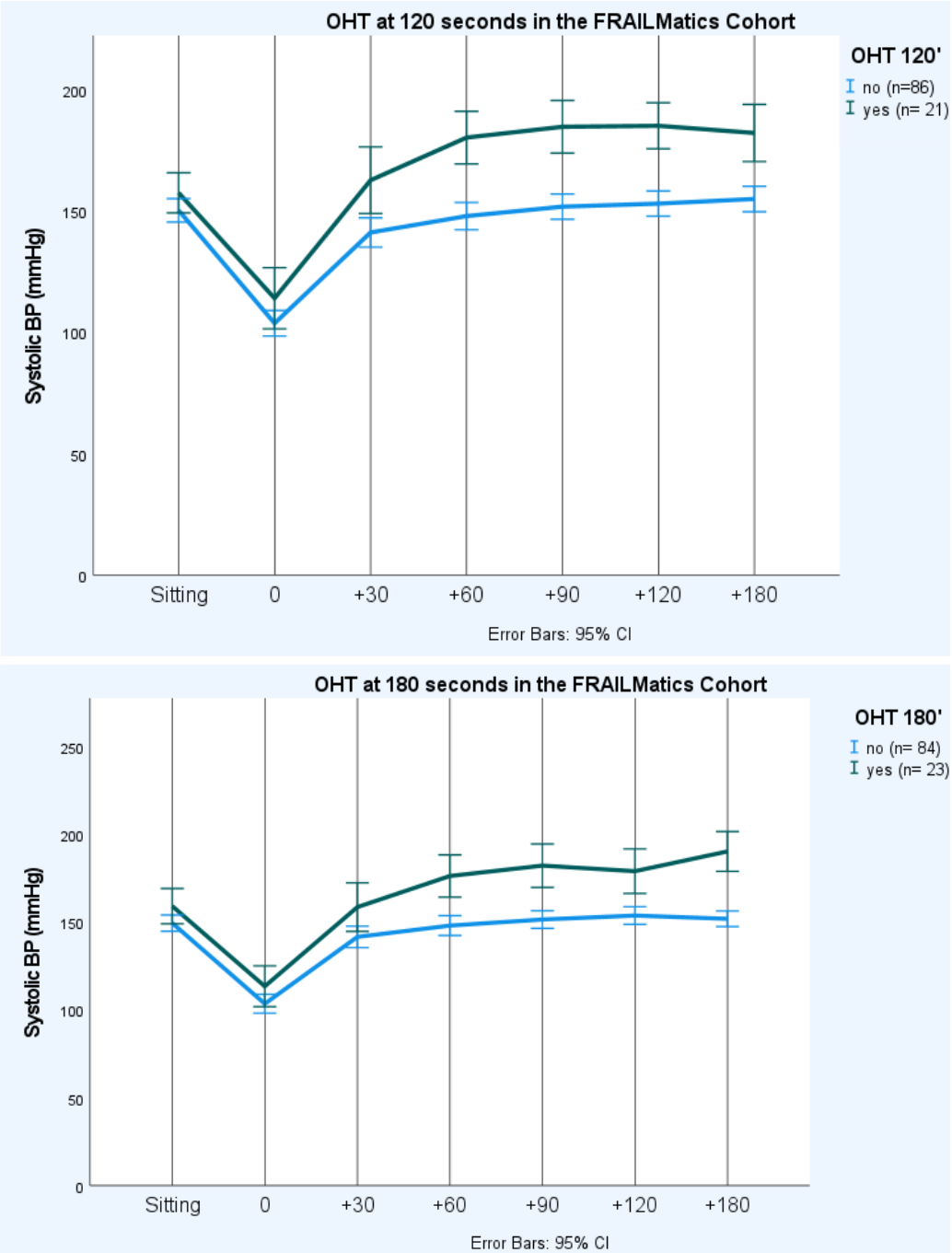

Figure 3-8. Mean change in SBP after standing grouped by OHT at 120 and 180 seconds in the FRAILMatics Cohort.

Demographics by orthostatic response status

In the FRAILMatics cohort, the prevalence of EOPR also increased slightly over time, ranging from 18.7% at 60 seconds to 24.3% at 180 seconds post-standing. Characteristics of the study population, grouped by EOPR status, are detailed in Tables 3-11 to 3-14, corresponding to the 60-, 90-, 120-, and 180-second time points, respectively.

At 60 seconds, no statistically significant differences were observed between participants with and without EOPR. By 90 seconds, several differences became apparent. Participants with EOPR had significantly higher BMI (mean 28.7 vs. 25.8 kg/m², $p = 0.031$), higher fat mass (mean 29.4 vs. 22.6 kg, $p = 0.009$), and lower percentage of body water (mean 44.1% vs. 47.4%, $p = 0.012$). At 120 seconds, percentage of body water remained significantly lower among those with EOPR (44.8% vs. 47.3%, $p = 0.022$), although other differences observed at 90 seconds were no longer statistically significant. At 180 seconds, EOPR prevalence reached its highest (24.3%), but no statistically significant associations were observed at this time point.

Table 3-11. Clinical characteristics of participants with and without EOPR at 60 seconds in the FRAILMatics Cohort.

EOPR at 60 seconds in the FRAILMatics Cohort			
	No EOPR	**EOPR**	**P**
N (n %)	87 (81.3)	20 (18.7)	
Age, years (mean SD)	69.2 (10.6)	72.3 (9.2)	0.235
Female (n %)	49 (56.3)	12 (60.0)	0.764
BMI (mean SD)	26.0 (4.4)	28.0 (5.0)	0.115
Hypertension (n %)	39 (44.8)	12 (60.0)	0.221
Ischemic heart conditions (n %)	9 (10.3)	3 (15.0)	0.552
Muscle mass, kg (mean SD)	48.1 (10.9)	46.8 (7.8)	0.820
Percentage of body water, % (mean SD)	45.8 (5.3)	45.5 (7.2)	0.135
Fat mass, kg (mean SD)	23.4 (8.8)	26.7 (9.8)	0.154
Betablockers (n %)	16 (18.4)	4 (20.0)	0.868
Diuretics (n %)	8 (9.2)	1 (5.0)	0.542

*****Statistically significant difference ($P < 0.05$); EOPR: Exaggerated orthostatic pressor response; BMI: Body mass index; SD: Standard deviation.

Table 3-12. Clinical characteristics of participants with and without EOPR at 90 seconds in the FRAILMatics Cohort.

EOPR at 90 seconds in the FRAILMatics Cohort			
	No EOPR	**EOPR**	**P**
N (n %)	85 (79.4)	22 (20.6)	
Age, years (mean SD)	69.5 (10.6)	70.6 (9.5)	0.708
Female (n %)	47 (55.3)	14 (63.6)	0.481
BMI (mean SD)	25.8 (3.9)	28.7 (5.9)	**0.031***
Hypertension (n %)	40 (47.1)	11 (50.0)	0.806
Ischemic heart conditions (n %)	10 (11.8)	2 (9.1)	0.723
Muscle mass, kg (mean SD)	48.0 (11.0)	47.3 (7.3)	0.896
Percentage of body water, % (mean SD)	47.4 (5.1)	44.1 (7.1)	**0.012***
Fat mass, kg (mean SD)	22.6 (7.7)	29.4 (11.5)	**0.009***
Betablockers (n %)	16 (20.0)	4 (13.6)	0.495
Diuretics (n %)	7 (8.2)	2 (9.1)	0.897

***Statistically significant difference ($P < 0.05$); EOPR: Exaggerated orthostatic pressor response; BMI: Body mass index; SD: Standard deviation.

Table 3-13. Clinical characteristics of participants with and without EOPR at 120 seconds in the FRAILMatics Cohort.

EOPR at 120 seconds in the FRAILMatics Cohort			
	No EOPR	**EOPR**	**P**
N (n %)	83 (77.6)	24 (22.4)	
Age, years (mean SD)	70.0 (11.0)	68.8 (7.8)	0.407
Female (n %)	44 (53.0)	17 (70.8)	0.120
BMI (mean SD)	26.0 (3.9)	28.0 (6.2)	0.282
Hypertension (n %)	39 (47.0)	12 (50.0)	0.795
Ischemic heart conditions (n %)	10 (12.0)	2 (8.3)	0.611
Muscle mass, kg (mean SD)	48.3 (11.0)	46.2 (7.9)	0.555
Percentage of body water, % (mean SD)	47.3 (5.1)	44.8 (7.3)	**0.022***
Fat mass, kg (mean SD)	22.8 (7.3)	28.1 (12.6)	0.116
Betablockers (n %)	18 (21.7)	2 (8.3)	0.139
Diuretics (n %)	8 (9.6)	1 (4.2)	0.395

***Statistically significant difference ($P < 0.05$); EOPR: Exaggerated orthostatic pressor response; BMI: Body mass index; SD: Standard deviation.

Table 3-14. Clinical characteristics of participants with and without EOPR at 180 seconds in the FRAILMatics Cohort.

EOPR at 180 seconds in the FRAILMatics Cohort			
	No EOPR	**EOPR**	**P**
N (n %)	81 (75.7)	26 (24.3)	
Age, years (mean SD)	70.5 (10.7)	67.5 (9.0)	0.140
Female (n %)	45 (55.6)	16 (61.5)	0.592
BMI (mean SD)	25.9 (3.9)	27.9 (6.0)	0.248
Hypertension (n %)	35 (43.2)	16 (61.5)	0.104
Ischemic heart conditions (n %)	10 (12.3)	2 (7.7)	0.513
Muscle mass, kg (mean SD)	48.0 (10.8)	47.3 (8.8)	0.977
Percentage of body water, % (mean SD)	46.9 (7.3)	46.2 (7.3)	0.477
Fat mass, kg (mean SD)	23.3 (7.3)	26.4 (12.8)	0.682
Betablockers (n %)	17 (21.0)	3 (11.5)	0.282
Diuretics (n %)	7 (8.6)	3 (7.7)	0.879

*****Statistically significant difference ($P < 0.05$); EOPR: Exaggerated orthostatic pressor response; BMI: Body mass index; SD: Standard deviation.

The characteristics of individuals meeting criteria for OHT are summarised in Tables 3-15 to 3-18. The prevalence of OHT increased slightly across time points, from 17.8% at 60 seconds, to 18.7% at 90 seconds, 19.6% at 120 seconds, and 21.5% at 180 seconds.

At 60 seconds, participants with OHT had a significantly higher BMI (28.4 vs. 26.0 kg/m², p = 0.045) and lower percentage of body water (44.4% vs. 47.2%, p = 0.043) than those without OHT. The strongest differences were observed at 90 and 120 seconds. At 90 seconds, participants with OHT had significantly higher BMI (29.2 vs. 25.8 kg/m², p = 0.005), significantly greater fat mass (30.4 vs. 22.5 kg, p = 0.015), and significantly lower body water percentage (43.2% vs. 47.5%, p = 0.013). These associations remained consistent at 120 seconds, with significant differences again observed in fat mass (29.9 vs. 22.6 kg, p = 0.015) and body water (43.8% vs. 47.4%, p = 0.007). At 180 seconds, the prevalence of OHT reached 21.5%. While BMI remained significantly higher in the OHT group (28.7 vs. 25.8 kg/m², p = 0.044), differences in fat mass and body water were no longer statistically significant.

Overall, these findings indicate that OHT in the FRAILMatics cohort is consistently associated with higher adiposity and lower body water percentage, particularly at 90 and 120 seconds.

Table 3-15. Clinical characteristics of participants with and without OHT at 60 seconds in the FRAILMatics Cohort.

OHT at 60 seconds in the FRAILMatics Cohort			
	No OHT	**OHT**	**P**
N (n %)	88 (82.2)	19 (17.8)	
Age, years (mean SD)	69.1 (10.56)	72.6 (9.3)	0.178
Female (n %)	49 (55.7)	12 (63.2)	0.551
BMI (mean SD)	26.0 (4.47)	28.4 (4.6)	**0.045***
Hypertension (n %)	39 (44.3)	12 (63.2)	0.136
Ischemic heart conditions (n %)	9 (10.2)	3 (15.8)	0.486
Muscle mass, kg (mean SD)	48.1 (10.85)	46.7 (8.0)	0.810
Percentage of body water, % (mean SD)	47.2 (5.7)	44.4 (5.6)	**0.043***
Fat mass, kg (mean SD)	23.2 (8.8)	27.6 (9.2)	0.064
Betablockers (n %)	16 (18.2)	4 (21.1)	0.771
Diuretics (n %)	8 (9.1)	1 (5.3)	0.586

*Statistically significant difference ($P < 0.05$); OHT: orthostatic hypertension; BMI: Body mass index; SD: Standard deviation.

Table 3-16. Clinical characteristics of participants with and without OHT at 90 seconds in the FRAILMatics Cohort.

OHT at 90 seconds in the FRAILMatics Cohort			
	No OHT	**OHT**	**P**
N (n %)	87 (81.3)	20 (18.7)	
Age, years (mean SD)	69.3 (10.72)	71.9 (8.8)	0.625
Female (n %)	48 (55.2)	13 (65.0)	0.423
BMI (mean SD)	25.8 (4.0)	29.2 (5.8)	**0.005***
Hypertension (n %)	40 (46.0)	11 (55.0)	0.466
Ischemic heart conditions (n %)	10 (11.5)	2 (10.0)	0.849
Muscle mass, kg (mean SD)	48.0 (10.9)	47.2 (7.7)	0.237
Percentage of body water, % (mean SD)	47.5 (5.5)	43.2 (5.5)	**0.013***
Fat mass, kg (mean SD)	22.5 (7.8)	30.4 (11.2)	**0.015***
Betablockers (n %)	17 (19.5)	3 (15.0)	0.639
Diuretics (n %)	7 (8.0)	2 (10.0)	0.776

***Statistically significant difference ($P < 0.05$); OHT: orthostatic hypertension; BMI: Body mass index; SD: Standard deviation.

Table 3-17. Clinical characteristics of participants with and without OHT at 120 seconds in the FRAILMatics Cohort.

OHT at 120 seconds in the FRAILMatics Cohort			
	No OHT	**OHT**	**P**
N (n %)	86 (80.4)	21 (19.6)	
Age, years (mean SD)	70.0 (10.8)	68.9 (8.3)	0.495
Female (n %)	46 (53.5)	15 (71.4)	0.137
BMI (mean SD)	25.8 (3.9)	28.8 (6.2)	0.060
Hypertension (n %)	39 (45.3)	12 (57.1)	0.332
Ischemic heart conditions (n %)	10 (11.6)	2 (9.5)	0.784
Muscle mass, kg (mean SD)	48.1 (10.8)	46.8 (8.2)	0.808
Percentage of body water, % (mean SD)	47.4 (5.4)	43.8 (6.3)	**0.007***
Fat mass, kg (mean SD)	22.6 (7.4)	29.9 (12.4)	**0.015***
Betablockers (n %)	18 (20.9)	2 (9.5)	0.229
Diuretics (n %)	8 (9.3)	1 (4.8)	0.502

***Statistically significant difference ($P < 0.05$); OHT: orthostatic hypertension; BMI: Body mass index; SD: Standard deviation.

Table 3-18. Clinical characteristics of participants with and without OHT at 180 seconds in the FRAILMatics Cohort.

OHT at 180 seconds in the FRAILMatics Cohort			
	No OHT	**OHT**	**P**
N (n %)	84 (78.5)	23 (21.5)	
Age, years (mean SD)	70.2 (10.6)	68.0 (9.4)	0.291
Female (n %)	47 (56.0)	14 (60.9)	0.673
BMI (mean SD)	25.8 (3.9)	28.7 (5.9)	**0.044***
Hypertension (n %)	36 (42.9)	15 (65.2)	0.057
Ischemic heart conditions (n %)	10 (11.9)	2 (8.7)	0.666
Muscle mass, kg (mean SD)	47.8 (10.8)	48.1 (8.9)	0.585
Percentage of body water, % (mean SD)	47.1 (5.5)	45.2 (6.4)	0.172
Fat mass, kg (mean SD)	22.9 (7.4)	27.9 (12.7)	0.195
Betablockers (n %)	18 (21.4)	2 (8.7)	0.165
Diuretics (n %)	7 (8.3)	2 (8.7)	0.956

***Statistically significant difference ($P < 0.05$); OHT: orthostatic hypertension; BMI: Body mass index; SD: Standard deviation.

Multivariate Logistic Regression

A multivariate logistic regression was conducted, independently at each time point to identify potential predictors, adjust for confounding factors, and assess the independent effects of each variable on that time point. Due to the inconstant statistically significant associations at the 60 seconds time point, the multivariate analysis was limited to the 90-, 120- and 180-seconds mark. To determine the variables included in the models, multicollinearity was assessed through correlation analysis among predictor variables and no strong correlations were identified (defined as $r > 0.6$), allowing for their inclusion in the regression models. BMI was excluded from the analysis due to redundancy with other body composition measures (muscle mass, fat mass, and body water). Additionally, as in the previous study, the inclusion of pharmacological treatments was not feasible given the small number of participants in the corresponding subgroups.

Among participants who met the criteria for EOPR at 90 seconds, female sex was significantly associated with a lower likelihood of exhibiting an exaggerated response (OR = 0.05, 95% CI: 0.00–0.85, p = 0.038). However, this association was not observed at subsequent time points. At the same time point, and higher muscle mass appeared to have a protective effect, as indicated by an OR of 0.87 (95% CI: 0.77–0.99, p = 0.036). On the other hand, a higher amount fat mass was associated with an increased likelihood of EOPR (OR= 1.15, 95% CI: 1.02–1.30, p = 0.026). At 120 seconds, the relationship between muscle mass and EOPR remained significant, with an OR of 0.88 (95% CI: 0.79–1.00, p = 0.045), and the fat mass was again positively associated with an exaggerated response (OR= 1.18, 95% CI: 1.05–1.33, p = 0.005).

By 180 seconds, muscle mass remained protective (OR= 0.89, 95% CI: 0.80–1.00, p = 0.042), while the fat mass continued to be associated with increased risk, as indicated by an odds ratio of 1.26 (95% CI: 1.02–1.26, p = 0.017).

Table 3-19. Multivariate logistic regression for EOPR at 90 seconds in the FRAILMatics Cohort.

EOPR 90 seconds	Odds ratio	95% Conf Interval		P
Age	0.98	0.92	1.05	0.639
Female	0.05	0.00	0.85	**0.038***
Hypertension	0.53	0.17	1.66	0.278
Muscle mass	0.87	0.77	0.99	**0.036***
Percentage body water	0.92	0.72	1.17	0.480
Fat mass	1.15	1.02	1.30	**0.026***

*Statistically significant result ($P < 0.05$); EOPR: exaggerated orthostatic pressor response.

Table 3-20. Multivariate logistic regression for EOPR at 120 seconds in the FRAILMatics Cohort.

EOPR 120 seconds	Odds ratio	95% Conf Interval		P
Age	0.96	0.90	1.02	0.175
Female	0.56	0.04	7.10	0.654
Hypertension	0.76	0.26	2.24	0.622
Muscle mass	0.88	0.79	1.00	**0.045***
Percentage body water	1.14	0.93	1.39	0.207
Fat mass	1.18	1.05	1.33	**0.005***

*Statistically significant result ($P < 0.05$); EOPR: exaggerated orthostatic pressor response.

Table 3-21. Multivariate logistic regression for EOPR at 180 seconds in the FRAILMatics Cohort.

EOPR 180 seconds	Odds ratio	95% Conf Interval		P
Age	0.93	0.87	0.99	**0.015***
Female	0.51	0.04	5.93	0.590
Hypertension	2.44	0.82	7.22	0.108
Muscle mass	0.89	0.80	1.00	**0.042***
Percentage body water	1.16	0.96	1.40	0.125
Fat mass	0.66	1.02	1.26	**0.017***

*Statistically significant result ($P < 0.05$); EOPR: exaggerated orthostatic pressor response.

The analysis of participants who met the criteria for OHT is presented in Tables 3-22, 3-23, and 3-24 for the 90-, 120-, and 180-second time points, respectively. At 90 seconds, female sex was significantly associated with a reduced likelihood of exhibiting an exaggerated hypertensive response (OR = 0.01, 95% CI: 0.00–0.28, $p = 0.007$). However, once again, this association was not observed at later time points. Muscle mass also demonstrated a protective effect at 90 seconds (OR = 0.86, 95% CI: 0.75–1.00, $p = 0.043$). At 120 seconds, fat mass emerged as a significant risk factor for OHT (OR = 1.18, 95% CI: 1.04–1.33, $p = 0.011$), while muscle mass continued to be protective (OR = 0.87, 95% CI: 0.77–1.00, $p = 0.043$). By 180 seconds, the protective effect of muscle mass was no longer statistically significant, and fat mass showed a borderline association with OHT ($p = 0.065$).

Overall, findings from the FRAILMatics cohort indicate that muscle mass and fat mass are consistent predictors of both EOPR and OHT, while the role of sex appears to be more time-point specific. Although female sex was significantly associated with reduced odds of EOPR and OHT at 90 seconds, this association did not persist across later time points. In contrast, higher muscle mass consistently demonstrated a protective effect, particularly at 90 and 120 seconds, though its significance diminished by 180 seconds. Conversely, greater fat mass emerged as a stable risk factor, showing a consistent association with increased odds of both EOPR and OHT across most time points.

Table 3-22. Multivariate logistic regression for OHT at 90 seconds in the FRAILMatics Cohort.

OHT 90 seconds	Odds ratio	95% Conf Interval		P
Age	1.00	0.94	1.08	0.929
Female	0.01	0.00	0.28	**0.007***
Hypertension	0.62	0.19	2.08	0.443
Muscle mass	0.86	0.75	1.00	**0.043***
Percentage body water	0.74	0.53	1.01	0.060
Fat mass	1.11	0.97	1.27	0.142

*Statistically significant result ($P < 0.05$); OHT: orthostatic hypertension.

Table 3-23. Multivariate logistic regression for OHT at 120 seconds in the FRAILMatics Cohort.

OHT 120 seconds	Odds ratio	95% Conf Interval		P
Age	0.96	0.89	1.02	0.177
Female	0.22	0.01	3.69	0.290
Hypertension	1.00	0.32	3.10	0.999
Muscle mass	0.87	0.77	1.00	**0.043***
Percentage body water	1.04	0.83	1.31	0.729
Fat mass	1.18	1.04	1.33	**0.011***

*Statistically significant result ($P < 0.05$); OHT: orthostatic hypertension.

Table 3-24. Multivariate logistic regression for OHT at 180 seconds in the FRAILMatics Cohort.

OHT 180 seconds	Odds ratio	95% Conf Interval		P
Age	0.94	0.88	1.00	0.052
Female	0.20	0.01	2.77	0.229
Hypertension	2.27	0.76	6.82	0.144
Muscle mass	0.90	0.80	1.01	0.078
Percentage body water	1.02	0.83	1.25	0.850
Fat mass	1.11	0.99	1.24	0.065

*Statistically significant result ($P < 0.05$); OHT: orthostatic hypertension.

Chapter 4: Discussion

Discussion

This study explored whether EOPR and OHT, as defined by recent consensus criteria (58), is associated with cardiovascular and metabolic conditions in older adults and examined the potential contribution of body composition to these associations. In addressing this question, we aimed to determine the prevalence of EOPR and OHT in two independent samples of older individuals, and to investigate their associations with cardiovascular comorbidities, metabolic markers, and body composition parameters. Furthermore, we sought to explore how differences in body composition might contribute to the underlying pathophysiological mechanisms involved.

Using the recent consensus definition, the prevalence of EOPR ranged from 7.0-24.3%, while that of OHT ranged from 7.0-21.5% across both studies. We observed that both EOPR and OHT were associated with cardiovascular comorbidities; metabolic parameters also played a role, as higher body mass index (BMI) and differences in body composition were related to greater risk. Furthermore, markers of nutritional and metabolic status were significantly associated with the development of EOPR and OHT. These findings indicate that elevation of BP upon standing is relatively common in community-dwelling older adults and provides insight on the factors associated with orthostatic BP regulation.

Body composition, particularly the differential effects of fat mass and muscle mass, emerged as a key determinant of EOPR and OHT. Across both samples, a higher BMI was associated with these conditions ($p = 0.033$, OR = 1.0, 95% CI: 1.0–1.1), in line with previous studies

(46, 50), although methodological differences between studies must be considered and are discussed later. However, unlike previous studies, the present work extends existing knowledge by dissecting the contributions of specific body compartments. Our analysis indicates that higher fat mass increased the likelihood of EOPR and OHT ($p = 0.026$, OR = 1.1, 95% CI: 1.0–1.3), whereas greater muscle mass appeared to confer a protective effect ($p = 0.036$, OR = 0.8, 95% CI: 0.7–0.9). Fat mass has been linked to increased sympathetic activity and reduced baroreflex sensitivity, contributing to exaggerated BP responses upon standing (75). In contrast, muscle mass has been associated with enhanced arterial wall elasticity and lower arterial stiffness, factors that may protect against orthostatic blood pressure dysregulation (74, 83). These findings add weight to the hypothesis that metabolism contributes to the sympathetic hyperactivity underlying EOPR/OHT and underscore the importance of considering not only body size but also body composition when assessing cardiovascular risk in older adults.

In addition to body composition, we observed significant associations with cardiovascular conditions such as heart failure (HF) ($p = 0.019$, OR = 2.5, 95% CI: 1.1–5.4), which may reflect shared underlying mechanisms, particularly autonomic dysfunction and vascular alterations (84). In HF, overactivation of the sympathetic nervous system (SNS) and impairment of baroreflex function are well-documented phenomena that tend to worsen as the condition progresses (85, 86). These autonomic disturbances, along with other physiological changes that occur in HF, such as increased vascular stiffness and altered volume regulation, may contribute to both EOPR and OHT (87). Although previous studies have linked OHT to broader cardiovascular risk, including the work by Veronese et al. (44) which established OHT as a

cardiovascular risk factor, its specific relationship with HF has been less explored (38, 40-42, 51). Our results suggest that HF may increase the likelihood of OHT, potentially due to the cardiovascular burden and through its effects on baroreflex function.

Beyond cardiovascular conditions, serum biomarkers also contributed to risk profiles. Lower albumin levels were linked to the presence of both EOPR and OHT, and subsequent analysis indicated that higher albumin concentrations may exert a protective effect ($p = 0.041$, OR = 0.85, 95% CI: 0.7–0.9). In contrast, although haemoglobin levels were not significantly associated in initial analyses, higher concentrations were associated with increased risk in later models ($p = 0.050$, OR = 1.4, 95% CI: 1.0–2.0). Whilst no previous data have directly linked these biomarkers to OHT, the observed patterns are biologically plausible. Albumin is known to exert anti-inflammatory and antioxidant effects and plays a role in transporting molecules involved in endothelial function (88, 89), supporting vascular function. Elevated haemoglobin levels, on the other hand, have been associated with increased cardiovascular risk, possibly due to higher blood viscosity and reduced nitric oxide (NO) availability, impacting flow-mediated dilatation and increasing peripheral vascular resistance (90). Thus, alterations in albumin and haemoglobin concentrations may influence vascular responses to orthostatic stress through their effects on inflammation, endothelial function, and haemodynamic properties.

Few studies have explored similar aims to the present research, particularly using the recent consensus definition. In this study, we examined independently the prevalence of EOPR and OHT, something that to our knowledge has not been done before. However, our epidemiology

is comparable to previous reports in community-dwelling older adults, where rates have ranged between 5% and 30% for OHT, defined in different forms (44-46). In agreement with the findings reported by Choi et al. (56), previous literature has suggested an association between female sex and OHT. However, our results did not consistently replicate this finding across both cohorts. In further modelling, female sex emerged as risk factor for EOPR/OHT at the TRIL study but appeared protective in the FRAILMatics cohort at the 90-second mark, with no significant associations observed at later time points. We hypothesized that this discrepancy may be due to differences in the populations, as the FRAILMatics cohort is younger and has a smaller comorbidity burden on cardiovascular conditions (44). However, methodological factors, sample size variation, or the influence of unmeasured confounders cannot be excluded, and future studies are needed to clarify the role of sex in orthostatic pressor responses.

Studies examining the association between OHT and BMI employed methodological approaches distinct from those utilised in the present study. Some, such as Bursztyn et al. (46), identified the association at the 60-second mark, whereas Alagiakrishnan et al. (38), reported it following three minutes of standing. As far as we are aware, the present study is the first to describe these associations at multiple specific time points. We observed a positive association at all measurement points after 60 seconds, although not precisely at the 60-second mark. Furthermore, although there is no established consensus regarding the definition of sustained orthostatic responses, our findings suggest a sustained nature, as the proportion of individuals meeting the criteria for EOPR and OHT increased after 90 seconds in both samples. This suggest that orthostatic pressor responses may be more reliably detected with prolonged

standing measurements. These findings highlight the importance of measurement timing in the detection of EOPR and OHT.

Regarding body composition parameters, no prior studies have specifically examined the role of fat mass and muscle mass in relation to EOPR or OHT. However, while visceral adiposity appears to increase sympathetic tone, its influence on baroreflex sensitivity remains controversial (91). Therefore, although the influence of fat and muscle mass on sympathetic tone and vascular elasticity is well established, further studies are needed to clarify the effect on baroreflex modulation. Meanwhile, we hypothesise that the associations observed in our study may be explained by the contribution of fat mass to sympathetic activation and reduced vascular distensibility, two mechanisms central to the proposed pathophysiology of OHT (92, 93). Conversely, greater muscle mass may help preserve vascular function and buffer orthostatic BP changes (5).

In addition to body composition, age-related physiological changes and chronic conditions may further impair vascular compliance and autonomic function. As previously noted, excessive venous pooling is not the primary mechanism underlying OHT in older adults; rather, it is an increase in vascular resistance (63, 64). Ageing is associated with reduced venous compliance, driven by venous wall thickening and an increased collagen-to-elastin ratio, which together diminish venous distensibility (94, 95). These structural alterations, mediated by local myogenic and humoral mechanisms, influence venous biomechanics and reduce the capacity of the venous system to accommodate changes in BP upon standing (96-98). Consequently,

this may result in an exaggerated rise in BP during orthostasis, particularly when baroreflex buffering is impaired.

Taken together, these physiological mechanisms offer a plausible explanation for the exaggerated orthostatic pressor responses observed in older adults. Nonetheless, these findings must be interpreted within the context of the study's strengths and limitations. This study has several strengths, including the use of two independent and well-characterised samples of older adults, the application of recent consensus definitions for EOPR and OHT, and a detailed assessment of body composition parameters extending beyond traditional measures.

Although two independent populations were included, they differed in important ways: one cohort consisted of generally healthier, younger individuals with fewer comorbidities, while the other comprised older adults with a greater burden of cardiovascular risk factors. This heterogeneity may have introduced variability into the observed associations. Other limitations include that the report of conditions was made through self-report, the intrinsic constraints of BIA in estimating muscle mass (99), information regarding the timing of medication administration relative to the active stand test was not available and the medication analysis was not included in multivariate models due to the limited sample size, and potential confounding effects from pharmacological treatments cannot be entirely ruled out. Furthermore, while BP measurements were taken at multiple time points, they were not assessed longitudinally within individuals. Although this approach allowed for the exploration of BP behaviour across different phases of standing, it limits the ability to draw conclusions about dynamic BP recovery patterns over time.

The findings of the present study are significant for several reasons. Firstly, from a pathophysiological perspective, they provide new insights into the factors involved in the development of exaggerated orthostatic pressor responses. As far as we are aware, no previous study has specifically addressed which cardiovascular and metabolic factors are associated individually with the two recently proposed definitions of EOPR and OHT (58). Secondly, EOPR and OHT are increasingly recognized as markers of cardiovascular risk, with some authors identifying OHT as a potential pre-hypertensive state (13, 100), and the observed associations with modifiable factors such as fat mass and muscle mass suggest opportunities for intervention. Strategies aimed at reducing adiposity and preserving muscle mass may not only improve overall metabolic health but could also help mitigate orthostatic BP alterations, supporting the view that these responses are markers of metabolic dysfunction. Moreover, these findings highlight the importance of incorporating orthostatic BP testing and body composition assessment into the routine evaluation of older adults, particularly those at elevated cardiovascular risk.

Conclusion

In conclusion, the recent consensus definitions of EOPR and OHT provide a more uniform framework to guide future research in this area. This study offers new insights into the associations between exaggerated orthostatic pressor responses and cardiovascular, metabolic, and body composition factors in older adults. By applying the recently established consensus definitions, this study contributes to standardising the evaluation of orthostatic blood pressure alterations, facilitating more consistent comparisons across future research. Based on these findings, we propose that EOPR and OHT may have a metabolic origin or are closely linked to metabolic syndrome. Confirmation of this hypothesis requires further investigation through longitudinal studies and interventional trials. By highlighting the contribution of modifiable factors such as fat and muscle mass, these results underscore the need for new strategies aimed at reducing cardiometabolic risk and improving vascular regulation in ageing populations.

References

1. Smith JJ, Porth CM, Erickson M. Hemodynamic response to the upright posture. J Clin Pharmacol. 1994;34(5):375-86.

2. C. Gunnar Blomqvist HLS. Comprehensive Physiology Cardiovascular Adjustments to Gravitational Stress. Handbook of Physiology, The Cardiovascular System, Peripheral Circulation and Organ Blood Flow2011.

3. Finucane C, van Wijnen VK, Fan CW, Soraghan C, Byrne L, Westerhof BE, et al. A practical guide to active stand testing and analysis using continuous beat-to-beat non-invasive blood pressure monitoring. Clin Auton Res. 2019;29(4):427-41.

4. Harms MPM, Finucane C, Pérez-Denia L, Juraschek SP, van Wijnen VK, Lipsitz LA, et al. Systemic and cerebral circulatory adjustment within the first 60 s after active standing: An integrative physiological view. Auton Neurosci-Basic. 2021;231.

5. Duggan E. Sarcopenia and Orthostatic Hypotension: Investigating the Underlying Haemodynamics: Trinity College Dublin; 2025.

6. Wehrwein EA, Joyner MJ. Regulation of blood pressure by the arterial baroreflex and autonomic nervous system. Handb Clin Neurol. 2013;117:89-102.

7. Izzo JL, Jr., Taylor AA. The sympathetic nervous system and baroreflexes in hypertension and hypotension. Curr Hypertens Rep. 1999;1(3):254-63.

8. Eckberg DL, Sleight P. Human Baroreflexes in Health and Disease: Oxford University Press; 1992 31 Oct 2023.

9. Wieling WK, John. Measurement of heart rate and blood pressure to evaluate disturbances in neurocardiovascular control. Communication Research - COMMUN RES. 1999:196-210.

10. Sprangers RL, van Lieshout JJ, Karemaker JM, Wesseling KH, Wieling W. Circulatory responses to stand up: discrimination between the effects of respiration, orthostasis and exercise. Clin Physiol. 1991;11(3):221-30.

11. Norsk P. Gravitational stress and volume regulation. Clin Physiol. 1992;12(5):505-26.

12. Abboud FM. The sympathetic system in hypertension. State-of-the-art review. Hypertension. 1982;4(3 Pt 2):208-25.

13. Kario K. Orthostatic hypertension-a new haemodynamic cardiovascular risk factor. Nat Rev Nephrol. 2013;9(12):726-38.

14. Bannister R, Sever P, Gross M. Cardiovascular reflexes and biochemical responses in progressive autonomic failure. Brain. 1977;100(2):327-44.

15. Ziegler MG, Lake CR. Autonomic degeneration and altered blood pressure control in humans. Fed Proc. 1984;43(1):62-6.

16. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology. 1996;46(5):1470.

17. Hiitola P, Enlund H, Kettunen R, Sulkava R, Hartikainen S. Postural changes in blood pressure and the prevalence of orthostatic hypotension among home-dwelling elderly aged 75 years or older. J Hum Hypertens. 2009;23(1):33-9.

18. Low PA. Prevalence of orthostatic hypotension. Clin Auton Res. 2008;18 Suppl 1:8-13.

19. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. Hypertension. 1992;19(6 Pt 1):508-19.

20. Romero-Ortuno R. Orthostatic Hypotension as a marker of Frailty in Older People: Trinity College Dublin; 2011.

21. Shaw BH, Claydon VE. The relationship between orthostatic hypotension and falling in older adults. Clin Auton Res. 2014;24(1):3-13.

22. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. Eur Heart J. 2015;36(25):1609-17.

23. Robertson D. The pathophysiology and diagnosis of orthostatic hypotension. Clin Auton Res. 2008;18 Suppl 1:2-7.

24. Coon EA, Cutsforth-Gregory JK, Benarroch EE. Neuropathology of autonomic dysfunction in synucleinopathies. Mov Disord. 2018;33(3):349-58.

25. Kougias P, Weakley SM, Yao Q, Lin PH, Chen C. Arterial baroreceptors in the management of systemic hypertension. Med Sci Monit. 2010;16(1):RA1-8.

26. Hajduczok G, Chapleau MW, Abboud FM. Increase in sympathetic activity with age. II. Role of impairment of cardiopulmonary baroreflexes. Am J Physiol. 1991;260(4 Pt 2):H1121-7.

27. O'Malley K, Docherty JR, Kelly JG. Adrenoceptor status and cardiovascular function in ageing. J Hypertens Suppl. 1988;6(1):S59-62.

28. Osterziel KJ, Dietz R, Manthey J, Schmid W, Kubler W. Haemodynamic changes caused by alteration of autonomic activity in patients with heart failure. Br Heart J. 1990;63(4):221-4.

29. Fessel J, Robertson D. Orthostatic hypertension: when pressor reflexes overcompensate. Nat Clin Pract Nephr. 2006;2(8):424-31.

30. Palatini P. Orthostatic Hypertension: A Newcomer Among the Hypertension Phenotypes. Hypertension. 2023;80(10):1993-2002.

31. Schneider E. A STATISTICAL STUDY OF THE PULSE RATE AND THE ARTERIAL BLOOD PRESSURES IN RECUMBENCY, STANDING, AND AFTER A STANDARD EXERCISE. American Journal of Physiology-Legacy Content. 1922;61:429-74.

32. McCANN WS, ROMANSKY MJ. ORTHOSTATIC HYPERTENSION: THE EFFECT OF NEPHROPTOSIS ON THE RENAL BLOOD FLOW. Journal of the American Medical Association. 1940;115(8):573-8.

33. Jordan J, Ricci F, Hoffmann F, Hamrefors V, Fedorowski A. Orthostatic Hypertension: Critical Appraisal of an Overlooked Condition. Hypertension. 2020;75(5):1151-8.

34. Kario K, Eguchi K, Nakagawa Y, Motai K, Shimada K. Relationship between extreme dippers and orthostatic hypertension in elderly hypertensive patients. Hypertension. 1998;31(1):77-82.

35. Townsend RR, Chang TI, Cohen DL, Cushman WC, Evans GW, Glasser SP, et al. Orthostatic changes in systolic blood pressure among SPRINT participants at baseline. J Am Soc Hypertens. 2016;10(11):847-56.

36. Yoshinari M, Wakisaka M, Nakamura U, Yoshioka M, Uchizono Y, Iwase M. Orthostatic hypertension in patients with type 2 diabetes. Diabetes Care. 2001;24(10):1783-6.

37. Kario K, Eguchi K, Hoshide S, Hoshide Y, Umeda Y, Mitsuhashi T, Shimada K. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. J Am Coll Cardiol. 2002;40(1):133-41.

38. Alagiakrishnan K, Masaki K, Schatz I, Curb JD, Blanchette P. Postural hypertension in elderly men--the Honolulu Heart Program. Hawaii Med J. 2000;59(2):48-50.

39. Tanaka H, Sjoberg BJ, Thulesius O. Cardiac output and blood pressure during active and passive standing. Clin Physiol. 1996;16(2):157-70.

40. Eguchi K, Kario K, Hoshide S, Hoshide Y, Ishikawa J, Morinari M, et al. Greater change of orthostatic blood pressure is related to silent cerebral infarct and cardiac overload in hypertensive subjects. Hypertens Res. 2004;27(4):235-41.

41. Hoshide S, Matsui Y, Shibasaki S, Eguchi K, Ishikawa J, Ishikawa S, et al. Orthostatic hypertension detected by self-measured home blood pressure monitoring: a new cardiovascular risk factor for elderly hypertensives. Hypertens Res. 2008;31(8):1509-16.

42. Fan XH, Wang Y, Sun K, Zhang W, Wang H, Wu H, et al. Disorders of orthostatic blood pressure response are associated with cardiovascular disease and target organ damage in hypertensive patients. Am J Hypertens. 2010;23(8):829-37.

43. Yatsuya H, Folsom AR, Alonso A, Gottesman RF, Rose KM, Investigators AS. Postural changes in blood pressure and incidence of ischemic stroke subtypes: the ARIC study. Hypertension. 2011;57(2):167-73.

44. Veronese N, De Rui M, Bolzetta F, Zambon S, Corti MC, Baggio G, et al. Orthostatic Changes in Blood Pressure and Mortality in the Elderly: The Pro.V.A Study. Am J Hypertens. 2015;28(10):1248-56.

45. Agnoletti D, Valbusa F, Labat C, Gautier S, Mourad JJ, Benetos A, Investigators Ps. Evidence for a Prognostic Role of Orthostatic Hypertension on Survival in a Very Old Institutionalized Population. Hypertension. 2016;67(1):191-6.

46. Bursztyn M, Jacobs JM, Hammerman-Rozenberg A, Stessman J. Prevalence of orthostatic hypertension in the very elderly and its relationship to all-cause mortality. J Hypertens. 2016;34(10):2053-8.

47. Velilla-Zancada SM, Escobar-Cervantes C, Manzano-Espinosa L, Prieto-Diaz MA, Ramalle-Gomara E, Vara-Gonzalez LA. Impact of variations in blood pressure with orthostatism on mortality: the HOMO study. Blood Press Monit. 2017;22(4):184-90.

48. Bhuachalla BN, McGarrigle CA, O'Leary N, Akuffo KO, Peto T, Beatty S, Kenny RA. Orthostatic hypertension as a risk factor for age-related macular degeneration: Evidence from the Irish longitudinal study on ageing. Exp Gerontol. 2018;106:80-7.

49. Kostis WJ, Sargsyan D, Mekkaoui C, Moreyra AE, Cabrera J, Cosgrove NM, et al. Association of orthostatic hypertension with mortality in the Systolic Hypertension in the Elderly Program. J Hum Hypertens. 2019;33(10):735-40.

50. Rouabhi M, Durieux J, Al-Kindi S, Cohen JB, Townsend RR, Rahman M. Orthostatic Hypertension and Hypotension and Outcomes in CKD: The CRIC (Chronic Renal Insufficiency Cohort) Study. Kidney Med. 2021;3(2):206-15 e1.

51. Palatini P, Mos L, Saladini F, Rattazzi M. Blood Pressure Hyperreactivity to Standing: a Predictor of Adverse Outcome in Young Hypertensive Patients. Hypertension. 2022;79(5):984-92.

52. Barzkar F, Myint PK, Kwok CS, Metcalf AK, Potter JF, Baradaran HR. Prevalence of orthostatic hypertension and its association with cerebrovascular diagnoses in patients with suspected TIA and minor stroke. BMC Cardiovasc Disord. 2022;22(1):161.

53. Strumia M, Vidal JS, Cestac P, Sallerin B, Hanon O, Rouch L, Investigators SA. Orthostatic hypotension and orthostatic hypertension are both associated with lower cognitive function: The S.AGES cohort. J Am Geriatr Soc. 2023;71(12):3721-30.

54. Palatini P, Mos L, Rattazzi M, Ermolao A, Battista F, Vriz O, et al. Exaggerated blood pressure response to standing in young-to-middle-age subjects: prevalence and factors involved. Clin Auton Res. 2023;33(4):391-9.

55. Ma Y, Zhang Y, Coresh J, Viswanathan A, Sullivan KJ, Walker KA, et al. Orthostatic Blood Pressure Change, Dizziness, and Risk of Dementia in the ARIC Study. Hypertension. 2024;81(1):96-106.

56. Choi JY, Ryu DR, Lee HY, Lee JH, Hong Y, Park SK, et al. Association Between Orthostatic Hypertension and Frailty Among Older Patients With Hypertension. Hypertension. 2024.

57. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874-2071.

58. Jordan J, Biaggioni I, Kotsis V, Nilsson P, Grassi G, Fedorowski A, Kario K. Consensus statement on the definition of orthostatic hypertension endorsed by the American Autonomic Society and the Japanese Society of Hypertension. Hypertens Res. 2023;46(2):291-4.

59. Brunkwall L, Jonsson D, Ericson U, Hellstrand S, Kennback C, Ostling G, et al. The Malmo Offspring Study (MOS): design, methods and first results. Eur J Epidemiol. 2021;36(1):103-16.

60. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). Eur Heart J. 2010;31(1):85-91.

61. Kario K. Orthostatic hypertension: a measure of blood pressure variation for predicting cardiovascular risk. Circ J. 2009;73(6):1002-7.

62. Araki K, Ueda Y, Kono I, Ookawara T, Kashima K. A case of neurogenic orthostatic hypertension. Jpn J Med. 1991;30(5):446-51.

63. Streeten DH, Auchincloss JH, Jr., Anderson GH, Jr., Richardson RL, Thomas FD, Miller JW. Orthostatic hypertension. Pathogenetic studies. Hypertension. 1985;7(2):196-203.

64. Lee H, Kim HA. Orthostatic hypertension: An underestimated cause of orthostatic intolerance. Clin Neurophysiol. 2016;127(4):2102-7.

65. Buddineni JP, Chauhan L, Ahsan ST, Whaley-Connell A. An Emerging Role for Understanding Orthostatic Hyp'er'tension in the Cardiorenal Syndrome. Cardiorenal Med. 2011;1(2):113-22.

66. Thomas RJ, Liu K, Jacobs DR, Jr., Bild DE, Kiefe CI, Hulley SB. Positional change in blood pressure and 8-year risk of hypertension: the CARDIA Study. Mayo Clin Proc. 2003;78(8):951-8.

67. Schiffrin EL. Vascular stiffening and arterial compliance. Implications for systolic blood pressure. Am J Hypertens. 2004;17(12 Pt 2):39S-48S.

68. Kuriyan R. Body composition techniques. Indian J Med Res. 2018;148(5):648-58.

69. Borga M, West J, Bell JD, Harvey NC, Romu T, Heymsfield SB, Dahlqvist Leinhard O. Advanced body composition assessment: from body mass index to body composition profiling. J Investig Med. 2018;66(5):1-9.

70. Prentice AM, Jebb SA. Beyond body mass index. Obes Rev. 2001;2(3):141-7.

71. Bjorntorp P, Rosmond R. The metabolic syndrome--a neuroendocrine disorder? Br J Nutr. 2000;83 Suppl 1:S49-57.

72. Arrone LJ, Mackintosh R, Rosenbaum M, Leibel RL, Hirsch J. Cardiac autonomic nervous system activity in obese and never-obese young men. Obes Res. 1997;5(4):354-9.

73. Oikonomou EK, Antoniades C. The role of adipose tissue in cardiovascular health and disease. Nat Rev Cardiol. 2019;16(2):83-99.

74. Dvoretskiy S, Lieblein-Boff JC, Jonnalagadda S, Atherton PJ, Phillips BE, Pereira SL. Exploring the Association between Vascular Dysfunction and Skeletal Muscle Mass, Strength and Function in Healthy Adults: A Systematic Review. Nutrients. 2020;12(3).

75. Beske SD, Alvarez GE, Ballard TP, Davy KP. Reduced cardiovagal baroreflex gain in visceral obesity: implications for the metabolic syndrome. Am J Physiol Heart Circ Physiol. 2002;282(2):H630-5.

76. Piglowska M, Kostka T, Drygas W, Jegier A, Leszczynska J, Bill-Bielecka M, Kwasniewska M. Body composition, nutritional status, and endothelial function in physically active men without metabolic syndrome--a 25 year cohort study. Lipids Health Dis. 2016;15:84.

77. Pasdar Z, De Paola L, Carter B, Pana TA, Potter JF, Myint PK. Orthostatic hypertension and major adverse events: a systematic review and meta-analysis. Eur J Prev Cardiol. 2023;30(10):1028-38.

78. Rockwood K, Silvius JL, Fox RA. Comprehensive geriatric assessment. Helping your elderly patients maintain functional well-being. Postgrad Med. 1998;103(3):247-9, 54-8, 64.

79. Guss DA, Abdelnur D, Hemingway TJ. The impact of arm position on the measurement of orthostatic blood pressure. J Emerg Med. 2008;34(4):377-82.

80. Cullen B, Fahy S, Cunningham CJ, Coen RF, Bruce I, Greene E, et al. Screening for dementia in an Irish community sample using MMSE: a comparison of norm-adjusted versus fixed cut-points. Int J Geriatr Psychiatry. 2005;20(4):371-6.

81. O'Donoghue PJ, Claffey P, Rice C, Byrne L, Cunningham C, Kenny RA, Romero-Ortuno R. Association between gait speed and the SHARE Frailty Instrument in a Falls and Syncope Clinic. Eur Geriatr Med. 2021;12(5):1101-5.

82. Passant U, Warkentin S, Karlson S, Nilsson K, Edvinsson L, Gustafson L. Orthostatic hypotension in organic dementia: relationship between blood pressure, cortical blood flow and symptoms. Clin Auton Res. 1996;6(1):29-36.

83. Lee SW, Youm Y, Kim CO, Lee WJ, Choi W, Chu SH, et al. Association between skeletal muscle mass and radial augmentation index in an elderly Korean population. Arch Gerontol Geriatr. 2014;59(1):49-55.

84. Shrout TA, Pan S, Mitchell GF, Vasan RS, Xanthakis V. Association of orthostatic blood pressure response with incident heart failure: The Framingham Heart Study. PLoS One. 2022;17(4):e0267057.

85. Grassi G, Seravalle G, Mancia G. Sympathetic activation in cardiovascular disease: evidence, clinical impact and therapeutic implications. Eur J Clin Invest. 2015;45(12):1367-75.

86. Florea VG, Cohn JN. The autonomic nervous system and heart failure. Circ Res. 2014;114(11):1815-26.

87. Wei FF, Zhou Y, Thijs L, Xue R, Dong B, He X, et al. Visit-to-Visit Blood Pressure Variability and Clinical Outcomes in Patients With Heart Failure With Preserved Ejection Fraction. Hypertension. 2021;77(5):1549-58.

88. Ronit A, Kirkegaard-Klitbo DM, Dohlmann TL, Lundgren J, Sabin CA, Phillips AN, et al. Plasma Albumin and Incident Cardiovascular Disease: Results From the CGPS and an Updated Meta-Analysis. Arterioscler Thromb Vasc Biol. 2020;40(2):473-82.

89. Oda E. Decreased serum albumin predicts hypertension in a Japanese health screening population. Intern Med. 2014;53(7):655-60.

90. Madsen PL, Scheuermann Freestone M, Neubauer S, Channon K, Clarke K. Haemoglobin and flow-mediated vasodilation. Clin Sci (Lond). 2006;110(4):467-73.

91. Yano Y, Vongpatanasin W, Ayers C, Turer A, Chandra A, Carnethon MR, et al. Regional Fat Distribution and Blood Pressure Level and Variability: The Dallas Heart Study. Hypertension. 2016;68(3):576-83.

92. Grassi G, Dell'Oro R, Facchini A, Quarti Trevano F, Bolla GB, Mancia G. Effect of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensives. J Hypertens. 2004;22(12):2363-9.

93. Resnick LM, Militianu D, Cunnings AJ, Pipe JG, Evelhoch JL, Soulen RL. Direct magnetic resonance determination of aortic distensibility in essential hypertension: relation to age, abdominal visceral fat, and in situ intracellular free magnesium. Hypertension. 1997;30(3 Pt 2):654-9.

94. Tsutsui Y, Sagawa S, Yamauchi K, Endo Y, Yamazaki F, Shiraki K. Cardiovascular responses to lower body negative pressure in the elderly: role of reduced leg compliance. Gerontology. 2002;48(3):133-9.

95. Zachrisson H, Lindenberger M, Hallman D, Ekman M, Neider D, Lanne T. Diameter and compliance of the greater saphenous vein - effect of age and nitroglycerine. Clin Physiol Funct Imaging. 2011;31(4):300-6.

96. Molnar AA, Nadasy GL, Dornyei G, Patai BB, Delfavero J, Fulop GA, et al. The aging venous system: from varicosities to vascular cognitive impairment. Geroscience. 2021;43(6):2761-84.

97. Berczi V, Molnar AA, Apor A, Kovacs V, Ruzics C, Varallyay C, et al. Non-invasive assessment of human large vein diameter, capacity, distensibility and ellipticity in situ: dependence on anatomical location, age, body position and pressure. Eur J Appl Physiol. 2005;95(4):283-9.

98. Hyland L, Docherty JR. An investigation of age-related changes in pre- and postjunctional alpha-adrenoceptors in human saphenous vein. Eur J Pharmacol. 1985;114(3):361-4.

99. Sergi G, De Rui M, Stubbs B, Veronese N, Manzato E. Measurement of lean body mass using bioelectrical impedance analysis: a consideration of the pros and cons. Aging Clin Exp Res. 2017;29(4):591-7.

100. Kario K. Preceding linkage between a morning surge in blood pressure and small artery remodeling: an indicator of prehypertension? J Hypertens. 2007;25(8):1573-5.