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Sarcopenia and Orthostatic Hypotension: Investigating the Underlying Haemodynamics

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

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All participants in the studies gave explicit, full and informed consent. All studies adhered to the World Medical Association Declaration of Helsinki on ethical principles for heath research involving human subjects and ethical approval for all studies was granted by the relevant research ethics boards.

Eoin Duggan

23/09/2024

To Claire and Ailbhe

Summary

The ageing population worldwide is both one of the greatest successes of modern humanity and one of its greatest challenges. These challenges are numerous and include the geriatric syndromes of sarcopenia and orthostatic hypotension (OH). These two geriatric syndromes are increasingly recognised as important drivers of adverse outcomes in older adults. There is reason to suggest a pathophysiological link between the two conditions in the form of the skeletal muscle pump (SMP) of the lower limbs. The SMP is thought to aid venous return during standing via rhythmic activity of the skeletal limb muscles. One might hypothesise that the effects of sarcopenia on the muscles of the lower limbs might impair the SMP, increasing the risk of OH.

While the relationship between sarcopenia and OH has previously been investigated in a small number of studies, the early recovery of blood pressure (BP) on standing and the haemodynamic mechanisms underlying these relationships have not. In addition, the contribution of the SMP to orthostatic BP recovery and maintenance is poorly understood.

This doctoral investigation sought to examine the relationship between sarcopenia, BP recovery after standing and OH in people aged ≥ 50 years. It aimed to examine the haemodynamic factors underlying these relationships and to determine, in particular, any indirect evidence for the role of the SMP. It consisted of three independent studies: Study I, a population cohort from The Irish Longitudinal Study on Ageing (TILDA) (N = 2858); Study II, a clinical sample recruited from the Falls and Syncope Unit at St. James's Hospital Dublin (N = 109); and Study III a physiological sample of healthy community-dwelling older adults (N = 31).

Study I found that probable sarcopenia was independently associated with a significantly attenuated recovery of BP up to 30-40 s after standing, but not thereafter. Those defined as having probable sarcopenia by hand grip strength (HGS) criteria had a larger and longer BP attenuation compared to those defined by 5-chair stands test (5CST) criteria. In TILDA, probable sarcopenia with OH had a higher odds ratio for future falls compared to OH or sarcopenia alone.

Study II-A expanded these findings to sarcopenia confirmed by bioelectrical impedance analysis (BIA), finding that both probable sarcopenia and sarcopenia, with an incremental effect, were independently associated with an attenuated BP recovery rate in the 10–20 s

period after standing. The results were independent of heart rate (HR), indicating the need to examine underlying haemodynamic parameters.

Study II-B investigated the haemodynamic factors underlying the relationship between sarcopenia and BP recovery after standing. It found that the mean arterial pressure (MAP) changes after standing appeared to be driven by a blunted initial peak and a slower reduction from the peak of cardiac output (CO) in the sarcopenia group. This was followed by an attenuated recovery of total peripheral resistance (TPR) from nadir after standing in the sarcopenia group. The CO finding appeared to be driven by stroke volume (SV) rather than HR. Given that $MAP = CO \times TPR$ and $CO = SV \times HR$, these findings suggested that sarcopenia could reduce SV via reduction of SMP (preload), but also impair TPR response via reduced muscle sympathetic nervous activity, or potentially further reduce CO in association with reduced heart contractility in this clinical sample ("cardiosarcopenia").

Study III found that in a comparatively healthier sample, measures of muscle strength (again, HGS but not 5CST) and mass (by BIA and also by ultrasound-measured muscle thickness) were associated with BP recovery early after standing (10–30 s). HGS was associated with change in CO in the 10–20 s period (again, SV but not HR), and with change in TPR at 20–30 s. In an effort to further evidence the plausible role of the SMP during contemporaneous muscle activation, I found that early BP recovery after standing was associated with changes in haemoglobin concentration in the thigh as measured by near-infrared spectroscopy during the 10–20 s period, but not with thigh muscle activation as measured by surface electromyography (EMG). Furthermore, the effects of physical counterpressure manoeuvres (PCMs) were also studied in this sample, and during the latter changes in BP were associated with change in TPR, but not CO.

Overall, sarcopenia appeared to be related to an attenuated BP recovery early after standing. While the mechanisms underlying this relationship are not fully characterised, the SMP likely plays a role through effects on venous return and stroke volume, in addition to sympathetic nervous system activation. The latter seemed more important that the former during PCMs. Sarcopenia could contribute to falls by impairing BP recovery after standing, as well as through traditionally considered effects such as impairment of gait and balance. Unlike some other risk factors for OH, sarcopenia is potentially reversible. Therefore, it is important to screen for sarcopenia in falls clinics, especially in patients with OH. Future research on the effects of sarcopenia interventions on orthostatic BP recovery is needed.

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Dissemination of Research Findings

Peer-Reviewed Papers Included in this Thesis

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Other Peer-Reviewed Papers Related to This Thesis

- **Duggan, E**., Jennings, G., Monaghan, A., Byrne, L., Xue, F., & Romero-Ortuno, R. (2023). Characterising the Blood Pressure Response to Physical Counterpressure Manoeuvres Using Surface Electromyography in Adults with Long Covid. IEEE Journal of Translational Engineering in Health and Medicine, 1–1. https://doi.org/10.1109/JTEHM.2023.3273910
- Lionetti, E., **Duggan, E**., & Romero-Ortuno, R. (2024). The SHARE Frailty Instrument for Primary Care was Associated with Sarcopenia, as Measured by Bioelectrical Impedance, in Falls Clinic Attendees. Journal of Frailty, Sarcopenia and Falls, 9(1), 10–15. https://doi.org/10.22540/JFSF-09-010

Abstract Publications

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- **Duggan, E**., Knight, S., Rizzo, R., David, J., Kenny, R. A., & Romero-Ortuño, R. (2021). Longer Chair-Stand Time is Associated With Orthostatic Intolerance in an Older Irish Population. Age and Ageing, 50, afab219.81. https://doi.org/10.1093/ageing/afab219.81

Platform Presentations

- "Investigating the Causal Haemodynamic Factors Underlying the Relationship Between Sarcopenia and Orthostatic Blood Pressure Recovery", 27th Nordic Congress of Gerontology, Stockholm, 2024
- "Haemodynamic Factors Underlying the Relationship Between Sarcopenia and Orthostatic Hypotension in Older Adults", International Sarcopenia Translational Research Conference, Newcastle upon Tyne, 2023
- "The Association Between Sarcopenia and Blood Pressure Recovery After Standing", 19th Congress of the European Geriatric Medicine Society, Helsinki, 2023

Poster Presentations

- "Muscle mass measured by bioelectrical impedance analysis was associated with handgrip strength but not with chair stands time in older falls clinic attendees", 18th Congress of the European Geriatric Medicine Society, London, 2022

- "Investigating The Relationship Between Probable Sarcopenia and Orthostatic Hypotension: Findings From The Irish Longitudinal Study On Ageing", Irish Gerontological Society Annual Scientific Meeting, Cavan, 2022
- "Longer Chair-Stand Time Is Associated With Orthostatic Intolerance In An Older Irish Population", Irish Gerontological Society Annual Scientific Meeting, Online, 2021

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List of Abbreviations

5CST ..... five chair stands test
ASMM ..... appendicular skeletal muscle mass
AWGS ..... Asian Working Group in Sarcopenia
BIA ..... bioelectrical impedance analysis
BP ..... blood pressure
BPM ..... beats per minute
CGA ..... Comprehensive Geriatric Assessment
CI ..... confidence interval
CO ..... cardiac output
CT ..... computed tomography
DBP ..... diastolic blood pressure
DXA ..... dual-energy X-ray absorptiometry
EMG ..... electromyography
EWGSOP ..... European Working Group on Sarcopenia in Older People
EWGSOP2 .... European Working Group on Sarcopenia in Older People revised definition
FNIH ..... Foundation for the National Institutes of Health
HGS ..... hand grip strength
HR ..... heart rate
ICD-10 ..... International Classification of Diseases, Tenth Revision
MELoR ..... Malaysian Elders Longitudinal Research Study
MAP ..... mean arterial pressure
MRI ..... magnetic resonance imaging
MSNA ..... muscle sympathetic nerve activity
NIRS ..... near-infrared spectroscopy
OH ..... orthostatic hypotension
OH30 ..... orthostatic hypotension at 30 s after standing
OH40 ..... orthostatic hypotension at 40 s after standing
OR ..... odds ratio
PCM ..... physical counterpressure manoeuvre
POTS ..... postural orthostatic tachycardia syndrome
SARCUS ..... Sarcopenia Through Ultrasound Project
SBP ..... systolic blood pressure
SHARE-FI ..... Survey of Health, Ageing and Retirement in Europe Frailty Instrument

SMP ..... skeletal muscle pump

SPPB ..... Short Physical Performance Battery

SSCWD ..... Society of Sarcopenia, Cachexia and Wating Disorders

SV ..... stroke volume

TILDA ..... The Irish Longitudinal Study on Ageing

TPR ..... total peripheral resistance

TUG ..... Timed-Up and Go

US ..... ultrasound

Chapter 1 – Introduction

The Challenges of an Ageing Population

The population of the world is ageing. In Ireland at the 2016 Census there were 629,800 people over the age of 65 and this is projected to rise to nearly 1.6 million by 2051, with 549,000 over the age of 85 [1,2]. Worldwide by 2050, one in five people will be over the age of 60 [3]. The ageing population is a great success, the result of comprehensive improvements in living conditions, sanitation, access to clean food and water and advancements in medical science. However, it presents unique challenges to society in terms of the problems associated with ageing.

In 1956 Bernard Isaacs coined the term *Geriatric Giants* to summarise these key challenges associated with ageing [4]. He considered immobility, instability, incontinence and impaired intellect as the four key challenges. Over time these have been refined and Morley [5] later proposed frailty, sarcopenia, anorexia of ageing and cognitive impairment as the modern giants. However, from both research in Gerontology and practice in Geriatric Medicine we can identify further *Geriatric Syndromes* [6] including multimorbidity [7], polypharmacy [8] and orthostatic hypotension (OH) [9]. These giants and syndromes increase the risk of adverse outcomes in older adults: falls, fractures, loss of independence and institutionalisation [10,11].

There is a pressing economic argument for addressing these geriatric syndromes. It is projected that in Ireland by 2030, the cost of falls will reach €2 billion per year [12], and institutional long term care costs will rise to €4.4 billion by 2035 — an 8.3% annual growth rate [13]. However, there is also a moral argument — surveys of older adults suggest that it is quality of life and independence that they value most, rather than pure quantity of life [14,15]. Modern medicine and single-organ specialisation have made great strides in expanding the life span of the population but not necessarily the health span [16]. Geriatric Medicine seeks to tackle these issues with a holistic, multidomain approach termed Comprehensive Geriatric Assessment (CGA) which has been shown lead to an increased likelihood for older patients admitted to hospital to be alive and living in their own-homes after discharge from hospital [17]. Community-dwelling frail, older people who undergo CGA may have a reduced risk of hospital admission [18]. To perform CGA effectively, one needs to understand not just the geriatric syndromes but also the interactions between them, which previous research has shown that can be non-linear in nature [19].

It is against this backdrop that my doctoral investigation considers the relationship between two of these syndromes, namely sarcopenia and OH, which are both increasingly

recognised as key drivers of adverse events in older adults [20,21]. I then go beyond OH, which is a consensus rather than pathology-based diagnosis, to consider blood pressure (BP) recovery from standing in its entirety. An overview of sarcopenia, OH and orthostatic BP recovery follows, and consideration is then given to the possible pathophysiological links between them. A summary of existing research in this field is provided, and the research questions of this doctoral thesis are then outlined.

Sarcopenia

Sarcopenia, one of the modern day *Geriatric Giants*, is a condition of progressive and generalised degeneration of skeletal muscle that is associated with ageing and affects both muscle mass and function [22]. The term is derived from the Greek *sarx* meaning flesh and *penia* meaning loss [23]. It was originally proposed by Rosenberg in 1989 who identified that the decline in lean body mass with age was striking but had received little research attention [24]. Since that time, there has been significant progression of research in the area from 39 articles in 2001 to 2,767 in 2020, in MEDLINE and Web of Science [25]. Sarcopenia can be primary (age-related) or secondary (related to acute or chronic disease) [26]. Originally, it was defined as a loss of muscle mass but over time the definitions have evolved to include both mass and function. In 2016 it was included in the International Classification of Diseases, Tenth Revision (ICD-10) with the code M62.84 [27].

Epidemiology

The prevalence of sarcopenia varies widely depending on the definition used and the setting studied. Studies that use muscle mass solely for diagnosis show a prevalence of up to 27%, with those using the European Working Group on Sarcopenia in Older People revised definition (EWGSOP2) having a prevalence around 10% [28]. Some studies that have considered appendicular lean mass/weight have found a prevalence up to 40.4% in community dwelling participants [29]. In long-term care cohorts, studies have found a prevalence between 14 – 33% [30] and a meta-analysis of studies in patients in rehabilitation post-hospital stay found a prevalence of 56% with a wide variety of diagnostic criteria used. More locally, a recent study found the prevalence of sarcopenia in community-dwelling older adults attending a Geriatric Medicine Day Hospital in Ireland to be 27 – 37% using the EWGSOP2 criteria [31].

Aetiology and Pathophysiology

The mechanisms leading to sarcopenia are not completely understood. It is believed that ageing disrupts homeostasis in the skeletal muscle leading to an imbalance between

anabolic and catabolic processes involved in the production of protein [32]. This leads to an overall loss of skeletal muscle. There are also cellular changes in sarcopenia with reduction in the size and number of skeletal muscle fibres, in particular type II fibres, along with intramuscular and intermuscular fat infiltration [33]. Age-related changes in mitochondrial function have been demonstrated and this may lead to decreased muscle performance and function [34]. There may also be anabolic resistance of skeletal muscle to nutrition in older people [35]. Other factors such as: changes in neurological signalling and control [36], neuromuscular junction dysfunction [37], decreased number of motor units [38], inflammation [39], insulin resistance [40] and oxidative stress [41] may also contribute to the development of sarcopenia.

In terms of secondary causes, reduced physical activity may lead to decreased mitochondrial biogenesis and reduced levels of anabolic hormones [42]. Inactivity may induce chronic reactive oxygen species overproduction leading to increased protein breakdown and ultimately skeletal muscle atrophy [43]. Acute and chronic disease leading to up regulation of inflammatory cytokines such as Interleukin 6 and Tumour Necrosis Factor Alpha may also lead to increased catabolism of skeletal muscle [44].

Risk Factors

The risk factors for sarcopenia are numerous. Given the role of age in the definition of primary sarcopenia and the knowledge that muscle mass declines with age, it is one of the strongest risk factors for sarcopenia, with an odds ratio (OR) of 14 for those over 65 years old compared to those under-65 in a study from the UK Biobank [45]. In that same study, women, those with lower education, and underweight participants were more likely to have sarcopenia. Low physical activity is a significant risk factor for sarcopenia [46], as is low protein and energy intake [47]. Chronic diseases such as chronic obstructive pulmonary disease, chronic kidney disease, heart failure, diabetes mellitus and rheumatoid arthritis are some of the many disease-related risk factors for sarcopenia [48]. Hospitalisation is a risk factor for sarcopenia, and sarcopenia itself is a risk factor for hospitalisation [49]. Finally, a number of drugs and medications have been associated with sarcopenia including hydroxymethylglutaryl-Coenzyme A reductase inhibitors (statins), glucocorticoids, glucose-lowering drugs, chemotherapeutic agents and polypharmacy itself (i.e., being on 5 or more regular medications) [50].

Identification and Diagnosis of Sarcopenia

There are several different guidelines and definitions for sarcopenia, largely regionally based. Initially, sarcopenia was defined in terms of muscle mass alone. The European Working Group on Sarcopenia in Older People (EWGSOP) published their first definition in 2010 based on muscle mass, strength and physical performance [51]. However, they did not issue specific cut-offs but recommended a population normative approach. In 2011, The International Working Group on Sarcopenia and Society of Sarcopenia, Cachexia and Wating Disorders (SSCWD) released a definition based on muscle mass and physical performance [52]. The Asian Working Group in Sarcopenia (AWGS) adopted the same definition as the EWGSOP and proposed cut-offs for use in Asia in 2014 [53]. The Foundation for the National Institutes of Health (FNIH) in 2014 defined sarcopenia using muscle mass and strength and defined cut-offs, using physical performance as an outcome [54]. Finally in 2019, the EWGSOP revised their definition (EWGSOP2) [55] using a four step approach: Find-Assess-Confirm-Severity (Figure 1-1). First, they propose finding potential sarcopenia through a screening tool. Next, identification of probable sarcopenia by detection of low muscle strength. The diagnosis of sarcopenia is then confirmed by measuring muscle quantity or quality. In addition, if there is low physical performance, the sarcopenia is termed severe. A comparison of the various sarcopenia diagnostic criteria is shown in Table 1-1.

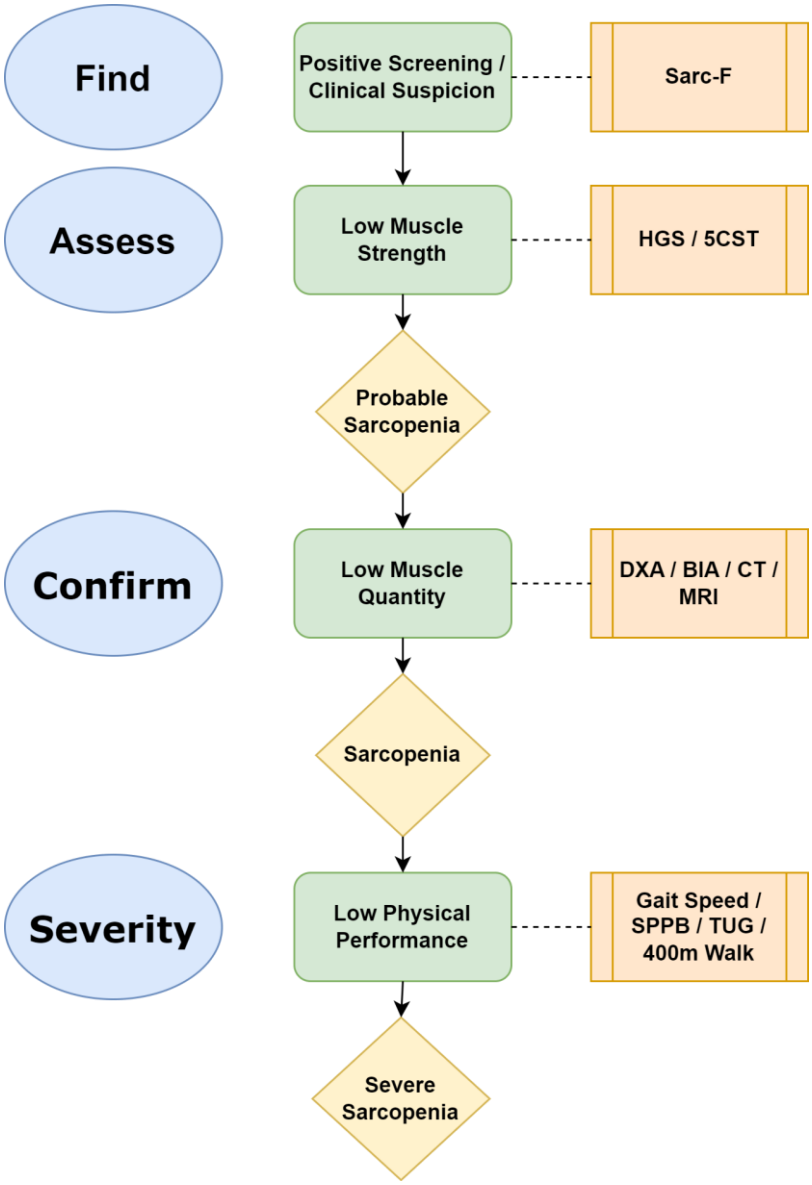

Figure 1-1: European Working Group on Sarcopenia revised guidelines (EWSOP2) algorithm for case-finding, making a diagnosis and quantifying severity in practice. Adapted from Cruz-Jentoft et al., 2019 [55] with permission. Sarc-f – sarcopenia screening tool; HGS – hand grip strength; 5CST – five chair stands test; DXA – dual energy x-ray absorptiometry; CT – computed tomography; MRI – magnetic resonance imaging; SPPB – short physical performance battery; TUG – timed up-and-go.

Table 1-1: Main sarcopenia diagnostic criteria in use

Diagnostic Criteria	Probable Sarcopenia / Low Muscle Strength	Sarcopenia	Severe Sarcopenia/ Low Physical Performance
EWGSOP2, 2019 [55]	HGS < 16 kg women <27 kg men Or 5CST > 15 s	ASMM < 15 kg women < 20 kg men Or ASMM/height^2 < 5.5 kg/m^2 women 7.0 kg/m^2 men	Gait speed ≤ 0.8 m/s TUG ≥ 20 s SPPB ≤ 8 points 400 m walk test non-completion or ≥ 6 minutes
FNIH, 2014 [54]	N/A	HGS < 16 kg women <26 kg men Or HGS/BMI <0.56 women <1.0 men And ALM <15.02 kg women <19.75 kg men Or ALM/BMI <0.512 women <0.789 men	N/A
AWGS, 2014 [53]	HGS < 16 kg women <27 kg men Or Gait speed < 1.0 m/s	ASMM/height^2 < 5.4 kg/m^2 women 7.0 kg/m^2 men	Gait speed ≤ 0.8 m/s SPPB ≤ 9 points
SCWD, 2011 [52]	N/A	Gait speed < 1.0 m/s And ALM/height^2 ≤ 5.67 kg/m^2 women ≤7.23 kg/m^2 men	N/A
EWGSOP, 2010 [51]	N/A	Gait speed < 0.8 m/s And ASMM < 2 SD below the mean reference value OR If Gait speed > 0.8 m/s HGS < 2 SD below the mean reference value And ASMM < 2 SD below the mean reference value	N/A

EWGSOP2 – European Working Group on Sarcopenia in Older People revised criteria; FNIH – Foundation for the National Institutes of Health criteria; AWGS – Asian Working Group for Sarcopenia criteria; SSCWD – Society on Sarcopenia, Cachexia, & Wasting Disorders International Working Group on Sarcopenia criteria; EWGSOP – European Working Group on Sarcopenia in Older People original criteria; HGS – hand grip strength, 5CST – 5 chair stands test; ASMM –

appendicular skeletal muscle mass; ALM – appendicular lean mass; BMI – body mass index; TUG – timed-up and go test; SPPB- short physical performance battery.

Case Finding

Identifying individuals who may potentially be sarcopenic can be opportunistic in nature, for example in those presenting with falls, gait imbalance, or reporting difficulties with activities of daily living. Alternatively, the EWGSOP2 recommend use of the SARC-F questionnaire to systematically screen for cases of potential sarcopenia. It is a five-item questionnaire that asks questions around: strength, walking, rising from a chair, stair climbing and falls [56]. It has a good specificity but moderate to poor sensitivity [57]. Other screening tools are more sensitive but most involve measurements of HGS which leads into the classification of probable sarcopenia [58].

Measurement of Muscle Strength

The most commonly used measures of muscle strength are hand grip strength (HGS), a measure of upper limb strength and five chair stands test (5CST) as a proxy for lower limb strength. The EWGSOP2 recommend measuring either or both. HGS is a strong predictor of adverse outcomes and mortality in older adults [59] and has been proposed as a vital sign given its predictive ability [60]. It is relatively simple to measure but requires a calibrated, validated handheld dynamometer. The Jamar dynamometer is one of the most utilised [61] and reference data for numerous populations exist, including in Ireland [62]. Many different measurement protocols have been used in research and clinical practice which can make comparisons across studies difficult [63].

The 5CST can be used as a proxy for lower limb strength. It measures the time it takes a participant to stand up and sit down five times from a sitting position without the use of arms [64]. Other variations of the test involve counting how many times a participants can stand up and sit down in 30 s. However, some consider these tests to be more of a test of endurance and physical performance than pure strength [65]. The EWGSOP2 gives chair-based tests a qualified recommendation given their convenience and lack of equipment needed.

Other measures of muscle strength or torque such as hand-held dynamometry, can be difficult to standardise [66] and the gold standard isokinetic dynamometers require specialist equipment and positioning [67].

Measurement of Muscle Quantity

There are a number of methods for measuring muscle quantity, each with relative strengths and limitations. Magnetic resonance imaging (MRI) and computed tomography (CT) are the gold standards for measurement of muscle mass. They are three-dimensional modalities that can give a measure of muscle cross-sectional area or volume. However, their use is largely precluded in clinical settings due to high cost, accessibility, higher dose of ionising radiation (CT), potential patient discomfort (MRI), and lack of well-defined cut-off points [68]. However, they may have a role in cancer patients who undergo CT or MRI imaging as part of their routine clinical care [69]. CT measures of muscle mass determined in patients with cancer may have a prognostic role [70].

Dual-energy X-ray absorptiometry (DXA) was originally developed to measure bone mineral density but can also be used to differentiate lean mass from fat mass. In this way, a three-compartment estimate of body composition in terms of bone, lean and fat mass can be derived. Lean mass is used as an estimate for muscle mass, assuming constant hydration and this is termed appendicular skeletal muscle mass (ASMM) [71]. It has been widely used in research and has validated cut-points. The dose of ionising radiation is minimal [72]. However, in clinical practice it too can be difficult to access, costly and different manufactures give differing results [73].

Bioelectrical impedance analysis (BIA) is a straightforward technique that measures whole-body electrical conduction from which an estimate of muscle mass can be derived. The estimates are referred to DXA for specific populations. BIA passes an alternating sinusoidal electric current, at one or more frequencies, through an active electrode and measures impedance – resistance and reactance – through a measuring electrode. As lean mass, which is largely water, conducts electricity better than fat mass, differences in impedance between the two tissues allow for estimation of total body water. This can be converted into fat free mass by use of population specific equations. ASMM can be predicted using equations that take into account, age, sex, weight and height and are referenced to DXA measurements of lean mass for a population. A number of such equations have been developed and validated in various populations [74]. Those in a Caucasian population include: Janssen et al. [75], Kyle et al. [76], Sergi et al. [77], and Scafoglieri et al. [78]. The Sergi equation is preferred by EWGSOP2 as it has been cross validated against DXA in external studies [79]. Manufactures of BIA devices often supply their own estimates of ASMM and body composition, however as the underlying equations

used are proprietary, and the reference population will differ, use of the raw impedance values with a published, validated equation is recommend in the EWGSOP2 [55].

The advantages of BIA are that it is affordable, non-ionising, easy to access, portable and quick. However, there are limitations in the measurements, hydration status and oedema can significantly affect the measurements and it is contraindicated in those with implanted electronic devices e.g. pacemakers [80].

Ultrasound (US) is an emerging approach that, with modern point-of-care US machines, shows promise for both bedside and community use [81]. It is relatively quick and device costs are falling. US has been used for some time in neuromuscular and sports medicine, and over the past decade it has been increasingly used in sarcopenia research [82]. It allows direct visualisation of the muscle at different sites, and a variety of measures can be taken such as: muscle thickness [83], cross-sectional area [84], and pennation angle [85]. Information about subcutaneous fat thickness and muscle architecture can also be determined. Intra- and inter-rater reliability has been a concern; however, studies have shown this to be good, at least in research settings [86]. Validity against other advanced imaging techniques has also been shown to be satisfactory [87]. Protocols for standardised measurements for sarcopenia assessment in clinical practice and research have been developed through the Sarcopenia Through Ultrasound Project (SARCUS) [88,89], however there is still much variability in methods used in the literature. Some of the major issues remaining are the lack of validated cut-offs for measurements, as well as a lack of consensus regarding the exact measures to take or the muscle groups to assess [90]. Additionally, patient positioning, differing transducers and machines, equipment settings and measurement protocols can all affect results [91].

Measurement of Muscle Quality

Muscle quality may be as important as, or even more important than, muscle quantity, and much research is ongoing in this area [92]. A definitive definition of muscle quality does not yet exist. It can refer to imaging properties such as fat infiltration and muscle attenuation seen on MRI or CT [93], or US parameters such as echogenicity [94]. Ratios of muscle strength to muscle mass have been proposed [95] and the phase angle of BIA has also been studied [96]. Owing to the lack of consensus, guidelines currently do not give cut-offs for muscle quality.

Measurement of Physical Performance

The current EWGSOP2 guidelines include physical performance as a determinant of severe sarcopenia. There are a number of different measures in use including gait speed, Timed-Up and Go (TUG), and the Short Physical Performance Battery (SPPB). Gait speed can be tested simply using a 4m usual walking test and a stopwatch, or with more sophisticated electronic gait devices [97]. The TUG test involves timing a participant standing from a chair, walking three metres, turning around, walking back and sitting down again [98]. The SPPB involves a combination of gait speed assessment, a balance test and 5CST [99].

Cut-offs for Sarcopenia

The EWGSOP2 definition document provides cut-offs based on available evidence in the European population [55]. For low muscle strength, the cut-offs are: a HGS of less than 27 kg in men and 16 kg in women; or a 5CST of greater than 15 s. For low muscle quantity, ASMM of less than 20 kg for men and 15 kg for women. If ASMM is adjusted for height, the cut-offs are less than 7.0 kg/m^2 for men and less than 5.5 kg/m^2 for women. For low physical performance, a gait speed of 0.8 m/s or less, or SPPB 8 points or less, or TUG of 20 s or more, will fulfil the criteria.

Differential Diagnosis

The main differentials for sarcopenia are malnutrition, cachexia and frailty, and all are closely related. Malnutrition is more closely linked to poor nutritional intake, measures of muscle mass have been incorporated in recent definitions, but there is less emphasis on muscle function [100]. Cachexia represents the significant weight loss and muscle wasting that can occur in pro-inflammatory states such as cancer, acquired immune deficiency syndrome and end-stage organ failure [101]. Sarcopenia can occur with cachexia and there is overlap in the definitions [102]. Frailty is a state of heightened risk to decompensation from stressors caused by dysregulation in multiple systems [103]. Of the various operationalisations of the concept of frailty, physical frailty (of the frailty phenotype) [61] is the most closely linked to sarcopenia and indeed overlaps [104,105]. In their postulated cycle of physical frailty, Linda Fried and Jeremy Walston postulated in 1998 that sarcopenia is central component of the physical frailty phenotype [106]. A recent study found significant overlap between sarcopenia and frailty in terms of metabolic, haematologic, and inflammatory biomarkers [107] and some authors have gone as far as

asserting that sarcopenia is the underlying biological substrate that defines physical frailty [108–110].

Management of Sarcopenia

The treatment of sarcopenia is largely non-pharmacological. The mainstay involves modifying reversible causes, nutrition, and physical exercise. Avoidance of sedentary behaviours and maintenance of physical activity in daily life are likely important for preventing sarcopenia [111]. There is also good evidence from meta-analyses for the role of resistance exercise in improving both muscle strength [112] and mass [113]. However, a major challenge is that there are low rates of habitual resistance exercise among older adults and both the design and adherence to programmes can be challenging [114].

In terms of nutrition, the traditionally recommended protein intake of 0.8 g/kg body weight [115] has been challenged and an intake of 1 – 1.2 g/kg body weight may be beneficial, and for those at risk of malnutrition 1.2 – 1.5 g/kg may be needed [116]. However, high-quality evidence supporting these expert consensus recommendations is lacking [117].

Supplementation of vitamin D for those with low levels may be beneficial for the prevention and treatment of sarcopenia [118]. It is unclear however whether supplementation of those with normal levels is of benefit to muscle mass or strength [119].

Omega-3 fatty acid [120], leucine [121], and its active metabolite beta-hydroxy-beta-methylbutyrate [122] are current research areas for their role in improving muscle mass and strength.

Overall, the most promising results have come from combined nutrition and exercise programmes. A recent European randomized control trial SPRINTT found that a multicomponent intervention consisting of moderate intensity exercise up to six times a week and personalised nutrition counselling lead to a reduction in the incidence of mobility disability [123]. A recent Irish study [124], trialled a three-month intervention of a home exercise regimen emphasising strength and dietary protein guidance of 1.2 g/kg body weight, and found a significant improvement in HGS and physical frailty, as measured by Survey of Health, Ageing and Retirement in Europe Frailty Instrument (SHARE-FI), compared to a control group.

In terms of pharmacological management, a number of treatments for sarcopenia have been investigated including hormone replacement, selective androgen receptor modulators,

myostatin modulators, modulators of neuromuscular functional and activators of mitochondrial biogenesis [125].

Testosterone has been found in trials to increase muscle mass and strength [126]; however, concerns regarding prostate cancer and cardiovascular side effects have hindered its progression [127]. Oestrogen and selective oestrogen receptor modulators have had conflicting results regarding muscle gains [128,129]. Dehydroepiandrosterone supplementation has also had mixed results in trials with some studies showing improvements in muscle strength and others inconclusive, and a systematic review concluded further large-scale trials are needed [130]. Selective androgen receptor modulators are agents that have the same anabolic effect on muscle tissue as testosterone but avoid its potential side effects. Small trials have been promising in terms of improvements in lean body mass and strength, but larger trials are needed to determine long term safety and efficacy [131].

Overall, despite many potential agents and much ongoing investigation, to date there remains no regulator-approved drug therapy for sarcopenia [132]. The reasons for this include: varying definitions and treatment cohorts, insufficient dosing, inappropriate endpoint selection, and the lack of comprehensive treatment strategy that includes drug therapy [133].

Outcomes of Sarcopenia

There are a number of adverse outcomes associated with sarcopenia. These include: mobility disability, functional decline, falls, fractures, reduced quality of life and mortality [134].

Sarcopenia has been shown to be associated with an OR of functional decline between 2.5 and 3 [135]. This can lead to disability and dependence in personal (basic) or instrumental (extended) activities of daily living. This can increase care needs and has both a quality of life and financial impact [136]. Sarcopenia has been shown to be associated with lower health related quality of life in several studies [137].

Sarcopenia can lead to mobility decline, reduced strength and balance and hence an increased rate of falls with hazard ratio of 2.3 to 3.2 [138]. This can lead to fractures, hospitalisation and significant morbidity [21]. There is an increased risk of fractures in sarcopenia, both through the occurrence of falls but also through hormonal interaction between muscle and bone giving risk to osteosarcopenia — combined muscle weakness

and low bone mineral density [139]. Those with sarcopenia are more likely to be hospitalised, have longer hospital stays and more likely to have complications [140–142].

The impaired balance in sarcopenia [143], can lead to increased fear of falling (OR 3.1) and fear of falling related activity restriction (OR 8.1) [144] with subsequent increase in falls risk [145].

Finally, overall, sarcopenia increases the OR of all-cause mortality between 1.6 to 3.6 [135,146,147], with higher odds in those older and for secondary sarcopenia [148]. HGS alone is also highly predictive of mortality [149].

Orthostatic Hypotension

OH, another important disorder associated with ageing, refers to an excessive drop in BP on standing. OH can be asymptomatic or lead to symptoms of orthostatic intolerance including light-headedness and pre-syncope. It is a major cause of both syncopal and non-syncopal falls [150]. It was first described in Western literature by Bradbury and Eggleston in 1925 who identified the cases of three patients who had precipitous drops in BP while standing [151]. Primary autonomic failure was later identified in a case series by Wagner and Braunwald in 1956 [152]. In 1960, Shy and Drager identified a Parkinson-like syndrome with autonomic nervous system involvement that later became known as Multiple System Atrophy [153]. However, there was no agreed definition of OH until 1996 when the American Autonomic Society and the American Academy of Neurology arranged a consensus conference to define OH, pure autonomic failure and multiple system atrophy. This conference culminated in the publication of a brief definition of OH: "a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing" [154]. This definition has essentially remained to this day, albeit in a refined version as will be discussed later.

The Haemodynamic Response to the Upright Posture

The upright posture poses a significant physiological challenge to humans. Initially on standing, an estimated 500 to 1000mL of blood are translocated from the thorax to the venous system of the lower limbs [155]. Without a counter-regulatory response, a precipitous fall in BP would occur, and cerebral hypoperfusion and loss of consciousness would follow.

The initial haemodynamic response to standing is mediated via the neural pathways of the autonomic nervous system. More prolonged orthostasis leads to changes mediated by the

humoral paths of the autonomic nervous system [156]. Central to the neural response of the of the autonomic nervous system are the arterial baroreceptors located in the carotid sinuses, the aortic arch and the coronary arteries, along with cardiopulmonary stretch receptors in the heart and lungs [157]. The arterial baroreceptors act with tonic inhibition on the sympathetic nervous system centres in the brainstem [158]. A decrease in BP on standing is sensed by the baroreceptors and leads to a decrease in this tonic inhibition and a decrease in the activity of the vagus nerve. This results in an increase in sympathetic nervous system activity with resultant increase in heart rate (HR), cardiac contractility and vasoconstriction [159]. While the change in HR is extremely fast, acting within one heartbeat, the sympathetically mediated increase in vasoconstriction is a slower but critical driver of BP maintenance, which is able to maintain venous return and cardiac filling during the post-standing period. An increase in the HR alone cannot sustain cardiac output (CO) without adequate venous return [160].

Interestingly, the initial 30 s period after standing differs significantly between active (normal) and passive (head-up tilt) standing [161]. On active standing, there is an initial drop in BP to a nadir which does not occur during head-up tilt. The initial drop in BP on active standing is hypothesised to result from a number of mechanisms [162]. Compression of the veins of the lower limbs and abdomen during active standing initially increases venous return to the heart, right atrial pressure, preload and CO. This is accompanied by a significant drop in total peripheral resistance (TPR) [163]. The rise in CO is not sufficient to make up for the drop in TPR and so BP falls. The reasons for the fall in TPR have not been fully elucidated but four mechanisms have been proposed [164]:

i. Contraction of the lower limb muscles causes transient local vasodilation.
ii. There is an increased arterio-venous pressure gradient in the lower limbs due to gravity.
iii. The initial increased venous return and increased right atrial pressure leads to cardiopulmonary baroreflex-mediated withdrawal of sympathetic tone, reducing peripheral and splanchnic vasoconstriction leading to reduced TPR.
iv. Similar to the cardiopulmonary baroreceptors, the arterial carotid baroreceptors, activated by the initial rise in BP during standing, trigger, reducing sympathetic activity leading to a reduced TPR.

Synchronous to these events, at the onset of standing there is a sharp increase in HR, within one heartbeat, due to vagal withdrawal. This is believed to be due to the exercise

pressor reflex, a reflex that initiates as soon as muscle contractions are performed [165]. A further increase in HR starts around 5 s after standing mediated by further vagal inhibition and by the arterial baroreceptors sensing a fall in BP and increasing sympathetic activity to the sinus node of the heart [166].

BP reaches a nadir in eight to ten seconds in healthy adults [164]. This corresponds with the nadir in TPR. The reduction in BP is sensed by the arterial baroreceptors leading to sympathetic mediated increase in peripheral and splanchnic vasoconstriction resulting in prompt recovery in TPR and hence BP. Splanchnic venoconstriction likely also contributes to venous return [167], but peripheral venoconstriction of the lower limbs is likely of little magnitude or importance [168]. While peripheral venoconstriction may not contribute to BP recovery and maintenance, mechanical compression of the veins may. Rhythmic contractions of the muscles of the lower limbs during standing reduces venous pooling and pumps venous blood back to the heart [169]. This is termed the skeletal muscle pump (SMP). As will be discussed later in this chapter, it is believed that postural sway during standing may activate the lower limb muscles, actively pumping blood back to the heart increasing venous return and thereby BP [170]. The haemodynamic response to standing is summarised in Figure 1-2.

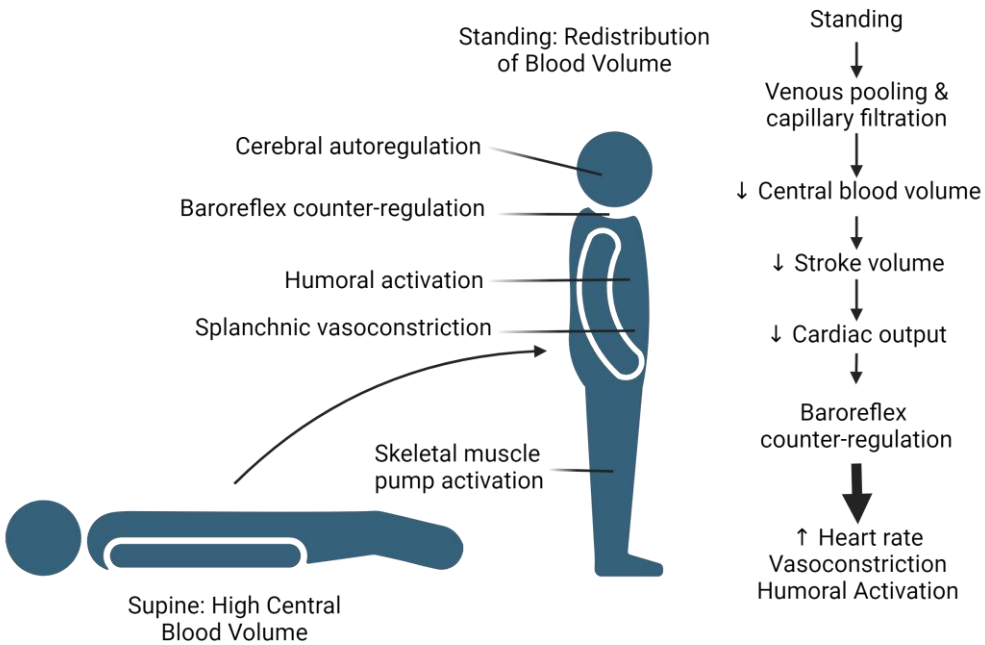

Figure 1-2: The haemodynamic response to orthostasis. Adapted from Wieling et al, 2022 [171] with permission.

The initial response to passive standing, head-up tilt, is quite different to that of active standing [172]. Without the muscular effort of standing, there is no initial drop in TPR and in fact there is immediate increase in HR, a fall in SV and a rise in TPR, resulting in ~10 mmHg increase in mean arterial pressure (MAP) around a minute after standing [173].

In both active and passive standing BP and HR recovery are completed by 30 s in healthy adults and the early steady state phase consists of an increased diastolic BP (DBP) ~ 10 mmHg, an increased HR of ~ 10 beats per minute (BPM) and little or no change in systolic BP (SBP) [164]. In health, BP is maintained well, with sympathetic mediated vasoconstriction playing a key role [174]. The SMP also likely plays a supporting role in maintaining BP in the upright posture by maintaining venous return to the heart [175]. Humoral mechanisms — the renin-angiotensin-aldosterone system and vasopressin are important in prolonged orthostasis, acting to maintain circulating blood volume by sodium and water retention [176]. If orthostasis is prolonged and sustained stroke volume (SV) gradually declines, HR increases to compensate but overall CO falls. If the fall in CO continues syncope is inevitable [177].

Diagnosis and Sub-Types

The 1996 definition of OH was updated in 2011 with a consensus statement from the American Autonomic Society, the European Federation of Autonomic Societies, the Autonomic Research Group of the World Federation of Neurology and the Autonomic Disorders section of the American Academy of Neurology [178]. They retained the 1996 definition of a sustained drop of greater than 20 mmHg in SBP and/or 10 mmHg in DBP within three minutes of standing, but added that in patients with supine hypertension a SBP drop of 30 mmHg may be a more appropriate criterion as the size of the BP drop on standing is dependent on the baseline BP. The 2011 OH definition is sometimes termed consensus OH. The 2011 statement also defined two further variants of OH: initial OH and delayed OH. Initial OH is defined as a drop of 40 mmHg SBP or 20 mmHg DBP within 15 s of standing [179]. Delayed OH is defined as a sustained drop in BP of 20mmg systolic or 10 mmHg diastolic or more occurring after three minutes of standing [178]. Subsequently, through the use of beat-to-beat BP monitoring in populations studies and syncope units [180,181], delayed BP recovery variants were recognised, sometimes termed OH at 30 s after standing (OH30) or OH at 40 s after standing (OH40). Delayed BP recovery is defined as a failure of BP to recover to within 20 mmHg systolic or 10 mmHg

diastolic within 30 – 40 s after standing [182]. The sub-types of OH are illustrated in Figure 1-3.

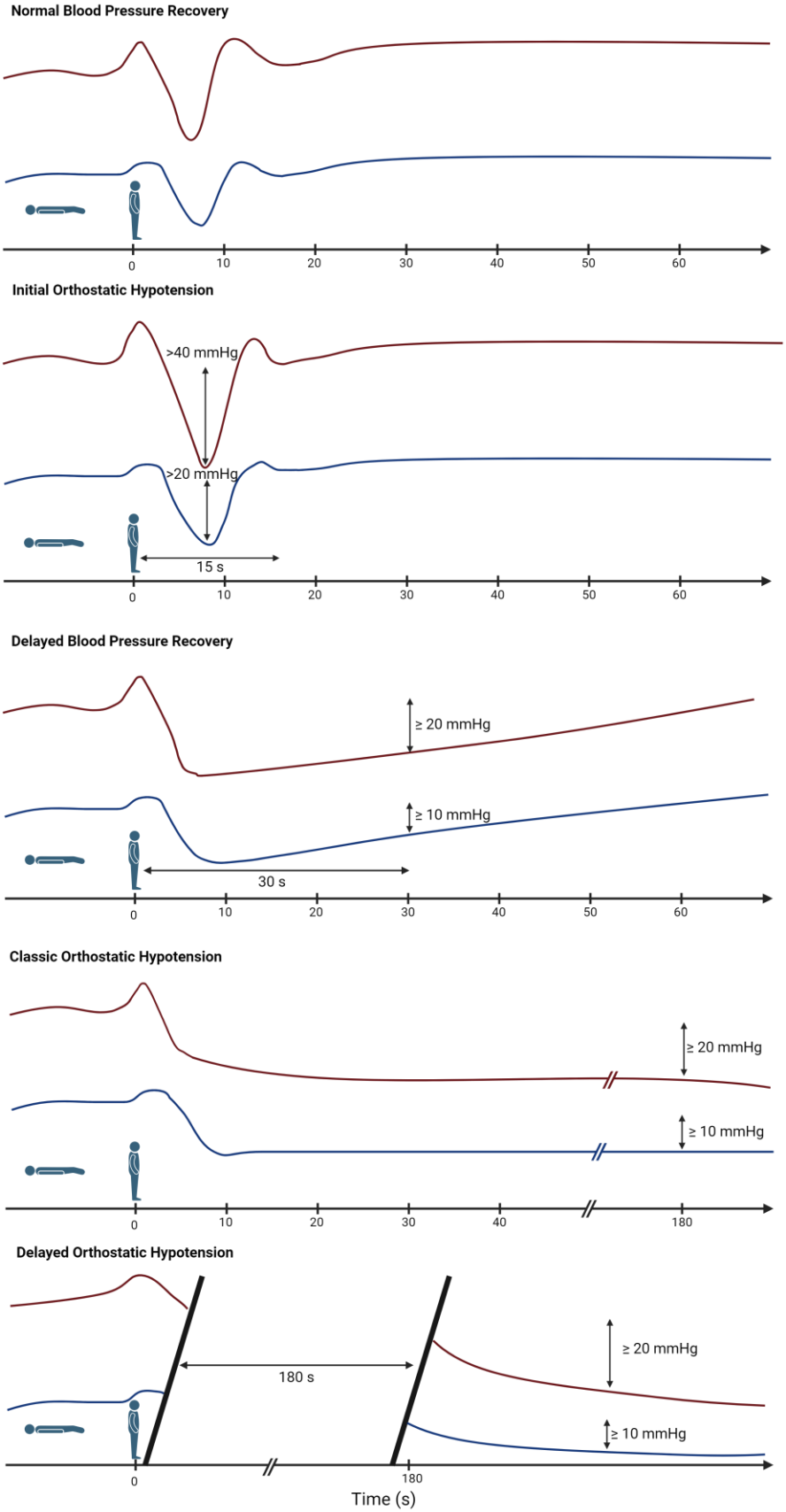

Figure 1-3: Subtypes of orthostatic hypotension. Systolic blood pressure (red), diastolic blood pressure (blue). Adapted from Wieling et al, 2022 [171] with permission.

Epidemiology

OH, as a clinical finding, is common, and its prevalence varies widely depending on the setting studied, age, co-morbidities and instrumentation used for identification. A recent systematic review of OH in those over 60 years of age included 20 studies with 24,967 community-dwelling older people and found a pooled prevalence of 22.2% (95% confidence interval (CI) 17 – 28%) [183]. In a long-term care setting six studies were included, with 2,694 participants, with a pooled prevalence of 23.9% (95% CI 18.2 – 30.1%). There was significant heterogeneity between studies. Even higher prevalence is found in diseases such as Parkinson's disease where up to 30% have OH [184]. In the relatively healthy population sample from The Irish Longitudinal Study on Ageing (TILDA), OH was found in 6.9% overall rising to 18.3% in those over 80 years [181]. Prevalence of initial OH has been estimated at up to 27.7% of those over 65 years of age in the general population and 35.2% in geriatric outpatients [185]. However, there is significant debate over whether initial OH is in fact pathological or physiological [179]. Indeed, the recent Malaysian Elders Longitudinal Research Study (MELoR) found better physical performance and cognition in those with initial OH [186].

Aetiology

The causes of OH can broadly be divided into neurogenic and non-neurogenic [187]. Neurogenic causes are either primary or secondary autonomic failure. Primary autonomic failure is caused by synucleinopathies, diseases characterised by α-synuclein deposition in the central or peripheral nervous system [188]. These include multiple-system atrophy, idiopathic Parkinson's disease, dementia with Lewy bodies and pure autonomic failure [189]. Secondary autonomic failure—peripheral autonomic dysfunction—can be caused by diabetes, amyloidosis, autoimmune conditions or paraneoplastic disorders [190]. Additionally, spinal cord injury can cause significant OH and autonomic dysfunction [191].

Non-neurogenic causes of OH include hypovolaemia, medications, heart failure or valvular heart disease [192]. Hypovolaemia can be caused by dehydration, adrenal insufficiency, haemorrhage, vomiting, dialysis, diabetes insipidus and diuretics [193]. A wide range of medications have been implicated in OH, in particular α-blockers, β-blockers, calcium channel blockers, diuretics, psychotropics and opioids [194]. OH is commonly found in heart failure, especially those with reduced ejection fraction, and resultant impairment in CO [195]. Valvular heart disease can also cause and exacerbate OH [196].

Cardiovascular deconditioning, whether through acute illness [197], bed-rest [198] or spaceflight [199] is also a known risk factor for OH and may act through both neurogenic and non-neurogenic pathways. In a similar way, as will be discussed later, sarcopenia has recently been found to be associated with OH [200] and may act through autonomic or mechanical pathways.

There is debate however, over the term non-neurogenic OH, with some experts in the field arguing that all OH has a neurogenic component, even if it is not the primary one [201]. They argue that OH is a spectrum of disease, from those cause primarily by autonomic failure, to those mainly caused by medications, deconditioning and volume depletion in susceptible individuals with poor compensatory autonomic reflexes.

Pathophysiology

The pathophysiology of neurogenic OH is the failure of those mechanisms described above in the haemodynamic response to the upright posture, to act to maintain erect BP [202]. Damage is caused to the central or peripheral baroreceptor and autonomic nervous system pathways by either deposition of α-synuclein in primary autonomic failure or small-fibre peripheral neuropathies in secondary autonomic failure [203]. This leads to reduced reflex peripheral and splanchnic vasoconstriction. This impairs the recovery of TPR from nadir, and hence BP. In addition, there is a pronounced fall in CO which compounds the failure of TPR to recover. This fall in CO is due to an impaired HR response, impaired cardiac contractility response and venous pooling in the lower limbs and splanchnic region resulting in reduced venous return to the heart [156].

The pathophysiology of non-neurogenic OH is less well described. In practice, sustained OH from non-neurogenic causes is less likely and delayed BP recovery more common from non-neurogenic causes. However, there may be a neurogenic component to the majority of cases of OH [201]. Hypovolaemia means that there is a reduced circulating blood volume and often relative supine hypotension, and this can be exacerbated on standing leading to OH. Heart failure may cause OH through a reduction in ejection fraction limiting CO [195]. Medications can contribute to OH through a number of mechanisms: by impairing vasoconstriction (α-blockers), impairing the inotropic and chronotropic response of the heart (β-blockers), vasodilation leading to venous pooling (nitrates) or hypovolaemia (diuretics) [204]. Psychotropic medications are strongly linked with OH, but a consistent mechanism has not been demonstrated [205]. Selective serotonin reuptake inhibitors can inhibit sodium, potassium and calcium channels leading

to reduced cardiac contractility [206]. Tricyclic antidepressants and anti-psychotics block post-synaptic α-adrenergic receptors and so may inhibit vasoconstriction [207,208]. Benzodiazepines cause muscle relaxation which may exacerbate the fall in TPR and venous pooling and additionally can be negatively inotropic [209].

Symptoms

OH can be asymptomatic or can lead to symptoms, often termed orthostatic intolerance. Asymptomatic OH is a common finding on routine checks of lying and standing BP. Manifestations of orthostatic intolerance, include light-headedness, dizziness, blurred vision, nausea, palpitations, asthenia, cognitive disturbance, tremor, neck pain and headache [210]. These symptoms can cause a significant burden and negatively affect quality of life [211].

Outcomes

Both symptomatic or asymptomatic OH can lead to falls, both syncopal and non-syncopal. A 2019 systematic review and meta-analysis [20] found OH to be independently associated with an increased OR of falls of 1.73 (95% CI 1.50 – 1.99). Subgroup analysis showed that the association was strongest for BP measured continuously rather than intermittently. Claffey et al. [212] found asymptomatic OH to be independently associated with unexplained falls in TILDA, with an OR of 2.01 (95% CI 1.11 – 3.65), and another study also from TILDA found that sustained OH, but not initial OH, was associated with all-cause falls (relative risk (RR) 1.40, 95% CI 1.12 – 2.24), unexplained falls (RR 1.81, 95% CI 1.06 – 3.09), and injurious falls (RR 1.58, (95% CI 1.12 – 2.24) [213].

OH is recognised as a cause of syncope [214] and can be found in a quarter to one-third of those with unexplained syncope [215,216].

OH has been found in meta-analyses to be associated with significantly increased risk of all-cause mortality (RR 1.50, 95% CI 1.24 – 1.81), incident coronary heart disease (RR 1.41, 95% CI 1.22 – 1.63), heart failure (RR 2.25, 95% CI 1.52 – 3.33), and stroke (RR 1.64, 95% CI 1.13 – 2.37) [217]. Subgroup analysis found a higher mortality risk in the under 65-years group, felt to be due to increased likelihood of neurogenic OH from a neurodegenerative disorder in that group.

Delayed BP recovery, as distinct from classic OH, has also been shown to be a risk factor for unexplained falls (RR 1.52, 95% CI 1.03 – 2.26) [213], fractures (OR 1.80, 95% CI 1.28 – 2.53) [218], and mortality (hazard ratio 3.00, 95% CI 1.17-7.68).

Assessment of Orthostatic BP

The assessment of the BP response to standing has developed over time as BP measurement technology has advanced. Traditionally, the auscultatory method of Korotkoff was used with a mercury sphygmomanometer [219]. Over time, mercury sphygmomanometers were replaced by aneroid manometers. Automated oscillometric measurement of BP was developed in the late 1970s, has been refined over time and has slowly taken over from manual methods of BP measurement [220]. Lying-to-standing and sitting-to-standing tests have been used, with great variability in the timing of measurement and standing [221]. Guidelines have been developed to try standardise the approach [222]. It is recommended that BP measurements are taken first with the patient lying for 5 minutes, and then the patient is asked to stand, and BP measurements are taken at 1, 2 and 3 minutes after standing. The disadvantage to these methods is that they provide intermittent measurements and in the case of most oscillometric devices, due to signal latency, cannot capture the BP changes in the first minute after standing [223]. Thus, continuous measures of BP are needed to identify initial OH and delayed BP recovery.

Continuous BP measurement was traditionally performed via intra-arterial pressure transducers; however, the invasive nature and potential for complications has restricted their use to perioperative and critical care settings [224]. Non-invasive continuous BP measurement was developed in response to this challenge and has allowed continuous BP measurement in both research and clinical settings [225].

Most non-invasive continuous BP devices use digital photoplethysmography. This is based on the volume-clamp method developed by Penaz in the 1970s [226] and refined by Wesseling [227]. A cuff containing an inflatable bladder and an infrared photoplethysmograph is placed around the digital artery of one of the fingers of the hand. The artery is clamped to a constant volume by equal pressure on each side of the arterial wall. The photoplethysmograph measures the volume and adjusts pressure continuously to keep arterial volume constant. This pressure is equivalent to the arterial pressure of the digital artery and thus a continuous arterial pressure waveform is obtained. The first device of this type was the Finapres. The Finapres system adjusts for changes in vascular tone and temperature by using a proprietary algorithm to recalculate, termed Physiocal [228]. In addition, height correction sensors, regression and signal processing methods are used to reconstruct the brachial artery waveform from the digital artery.

The Finapres devices can derive the haemodynamic parameters SV, CO and TPR from the arterial waveforms using a mathematical modelling approach called Modelflow [229]. Modelflow simulates the aortic flow waveform by computing a non-linear three-element model of aortic input impedance based on the age, height, weight and sex of the patient. The aortic waveform is integrated over one heartbeat to provide an estimate of SV. This is multiplied by the HR to give an estimate of CO. TPR is then derived by dividing the arterial pressure by the CO.

The Finapres Devices have been refined over time [230] and the current model the Finapres Nova (Finapres Medical Systems, Amsterdam, Netherlands) provides non-invasive haemodynamic monitoring as well as guided autonomic testing. A number of competing devices exist including the Task Force Monitor (CNSystems, Graz, Austria) and ClearSight, previously Nexfin, (Edwards Lifesciences, Irvine, CA, USA) both of which include similar features to the Finapres Nova.

Digital photoplethysmography has been used extensively in both the assessment of the haemodynamic response to standing and in the investigation and diagnosis of syncope. For the assessment of orthostatic BP it compares well to intra-arterial measurement [231]. Again, as with the standard sit-to-stand and lying-to-standing tests, methodologies have varied. Overtime the two predominant protocols used have been the active stand test and the passive stand, head-up tilt test.

An explicit protocol now exists for the active stand test [223] giving recommendations on indications, patient preparation, medications, instructions and set-up, baseline measurements, standing, measurements, signal quality and data processing. Crucially, there should be a supine resting phase of five to ten minutes with signal calibration taking place, followed by a prompt stand as quickly as the patient is able, followed by quiet standing for three minutes, without conversation other than questions regarding symptoms during this time. With continuous BP measurement during the active stand test, the initial BP drop, recovery, and maintenance periods can be characterised.

Head-up tilt testing is primarily used for the identification and diagnosis of syncope and a number of protocols exist, both unmedicated and medicated, usually with nitroglycerin or isoproterenol [232]. It is included in the European Society of Cardiology guidelines for the investigation of OH [214], but its utility mainly lies in the identification of delayed OH after three minutes for which prolonged stand times may be needed [233], or in those who cannot perform an active stand. As discussed above, given the differences in the

haemodynamic responses to active and passive standing, head-up tilt cannot be used in the identification of initial OH or delayed BP recovery.

Management

The management of OH is both non-pharmacological and pharmacological. Non-pharmacological interventions include education about the condition, discontinuation of offending drugs where possible, lifestyle measures such as increasing salt and water intake, graded compression stockings and physical counterpressure manoeuvres (PCMs) [234]. Overall, the evidence supporting non-pharmacological interventions is weak. A 2015 systematic review found evidence to support functional electrical stimulation in spinal cord injury, lower limb / abdominal compression, PCMs and smaller and more frequent meals in those with autonomic failure [235]. Subsequently, a 2020 trial found that combining bolus water drinking, PCMs and abdominal compression was no better than bolus water drinking alone, in terms of reducing the initial drop to nadir in BP on standing in older participants with OH [236]. Despite a lack of evidence, in clinical practice multiple non-pharmacological treatments are routinely advised as first line in patients with OH.

Education around the condition of OH is important. Particularly the warning symptoms, lifestyle measures such as avoiding: standing too quickly, prolonged standing, warm environments, and heavy meals [237]. Sleeping with the head of the bed raised is sometimes recommended but has not been shown to be efficacious in a randomised trial [238]. Showering in a seated position makes physiological sense but has not been tested in a trial.

Given the strong link between many medications and OH, general advice is that all medications should be reviewed and if possible, any offending agents dose-reduced or discontinued. Particular attention should be paid to α-blockers, β-blockers, diuretics and psychotropic medications. There are however no high-quality trials to support deprescribing [239], and caution must be taken with anti-hypertensives to balance the risk of supine hypertension with OH. One trial of deprescribing of anti-hypertensives, albeit not in the setting of OH, found increased adverse events after drug withdrawal compared to a usual care group [240].

Adequate hydration is essential to maintain circulating blood volume and is especially important in those with OH. Reducing caffeine intake to reduce diuresis is also of benefit. Bolus water drinking of 500 mL in 2 – 3 minutes can also help to increase BP via a pressor

effect mediated by the sympathetic nervous system [241] and was found in one trial to be the most effective single non-pharmacological intervention for OH [242].

Guidelines recommend that patients with OH should increase their sodium intake, aiming for up to 10 g of sodium chloride per day. This improves intravascular fluid retention and thereby boosts circulating blood volume and helps improve orthostatic tolerance. However, caution should be taken in those with concomitant supine hypertension to avoid worsening overall hypertension and cardiovascular risk. Also despite the clear physiological reasoning and benefit, there are no high quality trials to support the recommendations [243].

Compression garments are also recommended in the guidelines for the management of OH. However, evidence for their use is weak, a 2014 systematic review found abdominal compression and combined abdominal and lower limb compression may be of benefit but thigh- and knee-length compression are not [244]. Older patients in particular may have difficulties applying them and they may not be well tolerated by patients [245]. When added to bolus water drinking or PCMs they do not seem to improve orthostatic BP drop [236]. However, when compared to pharmacological therapy, they have the advantage of being removable at night to reduce the likelihood of nocturnal supine hypertension.

Exercise, and especially that involving the lower limbs is often advised for patients with OH, often with the rationale of improving lower limb strength and thereby venous return during standing. However, there is little data to back these recommendations. In one study, an eight-week home-based resistance training did not improve orthostatic BP in eight older participants with OH [246]. A more recent study with ten older people with OH who underwent an eight-week lower limb strengthening intervention did not find an improvement in orthostatic BP drop on standing [247].

PCMs are manoeuvres of the lower or upper limbs such as lower limb muscle tensing, leg-crossing or arm tensing that aim to increase BP temporarily and thereby maintain cerebral perfusion in OH or pre-syncope [248]. Their exact mechanism of action is debated in the literature however they seem to have a consistent effect on CO likely via increased venous return from activation of the SMP [249–252] but their effects on TPR are less consistent [252–255]. They have been used to good effect in patients with autonomic failure and vasovagal syncope and are recommended in syncope guidelines as well as in postural orthostatic tachycardia syndrome (POTS). A recent systematic review found PCMs improved symptom control in up to 72% of the patients studied [256].

The main pharmacological therapies used in the management of OH are fludrocortisone, a mineralocorticoid, and midodrine, an alpha-adrenergic receptor agonist. Other agents including droxidopa, a precursor for norepinephrine, are less commonly used.

Fludrocortisone is a synthetic mineralocorticoid that enhances sodium and water retention in the kidney with increased excretion of potassium, resulting in increased plasma volume. Its licensed indication is for adrenal insufficiency, but it is widely used off-label for OH, recurrent vasovagal syncope and POTS. It is recommended in both the 2018 European Society of Cardiology [214] and the 2017 American Heart Association [257] guidelines on syncope and OH. However, a recent Cochrane systematic review concluded the evidence of its benefit on BP and orthostatic symptoms was uncertain. There have been safety concerns with its use, especially in heart failure and it does appear to increase the risk of hospitalisation [258].

Midodrine is a pro-drug that is metabolised to desglymidodrine, an α-adrenergic agonist that causes systemic vasoconstriction, thereby increasing TPR and BP. It is licensed for the treatment of adults with severe OH due to autonomic dysfunction when reversible factors have been corrected. It is recommended in both European and American guidelines for the treatment of neurogenic OH and recurrent vasovagal syncope [214,257]. A 2014 systematic review concluded there was low/moderate evidence that midodrine gave symptom improvement in symptomatic OH [259]. Midodrine was not related to serious and life-threatening events with the most common side effects being pilomotor reactions, urinary urgency and retention and supine hypertension.

Droxidopa is a pro-drug of norepinephrine (noradrenaline) and acts to increase norepinephrine levels and thereby increases systemic vasoconstriction, increasing TPR and hence BP [260]. It has been used in Japan for neurogenic OH since the 1980s and in 2014 it was licensed in the USA for symptomatic neurogenic OH caused by primary autonomic failure, dopamine β-hydroxylase deficiency or nondiabetic autonomic neuropathy. It is included in the 2017 American Heart Association guidelines for the management of OH, but the 2018 European Society of Cardiology guidelines conclude that evidence is insufficient to confirm its efficacy for long-term use. A 2016 meta-analysis concluded that it was well tolerated and effective in neurogenic OH and did not increase the risk of supine hypertension [261]. However, despite this it remains unlicensed in Europe and is not widely used.

A number of other agents are used off-licence in selected cased for OH including pyridostigmine, atomoxetine, yohimbine, pseudoephedrine, octreotide; however, there is not high quality evidence to support their widespread use [262].

Previous Studies Investigating Sarcopenia and Orthostatic Hypotension

There is a paucity of literature examining the relationship between sarcopenia and OH. To the best of my knowledge at the time of writing, only two previous studies have directly investigated sarcopenia and OH [200,263], while three others have included sarcopenia in their investigations of frailty [264,265] and malnutrition [266]. These studies are summarised in Table 1-2.

The studies have mainly been set in Geriatric Medicine outpatient departments rather than being population-based studies and only two of the studies adjusted for potential confounders in their sarcopenia analyses [200,263]. All the previous studies used intermittent, oscillometric measurements of BP in either a lying-to-standing test or a head-up tilt test. The use of oscillometric measurement of BP means that these studies were unable to examine BP recovery in the first minute after standing.

Overall, the evidence is supportive for a relationship between sarcopenia and OH, finding higher prevalence of sarcopenia in OH groups [264,266]; and that sarcopenia [263], and especially severe sarcopenia is a significant predictor of OH [200].

Table 1-2: Previous studies investigating sarcopenia and orthostatic hypotension

Study	Country	Setting	N	Sarcopenia Assessment	OH Assessment	Statistics	Main Findings
Liguori et al., 2018 [264]	Italy	Geriatric Medicine Outpatients	510	HGS (not reported if mean or max) & BIA EWGSOP criteria	Oscillometric measurement at 1, 3 & 5 minutes during Lying & Standing test; modified COH	Unadjusted comparison of prevalence of sarcopenia by OH status	Sarcopenia prevalence 29.0% in those with OH, 14.0% in those without OH; P<0.01
Soysal et al., 2020 [200]	Turkey	Geriatric Medicine Outpatients	511	HGS (not reported if mean or max), Gait Speed & BIA EWGSOP2 criteria	Oscillometric measurement at 1, 3 & 5 minutes during Head-Up Tilt Test; modified COH	Logistic regression controlled for age, BMI, sex, education, falls, dementia, MMSE, GDS, Tinetti gait test, TUG, ADLs, MNA	Severe sarcopenia significant predictor of OH at 1 min & 5 mins (OR 4.3; 4.1)
Keskin et al., 2021 [263]	Turkey	Cardiology & Osteoporosis Outpatients	91	HGS – max, TUG & BIA EWGSOP criteria	Oscillometric measurement at 1, 3 & 5 minutes during Lying & Standing test; modified COH	Logistic regression controlled for age, sex, BMI & vitamin D levels	Sarcopenia significant predictor of OH (OR 7.8)
Kocyigit et al., 2021 [266]	Turkey	Geriatric Medicine Outpatients	692	EWGSOP2 criteria but no other details given	Oscillometric measurement at 3 minutes during Head-Up Tilt Test; COH	Unadjusted comparison of prevalence of sarcopenia by OH status	Sarcopenia prevalence 22.1% in those with OH, 11.8% in those without OH; P<0.01

Okyar Bas et al., 2022 [265]	Turkey	Geriatric Medicine Outpatients	102	HGS – max & BIA EWGSOP2 criteria	Oscillometric measurement at 1, 3, 5 & 10 minutes during Lying & Standing test; modified COH	Unadjusted comparison of prevalence of OH by sarcopenia status	No statistically significant difference in OH by sarcopenia

N–number of participants in the study; Max–maximum; OH–orthostatic hypotension; HGS–handgrip strength; BIA–bioelectrical impedance analysis; EWGSOP–European Working Group on Sarcopenia in Older People Original Criteria; EWGSOP2–European Working Group on Sarcopenia in Older People Revised Criteria; COH–consensus OH definition; BMI–body mass index; ADLs–activities of daily living; MNA–Mini-Nutritional Assessment; GDS–Geriatric Depression Scale; MMSE– Mini-Mental State Exam.

Previous Studies Investigating Muscle Strength or Mass and Orthostatic Hypotension

While few studies have specifically examined sarcopenia and OH, a number of studies have investigated related muscle parameters and OH, often while studying the link between frailty and OH. The studies are summarised in Table 1-3. They have either measured muscle strength via HGS [186,267–275] or 5CST [267,276–278], or measured muscle mass without specifically operationalising sarcopenia [279].

The previous studies show a wide variation in results with some studies finding no association between measures of muscle strength or mass and OH [269,271,271,272,275,277], others finding a direct association, i.e. increased risk or prevalence of OH with lower muscle strength [267,268,270,273,276,278,279], and one finding an inverse relationship, i.e. better muscle strength in those with OH [186].

In the above studies, there is significant heterogeneity in the populations studied, the methods for measuring BP, the definitions and timepoints taken, the statistical methods used, and the potential confounders considered, and this may account for the significant discrepancies between them. The majority of studies used intermittent measurements of BP and so were unable to study the initial 1 minute after standing. Many of the studies that used continuous BP measurement used initial OH or consensus OH definitions but did not examine BP recovery from standing.

Thus, the association between OH and muscle parameters — strength and mass — remains incompletely characterised, and the association of sarcopenia and BP recovery in the early phase after standing is unknown

Table 1-3: Previous studies investigating muscle strength or mass and orthostatic hypotension

Study	Country	Setting	N	Muscle Assessment	OH Assessment	Statistics	Main Findings
Masaki et al., 1998 [270]	Hawaii, USA	Community dwelling men	3,522	HGS – max	Auscultatory BP measurement at 3 minutes in a lying to standing test; COH	Comparison of group mean HGS, adjusted for age	OH group significantly lower HGS than no OH, 28.2kg vs 30.0 kg, P<0.001
Romero-Ortuno et al., 2011 [274]	Ireland	Community dwelling older adults	442	HGS – mean	Continuous beat-to-beat BP in active stand test; IOH & COH	Comparison of group median HGS, unadjusted	No significant difference in median HGS for IOH or COH
Kobayashi & Yamada, 2012 [269]	Japan	Community dwelling older adults	86	HGS & Knee extension strength – max	Continuous beat-to-beat BP in head-up tilt test; COH	Comparison of group mean HGS and knee extension strength, unadjusted	No significant difference in HGS or knee extensor strength between OH & no OH
O'Connell et al., 2015 [271]	Ireland	Community dwelling older adults	5,692	HGS – max	Oscillometric BP measurement at 1 minute in a sit-to-stand test, COH definition applied at 1 minute	Linear regression of OH and low HGS (Fried frailty criteria), adjusted for age, sex, BMI, smoking, CVD, anti-hypertensives, antidepressants, frailty criteria	No significant association between weak HGS and OH after adjustment for confounders
Shen et al., 2015 [275]	China	Hypertensive inpatients on Geriatric Medicine Ward	176	HGS – mean	Oscillometric BP measurement at 1& 3 minutes in a lying to standing test; COH	Comparison of group means, unadjusted	No significant difference in mean HGS between OH and no OH

Mol et al.,2018 [276]	Netherlands	Geriatric Medicine Outpatients	109	HGS – max & 5CST	Continuous beat-to-beat BP in active stand test; BP drop rate & magnitude 0–15s & 15–180 s	Linear regression between HGS/5CST & BP parameters, adjusted for age, sex, height & weight	Slower 5CST associated with steeper SBP drop; HGS not significantly associated.
O'Connell et al., 2018 [272]	Ireland	Community dwelling older adults	4,334	HGS – max	Continuous beat-to-beat BP in active stand test	Mixed-effect regression between SBP and DBP 10–20 s, 20–30 s & 30–110 s with low HGS (Fried frailty criteria) as a parameter in model while controlling for age, sex, BMI, smoking, depressive symptoms, CVD, anti-hypertensives & antidepressants & other frailty criteria (slowness, activity, exhaustion, weight loss)	Low HGS was not significantly associated with SBP or DBP changes at any of the time intervals after adjustment
Chen et al., 2019 [268]	China	Geriatric Medicine Inpatients	693	HGS – max	Auscultatory BP measurement at 3 minutes in a lying to standing test; COH	Logistic regression, OH and Low HGS, adjusted for age and sex	Low HGS significantly associated with OH (OR 2.1, $P<0.05$)
De Bruine et al., 2019 [267]	Netherlands	Geriatric Medicine Outpatients	299	HGS – max & 5CST	Continuous beat-to-beat BP in active stand test; IOH & COH	Logistic regression between tertiles of HGS & 5CST & OH,	Slowest tertile of 5CST had significantly higher odds of OH (OR

						adjusted for age, sex, weight & height	12 P<0.05). No significant association between HGS & OH
Saedon et al., 2020 [186]	Malaysia	Community dwelling older adults	1,245	HGS – mean	Continuous beat-to-beat BP in active stand test; IOH & COH	Multivariable linear regression of HGS by OH status (No OH, COH, IOH & COH, IOH) adjusted for age, sex, diabetes and baseline SBP	COH-IOH group significantly, positively associated with HGS vs no OH group (β 1.3, P<0.05)
Benton et al., 2021 [279]	USA	Community dwelling older adults	69	Muscle mass – BIA	Oscillometric BP measurement at 1 & 2 minutes in a lying to sitting to standing test	SBP drop compared between low & normal muscle mass groups, controlling for age	Significantly greater drop in SBP in low muscle group (-11.1 vs +1.1 mmHg, P<0.01)
Mol et al., 2021 [277]	Netherlands	Geriatric Medicine Outpatients	635	5CST	Oscillometric BP measurement at 1& 3 minutes in a lying to standing test; BP recovery at 1 & 3 minutes	Multivariable linear regression between 5CST & BP recovery, controlling for age & sex	BP recovery at 1 or 3 minutes not significantly associated with 5CST time
Mol et al., 2021 [278]	Netherlands	Geriatric Medicine Outpatients	168	5CST	Continuous beat-to-beat BP in active stand test; BP recovery 15–30 s, 30–60 s, 60–120 s & 120–180 s	Multivariable linear regression between 5CST & BP recovery, adjusted for age, sex, baseline BP and initial BP drop	DBP recovery in 30–60 s interval significantly associated with 5CST (β 0.2, P<0.05). SBP recovery not significantly associated with SBP

							recovery in adjusted models
Roca et al., 2022 [273]	France	Geriatric Medicine Outpatients	530	HGS – not reported if max or mean used	Oscillometric BP measurement at 1& 3 minutes in a lying to standing test; COH	Multivariable logistic regression for OH & Low HGS, controlling for age, sex, resting BP & diabetes	OH significantly associated with low HGS (OR 1.4, P<0.05)

N–number of participants in the study; Max–maximum; OH–orthostatic hypotension; HGS–handgrip strength; 5CST– five chair stands test; BIA–bioelectrical impedance analysis; COH–consensus OH definition; IOH–initial OH definition; BMI–body mass index; CVD–cardiovascular diseases; SBP – systolic blood pressure; DBP–diastolic blood pressure.

The Skeletal Muscle Pump — The Potential Link Between Sarcopenia and Orthostatic Hypotension

While OH has been previously associated with other geriatric syndromes including frailty [280,281], multimorbidity [282] and cognitive impairment [283,284], there may be a pathophysiological link between sarcopenia and OH in the form of the SMP. The SMP refers to the physiological mechanism of the muscles of the lower limbs acting to return venous blood to the heart during orthostasis and exercise via rhythmic muscular activity. Theoretically, the effect of sarcopenia on the muscles of the lower limbs could reduce the efficacy of the SMP. If one considers the well-established physiological equation $MAP = CO \times TPR$, then a hypothesis of how sarcopenia could lead to delayed BP recovery and OH can be developed. Reduced SMP efficacy could lead to diminished venous return, thereby decreasing right atrial filling pressures, and reducing preload. This would reduce SV and hence CO, leading to impaired BP recovery and potentially OH. However, as described earlier, the BP response to standing is complex and largely controlled by the baroreflex response.

Furthermore, while the role of the SMP is somewhat characterised in exercise [285,286] and augmentation of the SMP via PCMs or external adjuncts has been studied in OH and syncope [256], the role and contribution of the SMP to BP recovery and maintenance during ordinary standing is less well elucidated. Indirect evidence for the SMP has come from studies of augmentation of the SMP by lower limb muscle tensing, functional electrical stimulation, postural sway as a presumptive activator of the SMP, electromyography (EMG) studies, and comparison of active and passive standing. I will review these studies in a narrative fashion over the following sections.

Historical Studies

The effects of gravity on circulation were summarised as far back as 1897 with Hill and Bernard's treatise *The Influence of the Force of Gravity on the Circulation*, which emphasised the role of splanchnic vasoconstriction and the respiratory pump [287]. The role of the SMP was later developed, mainly through work by the pioneering female physiologist Frances Hellebrandt in the late 1930s–1940s [288–290]. In a number of experiments, Hellebrandt along with her female collaborators examined the role of the SMP in orthostasis culminating in her seminal 1949 paper *Relative Importance of the Muscle Pump in the Prevention of Gravity Shock* [291]. In this paper, she and her colleagues describe 105 experiments on 21 subjects in which they measure HR and BP with participants lying, standing immersed in

water, vertical but supported with restraints, and free quiet standing. From their results, they concluded that the vertical position itself does not have an effect on BP but rather it is the hydrostatic effect of gravity and that the SMP plays a key role in reducing this. They also found that augmenting the SMP with a suction pressure boot, massage of the lower limb muscles and electrical stimulation, all increased standing BP and reduced occurrence of syncope. They concluded that "The muscle pump plays a significant supportive role in the prevention of gravity shock".

Alongside this, another key early study was by Mayerson and Burch [292], who measured intramuscular gastrocnemius pressure in fainters and non-fainters. They found that when upright, non-fainters had pressures of 200–300 mmH_2O (15–24 mmHg), while fainters had only 80–120 mmH_2O (6–9 mmHg). This suggested that low skeletal muscle tension, perhaps representing a defective SMP, could lead to syncope.

The mechanisms of the SMP were further explored by Pollack and Wood [293] who demonstrated an increase in saphenous vein pressure between the supine (11.7 mmHg average), sitting (56.0 mmHg average) and quiet standing (86.8 mmHg). On walking, the pressure dropped to 22.3 mmHg on average, which the authors attributed to contraction of the calf muscle pumping blood out of the calf with each step. These finding were later confirmed when Ludbrook [294] measured intramuscular pressures of lower limb muscles in relaxed (9 mmHg), standing (16 mmHg) and maximally contracted states (140 mmHg), demonstrating the ability of muscle contraction to significantly elevate the intramuscular pressure and therefore presumably aiding venous return to the heart.

Stegall [169] studied the pumping action and power of the SMP further, measuring calf circumference, muscle pump ejection velocity, and intrathoracic and intra-abdominal pressures during standing and exercise. By measuring blood flow and pressure in the leg, he showed that the SMP contributes more than 30% of energy required to circulate blood during running and by measuring calf circumference that the calf volume is significantly increased on standing.

These early studies supported the role of the SMP in preventing syncope and provided evidence of its mechanism of action in pumping blood back to the heart. In particular, they underlined the role of the SMP during ambulation and exercise.

Muscle Tension and PCM

Supporting these early studies directly examining the SMP, the relationship between muscle activity and BP has been studied over time, and especially in recent years, the role of PCM in the prevention of orthostatic symptoms and syncope has demonstrated the SMP in action.

The link between muscle activity and increases BP was known from at least the 1960s with Arthur Guyton and colleagues [295] demonstrating that electrically induced skeletal muscle activity in dogs with transected spinal cords led to a rapid increase in CO and MAP. This effect persisted even after sympathetic blockade with hexamethonium but was blocked by skeletal muscle inhibition with decamethonium. As the cardiac reflexes were absent due to spinal cord transection, the authors concluded that the response could only have occurred through mechanical compression of the veins of the limbs and abdomen translocating blood to the heart and increasing SV and thus CO and BP.

For obvious ethical reasons, these experiments never been performed in humans but following on from this, Mitchell et al. [296] studied the relationship between BP, lower limb muscle contraction and muscle mass. They found that the BP response to a static exercise at 40% of maximum voluntary contraction was greater when a greater mass of skeletal muscle was involved, thus suggesting a link between muscle mass and BP. They also found a correlation between EMG activity and BP rise when force was held constant and between force and BP when EMG activity was held constant. They concluded that both central and peripheral nervous system control mechanisms were involved. Schibye et al. [297] observed an increase in MAP of 38 mmHg in healthy participants asked to performed a sustained contraction (knee extension) at 20% of maximum voluntary contraction. Smith [255] subsequently found that lower limb muscle tension lead to better tolerance of lower body negative pressure in eight healthy men.

These experiments linking muscle tension to BP led on to the investigation of muscle squeezes and exercises for therapeutic use in those with OH and autonomic failure. Van Lieshout [249], Ten Harkel [251] and colleagues studied the effects of PCMs by leg-crossing and tiptoeing in healthy volunteers and patients with severe neurogenic OH. Van Lieshout found that leg-crossing increased SBP 20 ± 9 mmHg in the patients and 4 ± 7 mmHg in the control group. On quiet standing, five of the seven patients reported light-headedness within 10 minutes and four could not remain standing, whereas with leg-crossing all patients were able to stand for 10 or more minutes. Ten Harkel found that

tiptoeing increased SBP 17 ± 9 mmHg in healthy subjects but there was no significant change in patients (4 ± 13 mmHg), while leg-crossing increased SBP 18 ± 18mmHg in patients but not significantly in healthy subjects (4 ± 7 mmHg). They considered that tiptoeing caused contraction of the muscles of the lower limbs pumping blood back to the right side of the heart, increasing SV and hence BP — a demonstration of the SMP. The authors proposed that leg crossing, in increasing intramuscular pressure, mechanically propels blood to the chest, increasing SV and subsequently systemic BP. They also proposed secondly that the increased intramuscular pressure activates mechanosensitive receptors eliciting a reflex rise in TPR leading to increased BP.

Krediet et al. [252] later demonstrated that PCMs involving lower body muscle tensing, with and without leg-crossing, raised BP without any significant change in TPR, concluding that the mechanism was mediated via increases in CO. There was an initial increase in HR seen, which the authors put down to a muscle heart reflex, and sympathetic mediated increase in cardiac contractility may also have contributed. However overall, the authors felt that the main effect was due to the mechanical effects of muscle pumping from the lower limbs.

These studies underlined how the SMP could be utilised with specific manoeuvres to elevate BP and thereby reduce orthostatic symptoms and abort syncope. However, they did not elucidate the role of the SMP in ordinary quiet standing.

Mechanical and Electrical Stimulation of the Lower Limb

By stimulating the muscles of the lower limbs either via mechanical vibration, functional electrical stimulation or intermittent compression, investigators have been able to demonstrate the effect of augmenting the SMP as a therapy in OH and syncope.

Plantar vibration stimulation was investigated in 30 healthy women aged 22–82 years, by Madhavan et al., with BP measured in the sitting position [298]. There was a mean decrease in BP of 8.95 ± 1.9mmHg during quiet sitting which was eliminated with planter vibration. The authors concluded that this provided evidence of the role of type IIa muscle fibre activity being enlisted in the SMP when stationary. Madhavan et al. [299] went on to extend that work evaluating the response to plantar vibration stimulation, during quiet sitting, in 30 adult women, aged 30-65 years old, 25% of whom had delayed OH (defined as a statistically significant fall in BP after 15 minutes of quiet sitting). They found activation of the calf muscle pump through plantar-based vibration-stimulation resulted in a significant increase in SBP and DBP compared to quiet sitting (+13.1 ± 2.4 mmHg and

+9.7 ± 2 mmHg respectively). The authors suggested that delayed OH may be due to a loss of tonic calf muscle activity, leading to inadequate venous return to the heart, thus suggesting the importance of the role of the SMP in orthostatic BP control.

Subsequently, McLeod and Jain [300] found that soleus muscle stimulation in 21 older women led to an average 6.1 mmHg increase in DBP during 30 minutes of quiet sitting. They concluded that soleus muscle stimulation was effective in augmenting the SMP.

Chi et al. [301] studied functional electrical stimulation of the lower limbs in 10 healthy subjects during head-up tilt test and compared it with control, passive mobilisation and a combination of functional electrical stimulation and mobilisation. They intermittently measured HR, BP and inferior vena cava blood flow with doppler US. They found that a combination of functional electrical stimulation and passive mobilisation was able to attenuate the decrease in blood flow through the inferior vena cava during head-up tilt compared to the other protocols. The authors suggested that the combination of functional electrical stimulation and passive mobilisation activated the SMP in a similar way to locomotion and thus enhanced venous blood flow through the inferior vena cava.

Hockin et al. compared static calf compression garments with intermittent calf compression during passive orthostasis (head-up tilt) in healthy young adults [302]. They found that intermittent compression prevented venous pooling, leading to improvement of SV in the upright position which allowed CO to be maintained with a reduced HR. There was no difference in BP however. They attributed the effects to increased muscle pumping due to the intermittent compression. They further extended the results in a study investigating tolerance to lower body negative pressure [303] in healthy young adults. They found intermittent calf compression improved orthostatic tolerance to lower body negative pressure, delaying the onset to presyncope and again showing reduced venous pooling and improved SV, allowing BP to be maintained at a lower HR.

Similar to the PCM studies, these investigations provide evidence for the augmentation of the SMP, and methods by which adjuncts might support the SMP to prevent OH and syncope.

Electromyographic and Near-Infrared Spectroscopy Studies

EMG has been used in a number of studies to illustrate the electrical activity of the muscles of the lower limb during standing, thereby suggesting its role in the maintenance

of BP. Near-infrared spectroscopy (NIRS) has also been used as a proxy of blood flow to demonstrate changes in haemoglobin concentration likely to be due to SMP activity.

Masterson et al. [304] found significantly greater BP and EMG activity of the lower limb muscles, with lower HR, during quiet standing, in older adults as compared to younger adults. The authors concluded that the greater lower limb EMG activity may have helped older subjects compensate for the reduced HR response and that increased lower limb muscle activity was important for maintaining BP as a person aged.

BP response and EMG activity was compared between active standing and passive standing (head-up tilt) in 23 young healthy female volunteers by Liporaci and colleagues [305]. They found higher EMG activity in the active stand compared to the head-up tilt supporting the theory that the SMP is more active in active standing than passive. They didn't find differences in HR between the two protocols; however they did not provide BP data so the haemodynamic effects of the increased SMP activity cannot be interpreted.

Some studies performed head-up suspension, where the lower limbs were not in contact with the ground and thus likely removing the effects of the SMP altogether. Shamsuzzaman et al. [306] compared head-up tilt to head-up suspension in 13 healthy young participants. They measured continuous haemodynamics using the Finapres, muscle sympathetic nerve activity (MSNA) of the tibial nerve, EMG of the soleus and tibialis anterior muscle and calf blood flow using impedance plethysmography. They found that head-up tilt resulted in an increased HR and reduced BP with increased MSNA, EMG activity and calf blood flow when compared to head-up suspension. The authors concluded that activity of the lower limb muscles, i.e. the SMP, augmented the baroreflex sympathetic response to the upright posture. However, they found decreased SV and CO in the head-up tilt experiment compared to head-up suspension which is contrary to what might be expected. The authors ascribe it to increased calf blood volume as indicated by the increased calf blood flow, leading to a reduction in SV and CO, however this goes against their proposed increased activity of the SMP.

The haemodynamic and EMG response to orthostasis was compared between younger and older participants by Gabbett and colleagues [307]. They measured continuous beat-to-beat BP, HR and EMG activity of the soleus, tibialis anterior and vastus medialis muscle between 18 younger and 15 older men in a 90-degree head-up tilt test. They did not find a significant difference in EMG activity between the supine and upright phase for either group. However, as the subjects were secured to the tilt-table with straps on the

chest, thigh and lower leg, the protocol may have been closer to a head-up suspension with inactivation of the muscles of the lower limbs, than a standard head-up tilt which would usually be between 60–80 degrees [308]. They also found more pronounced initial decrease in BP and increase in HR in the younger group, but both groups returned to a similar steady state.

Zhedyaev et al. [309] studied the haemodynamic response to the upright posture before and after 19 days of head-down bed rest in seven young men. They used a head-up tilt test in which the participants sat on a saddle with their legs dangling, so in effect head-up suspension. They measured continuous beat-to-beat haemodynamics with the Finapres, and haemoglobin concentration of the gastrocnemius muscle with NIRS. During orthostasis they found increased total haemoglobin concentration in the gastrocnemius with increased HR and decreased SV but similar MAP, post-bed rest when compared to pre-bed rest. The authors concluded that bed rest led to a decreased ability of the calf to vasoconstrict leading to venous pooling and a resultant decrease in SV. However, MAP did not differ, and they did not report TPR or CO. Is it plausible that the increased HR seen post bed rest was to compensate for the reduced peripheral vasoconstriction caused by the effects of bed rest on the gastrocnemius muscle.

Overall, these studies demonstrate that the more active the muscle of the lower limbs are in maintaining posture: active standing > head-up tilt > head-up suspension; the more EMG activity is measured, and the greater calf blood flow is present. This suggests greater SMP activity. However, unfortunately the studies are conflicting, or inconclusive as to the impact this has on BP in the upright position.

Postural Sway

Postural sway during quiet standing and its role in the maintenance of BP has been of interest for some time. It was demonstrated previously that the muscles of the lower limb are rhythmically active during quiet standing [310]. Subsequently, postural sway, EMG of the leg muscles and fluid volume changes in multiple compartments of the body during 40 minutes of quiet standing in 20 young men were studied by Inamura et al. [170]. They concluded that one-minute postural sway oscillations contribute to fluid shifts from lower limbs to upper body to help maintain BP. However, as they did not measure BP in the standing phase, they were unable to investigate whether the mechanism had an effect on BP.

Claydon and Hainsworth studied the role of postural sway in healthy volunteers with good and poor orthostatic tolerance [311], in addition to participants with posture-related syncope [312]. They showed that those with poor orthostatic tolerance had more postural sway than those without, postulating that those with poor orthostatic tolerance subconsciously adopt a strategy of increased lower limb movement during standing which aids venous return to the heart by rhythmically compressing leg veins. Those with posture-related syncope did not have increased rates of sway compared to those with good orthostatic tolerance suggesting that their lack of sway meant that they were not utilising the SMP and were therefore at risk of syncope.

The relationship between postural sway and orthostatic BP was further examined by Murata and colleagues [313]. In a study involving 63 women, they found a reduced SBP while standing (-5.0 ± 6.6mmHg) and that SBP was inversely correlated with movement of centre of pressure. The authors suggested that the reduced SBP on standing was associated with an increase in postural sway but did not comment on whether postural sway was a mechanism of BP recovery via the SMP. However, it is plausible that participants unconsciously increased their postural sway to compensate for a reduced BP.

Naruse et al. [314] compared normal standing to supported standing (a supporting device attached below the patella of each leg to reduce sway) in eight healthy young adults. They measured beat-to-beat BP, EMG activity of the soleus muscle and postural sway. They found an increased DBP and MAP during supported standing, compared to normal standing, without a difference in SBP or HR. They interpreted this as an increased TPR during supported standing, driving an increased DBP. They suggested that the inactivation of the SMP by the removal of postural sway led to an increased baroreflex-mediated sympathetic vasoconstriction, leading to increased TPR. They proposed that this provides evidence of the role of the SMP in normal standing as the postural sway in normal standing in their study activated the SMP meaning an exaggerated baroreflex response did not need to be employed. However, one could argue that this is a rather indirect way of demonstrating the role of the SMP.

This was explored further by Williams et al. [315] who examined the association between exaggerated postural sway and BP during standing in 20 young healthy adults. They found that exaggerated postural sway increased standing BP compared to normal standing with the magnitude of the sway being related to magnitude of the BP changes. The exaggerated sway also attenuated the fall in SV, suggesting that the sway was acting via the SMP to

return venous blood to the heart thereby increasing preload and SV. This was supported by the finding of a reduced increase in TPR with the exaggerated sway, suggesting that BP was not being maintained by vasoconstrictive effects. In addition, there was no significant change in HR. Overall the study provides supportive evidence for the role of the SMP and a useful dynamic manoeuvre that could be applied as a PCM by patients at risk of syncope or OH.

Measurement of the Calf Muscle Pump

The function of the SMP, and more specifically the calf muscle pump, has been measured using plethysmography in a number of studies over the last three decades.

Stewart et al. [316] investigated the calf SMP in in 19 young females with POTS and 10 young, healthy, female controls. They measured the calf ejection fraction using strain-gauge plethysmography during a tiptoe manoeuvre as recommended by guidelines on the investigation of venous insufficiency [317]. They also measured calf blood flow with strain-gauge plethysmography and blood volume with dye dilution. They found that the calf SMP ejection fraction was related to calf muscle mass and calf blood flow while supine. Thus, they demonstrated the activity of the calf SMP and suggested a relationship between muscle mass and SMP function. However, they did not relate the calf SMP to BP recovery or maintenance as the study was primarily focussed on determining whether the calf SMP was less active in patients with POTS and low peripheral blood flow, which they found to be the case.

The relationship between calf SMP function and surrogate measures of CO during cardiopulmonary exercise testing was examined by Kondo et al. in 23 controls and 65 heart failure patients [318]. Similar to Steward et al., they measured calf ejection fraction using strain-gauge plethysmography during a tiptoe manoeuvre. They demonstrated a significant positive correlation between calf ejection fraction and peak oxygen consumption during cardiopulmonary exercise in the heart failure group, but not in controls. They concluded that in heart failure patients, the calf SMP increases CO by increasing venous return and hence preload. However, there are several caveats to their conclusion, namely that the calf SMP measurements were taken at rest and thus were not temporally associated with the peak oxygen consumption. Although the study provides supportive evidence of the potential role of the calf SMP in heart failure, it does not further the knowledge in healthy physiology nor the relationship between SMP activity and BP in normal standing.

Frith et al. [247] investigated the effect of an eight-week strengthening programme on calf SMP function and orthostatic BP drop in ten older people with OH. They measured calf ejection fraction using air plethysmography in a tiptoe manoeuvre similar to the above studies and orthostatic BP response using an intermittent oscillometric BP device. They found a significant increase in calf muscle strength by 21% ($P<0.05$) post-exercise programme, but no significant change in calf ejection fraction (-10%, $P = 0.8$) and no improvement in SBP drop (0%, $P = 1.0$). They concluded that there was little excess venous pooling in older people with OH, and lower limb strengthening did not improve the efficacy of the calf SMP or orthostatic BP. They also felt that the small volume of blood ejected from the calf would likely have little impact on venous return and BP.

These studies further the work by earlier investigators on directly measuring the output from the calf SMP. However, they either did not investigate orthostatic BP [316,318] or did not find the calf SMP to be a significant contributor to orthostatic BP [247]. The small volume of blood ejected from the calf in the study by Frith et al. would be unlikely to be able to compensate for failure of the autonomic elements of orthostatic BP control. However, it is plausible that if it were feasible, measurement of all the muscles contributing to the SMP might demonstrate a greater volume and effect on BP.

Advanced Statistical Approaches

Finally, sophisticated mathematical approaches using the advanced statistical and signal processing techniques of wavelet transform coherence [319] and convergent cross mapping [320] have been used by one research group to investigate the relationship between orthostatic BP, EMG activity of the lower limbs and postural sway during quiet standing. They have proposed two pathways: postural sway → EMG activity → SBP: the SMP pathway; and also a SMP baroreflex pathway SBP → EMG activity → postural sway [321–324]. In the first pathway postural sway was found to drive changes in BP via EMG activity. In the second pathway, the group hypothesised a muscle-pump baroreflex in which a reduction in BP could lead to increased EMG activity via increased postural sway in a feedback mechanism.

These results provide an analytical model and pathway between the SMP and orthostatic BP. However, they do not provide us with a quantitative measure of the relative contribution of the SMP to BP maintenance, and *in vivo* validation of their findings has not been performed.

Conclusion

Overall, the SMP has been investigated in many studies, both in a direct and indirect manner. Early studies took an *in vivo* approach demonstrating the pumping action of the calf muscle and its role in the prevention of "Gravity Shock". Further study of the role of the SMP in patient subgroups supported its importance. The knowledge that muscle tension could increase BP both by mechanical and pressor effects was developed into a technique to exploit the SMP to reduce symptoms from OH and abort syncope. EMG studies demonstrated the activity of the muscles of the lower limb during standing and suggested that increased lower limb activity supported the maintenance of BP in the upright position. When comparing head-up suspension to head-up tilt, investigators demonstrated that the former inactivated the SMP when compared to the latter, however they did not manage to elucidate the effects this had on BP.

Postural sway appears to be a mechanism by which the body can, consciously or unconsciously, activate the SMP to maintain BP while standing, in a way a form of PCM that could be subtly used to improve orthostatic tolerance. Further to this, there is the suggestion of a muscle-pump baroreflex that might offer a counter-regulatory response to hypotension during orthostasis by increasing postural sway and lower limb muscle activity to increase venous return.

However, as seen, there is wide heterogeneity in the previous studies, with different populations, methods, aims and mechanisms explored. Few investigators have directly studied the role of the SMP in ordinary quiet standing. Its mechanism of supporting ordinary standing and the magnitude of its relative contribution when compared to the arterial baroreflex, is unknown. Furthermore, the potential effects of sarcopenia on the SMP and its contribution to orthostatic BP have been hinted at but remain unconfirmed.

Motivation and Research Questions

The motivation for this doctoral investigation departs from the basis that both sarcopenia and OH are major age-associated health challenges. Both are increasing in prevalence [325,326] and as seen earlier in this chapter are associated with significant adverse outcomes for older people.

Geriatric syndromes tend to co-occur [327] and their relationship may not be linearly additive but may in fact be non-linear [19]. While frailty, multimorbidity and cognitive impairment may be associated with OH it is not certain whether they are causative. There

is physiological reason however to suspect that sarcopenia, whilst certainly not being the sole cause of OH, may be a significant contributor. One could hypothesise that the effect of sarcopenia on the muscles of the lower limbs may impair the action of the SMP. This could reduce venous return during standing, impairing SV and so CO, subsequently leading to reduced MAP, increasing the risk of OH. This hypothesis is illustrated graphically in Figure 1-4. Ultimately this could lead to falls, fractures, increased morbidity and even death. This would be in addition to sarcopenia directly causing falls via gait and balance instability. Sarcopenia however may be reversible at least partially, or preventable [328]. This might contrast with other effects or causes of OH such as heart failure, age-related decline in baroreflex sensitivity and neurogenic causes [237]. However, while sarcopenia appears to be associated with OH at and after one minute of standing, the relationship with BP recovery before this time is unclear. Emerging evidence shows that delayed BP recovery may be as strong a risk for falls and fractures as traditional OH [182]. Thus, it is of clinical utility to determine their relationship.

The main primary research questions of this doctoral investigation are therefore:

What is the relationship between sarcopenia and BP recovery and maintenance after standing?

How is the relationship between sarcopenia, BP recovery and OH mediated in terms of the underlying haemodynamics?

Having explored the relationship between the pathological state of sarcopenia and OH, it might then be informative to study healthy ageing and the relationship in general between muscle and BP recovery, considering in particular the role of the SMP.

To this end two further primary research questions of this thesis are:

What is the relationship between measures of muscle strength and mass, and BP recovery in healthy ageing?

Is there indirect evidence for the role of SMP in this relationship?

From the review of the conditions of sarcopenia and OH in this chapter, a number of secondary issues arose. In the assessment of sarcopenia, muscle US was identified as an emerging technique. HGS and 5CST are recommended by the EWGSOP2 for assessment of muscle strength but other measures such as QMS exist. A secondary research question therefore is:

How are existing and emerging measures of muscle strength and mass related?

The role of PCM in the management of OH was reviewed in this chapter and the development of PCM as a tool to exploit the SMP was discussed. However, the potential effects of sarcopenia on PCM are not well known and an initial research question in this area is:

How do muscle mass and strength affect PCM efficacy in healthy ageing?

Finally, although PCM have been studied in younger cohorts, the haemodynamics of PCM with ageing are incompletely characterised and a final secondary research question can be posed:

What are the haemodynamics underlying PCM and is there indirect evidence for the possible role of the SMP therein?

To answer these questions, I undertook three studies. Study I, a population study based on a large sample from TILDA, in which I investigated the association between measures of probable sarcopenia and the continuous BP measurements from the active stand test. Study II-A, a clinical sample I recruited from MISA at St James's Hospital to extend the investigation to include BIA confirmed sarcopenia. Study II-B investigated the haemodynamic parameters underlying the associations found in Study II-A. Finally in Study III, in order to address some of the limitations of the previous studies in terms of confounding disease and lack of contemporaneous measurement of muscle activation, I recruited a healthier, physiological sample from a local active ageing group and studied the haemodynamic response to normal standing, using advanced instrumentation including EMG and NIRS and obtained a variety of measures of muscle strength and mass.

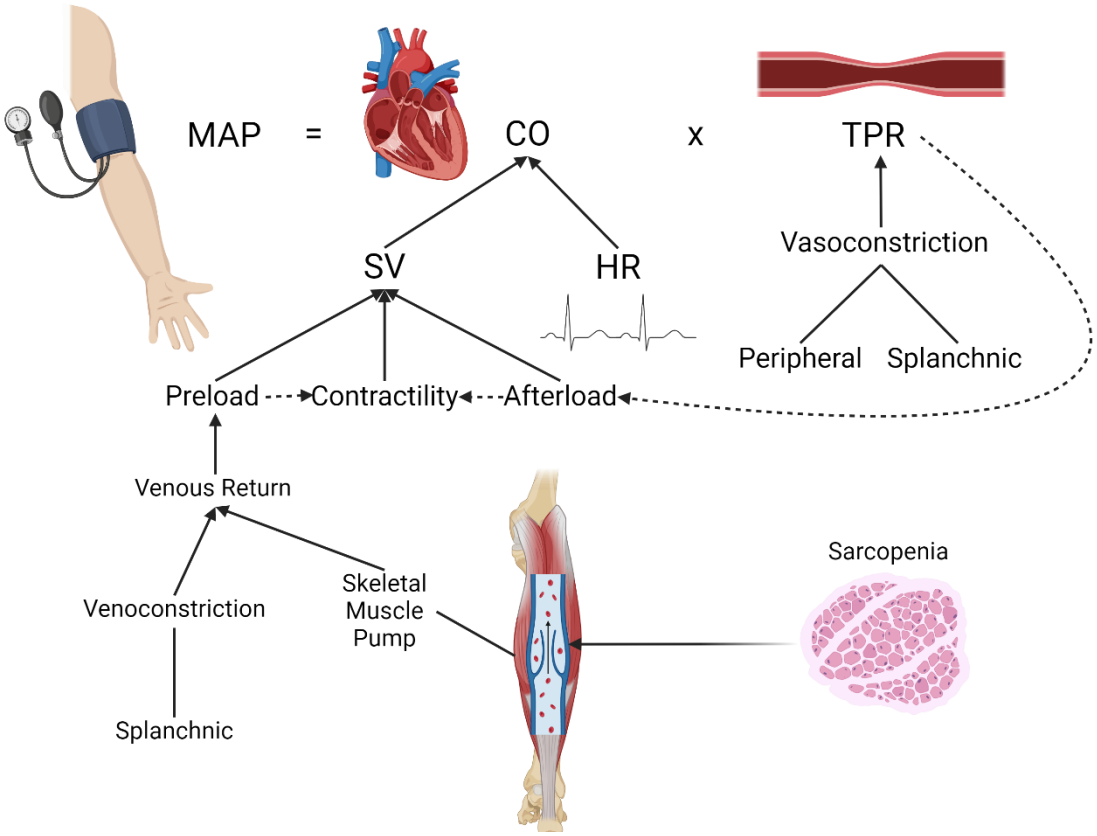

Figure 1-4: Hypothesised mechanism by which sarcopenia may be linked to orthostatic hypotension and delayed BP recovery via the skeletal muscle pump. MAP–mean arterial pressure; CO–cardiac output; TPR–total peripheral resistance; SV–stroke volume; HR–heart rate.

Chapter 2 – Methods

Introduction

My doctoral project consisted of four studies. The first study, the population cohort, was a secondary analysis of data from TILDA. I personally performed all statistical analyses. For the second study, the FRAILMatics clinical sample, I recruited patients who were new attendees to the Falls and Syncope Unit (FASU) at MISA in St James's Hospital, Dublin. The patients underwent a routinely performed active stand test in the clinic and I conducted all additional research assessments. For the third study, the FRAILMatics physiological sample, I recruited participants from a local healthy ageing group and performed all the research assessments with an assistant helping with the surface EMG and NIRS acquisition. Additionally for studies two, three and four, I personally performed all data pre-processing, signal processing and statistical analyses.

Research Settings and Study Populations

Study I: TILDA Population Cohort

TILDA is an ongoing, population-based longitudinal cohort study of adults aged 50 years and older in Ireland. TILDA commenced with Wave 1 in 2009 inviting a nationally representative sample of community dwelling adults aged 50 years or older and their spouses or partners to participate using a bespoke sampling procedure developed by the Economic and Social Research Institute [329]. The household response rate was 62.0%. The study consists of a two-yearly computer-assisted personal interview (CAPI), which addresses questions on socioeconomic, physical, cognitive and mental health factors. Participants are also invited to attend a dedicated health assessment centre for a research nurse-led comprehensive health assessment that takes place approximately four-yearly [330].

The main TILDA data used in this doctoral investigation were from Wave 3 (March 2014-December 2015), which included CAPI (version 3.5.0) and health assessment centre (version 3.2.2). Wave 3 was chosen as it included both assessments of HGS and 5CST, as 5CST was not performed at Wave 1. Inclusion criteria for the main analysis were: complete data for the active stand test, probable sarcopenia measurements and covariates listed below, and no self-reported diagnosis of idiopathic Parkinson's disease (in order to reduce the likelihood of participants with pure neurogenic OH).

For the longitudinal assessment of the association between probable sarcopenia, OH and falls, baseline data was obtained from TILDA Wave 1 and longitudinal follow-up across

the Waves 2 to 6 was performed. The details and timing of each wave are shown in Figure 2-1.

The sample size for TILDA was determined as part of the original nationally representative sample at Wave 1 and so the sample size available was that of those remaining at Wave 3 minus exclusions, withdrawals from the study, those deceased and those lost to follow-up.

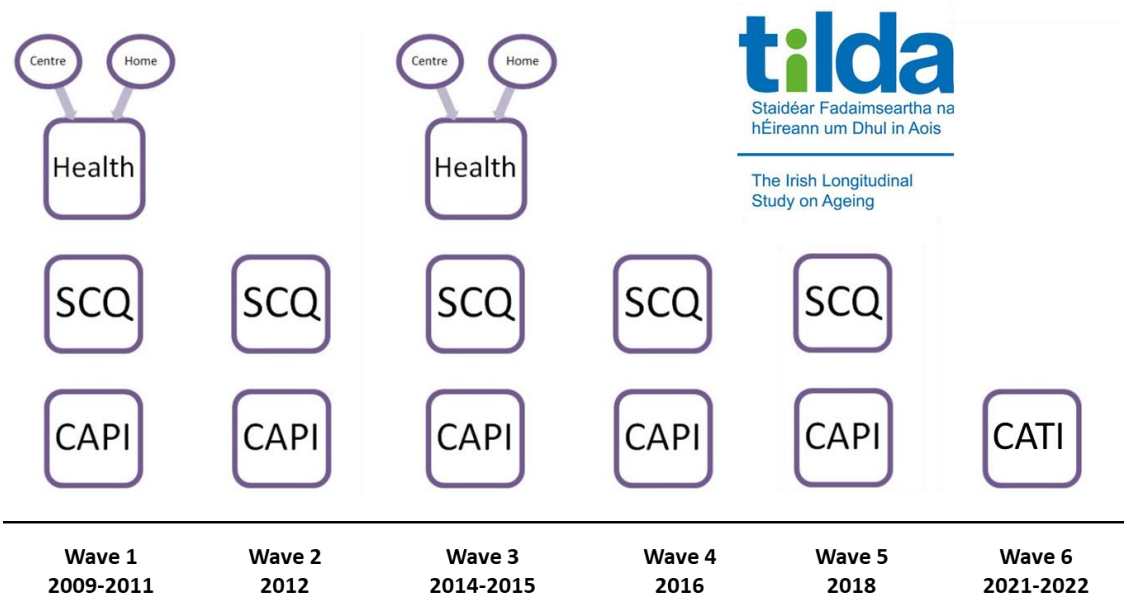

Figure 2-1: The Irish Longitudinal Study on Ageing (TILDA) waves timing and details. Health – TILDA health assessment; SCQ – self-completion questionnaire; CAPI – computer-assisted personal interview; CATI – computer-assisted telephone interview

Studies II A and B: FRAILMatics Clinical Sample

FRAILMatics is a Science Foundation Ireland-funded research programme (18/FRL/6188) that aims to identify more accurate tools to detect early frailty without expert input. To do this, it aims to identify signals of multisystem physiological dysregulation in the population cohort of TILDA and the MISA clinical samples. In the latter, signals from the population-based study are re-tested with a view to evaluating their consistency and clinical translation potential. An overall infographic describing the FRAILMatics research programme is shown in Figure 2-2.

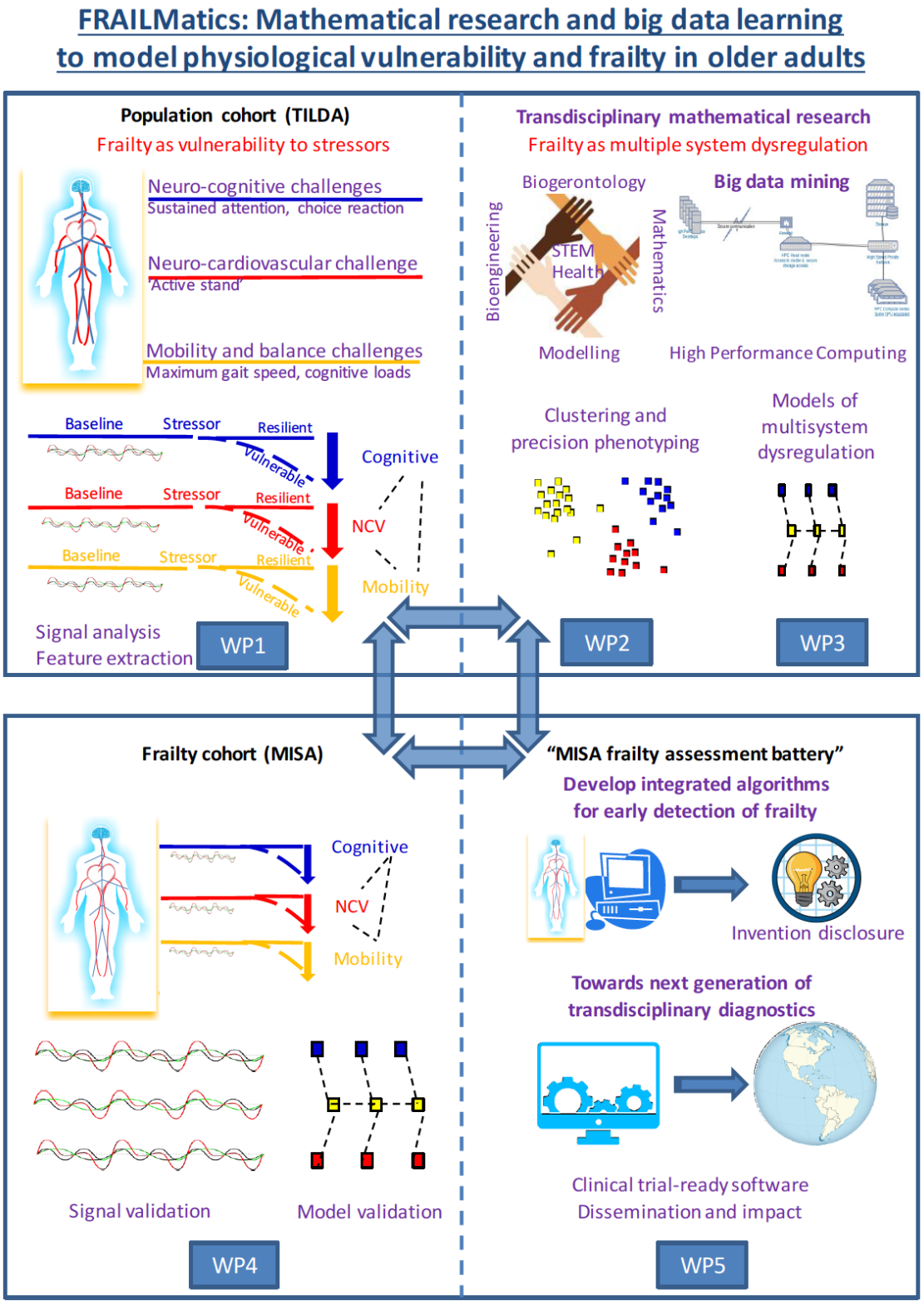

Figure 2-2: FRAILMatics Research Programme Infographic. TILDA – The Irish Longitudinal Study on Ageing; MISA – Mercer's Institute for Successful Ageing; WP – work package.

Recruitment for the FRAILMatics clinical sample took place between November 2021 and 2022. I prospectively recruited new attendees to FASU during this period, on average two days per week. Inclusion criteria for the clinical sample were: age 50 years or older, able to provide written informed consent, able to mobilise independently (with or without aid), and able to transfer with minimal assistance of one person from lying to standing. Exclusion criteria were: history of confirmed or presumed neurogenic OH, or contraindication to BIA (e.g., presence of an indwelling electronic device such as a cardiac pacemaker).

Sample size for this recruitment was calculated in Stata version 15.1 on the basis of the proportion of OH between groups with and without sarcopenia in a previous study [263]. To have a power $(1 - \beta)$ of 0.8, at a significance level (α) of 0.05, a sample size of 107 participants was calculated to be needed.

Study III: FRAILMatics Physiological Sample

I recruited participants from May to July 2023 from the membership of a local healthy ageing group. Recruitment finished at the end of July 2023 for staffing and logistical reasons. Participants were invited to attend FASU for a dedicated research assessment. Inclusion criteria were: age 50 years or older, able to provide written informed consent, able to mobilise independently (with or without aid), and able to transfer with minimal assistance of one person from lying to standing. The exclusion criterion was a contraindication to BIA (e.g., presence of an indwelling electronic device such as a cardiac pacemaker).

As this was an exploratory, pilot analysis, a specific sample size was not calculated, but a target of at least 30 participants was set given the available time for recruitment.

Ethics and Consent

Study I

Ethical approval for each wave of TILDA was granted by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin. The study adhered to the World Medical Association Declaration of Helsinki on ethical principles for heath research involving human subjects, and all participants provided written informed consent.

Studies II-A and II-B

Ethics approval for the FRAILMatics research programme was granted from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (Project ID:

0221; approval date: 4 May 2021). Approval was also granted by St James's Hospital Research & Innovation Office (Reference: 6567, approval date: 26 July 2021). The study adhered to the Declaration of Helsinki and all participants provided written informed consent.

Study III

Ethical approval for this study was granted as an amendment to the original FRAILMatics study by the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (Project ID: 0221; approval date: 2 August 2022). The study adhered to the Declaration of Helsinki and all participants provided written informed consent.

Co-morbidities, Medications and Anthropometrics

Study I

Self-reported information on medical conditions and medication use was taken from the CAPI. Self-reported cardiovascular medications were defined as per World Health Organization Anatomical Therapeutic Chemical (ATC) Classification codes: C01 – anti-arrhythmics, C02 – anti-hypertensives, C03 – diuretics, C04 – vasodilators, C07 – beta-blocking agents, C08 – calcium channel blockers, and C09 – agents acting on renin-angiotensin system. Self-reported psychotropic medications were defined as ATC codes N03A – anti-epileptics, N05 – anti-psychotics, anxiolytics, hypnotics and sedatives, and N06A – anti-depressants. Height was measured with a Seca 240 (Seca, Birmingham, UK) wall-mounted measuring rod, without footwear to the nearest 0.01m. Weight was measured with a Seca electronic floor scale (Seca, Birmingham, UK), without shoes or outer garments to the nearest 0.1kg.

Studies II-A and II-B

Participants' disease status and medication use were obtained from a combination of self-report, electronic patient record review and correspondence from the participants' General Practitioner where available. Multimorbidity was defined as two or more chronic conditions and polypharmacy as five or more regular medications excluding supplements. Physical frailty status was determined using the SHARE-FI [331]. Nutritional status was assessed using the Mini-Nutritional Assessment Short-Form (MNA-SF) [332]. Cardiovascular and psychotropic medication use were defined as in Study I. Height was measured to the nearest 0.01 m, with footwear on, with a Seca 222 Stadiometer (Seca Ltd, Birmingham, UK). Weight was measured with the TANITA DC-430 MAP Body Composition Analyser (Tanita Europe, Amsterdam, The Netherlands). For the latter,

participants were asked to remove their outerwear, shoes and socks and empty their pockets, and 0.5 kg was entered as a standard tare value for clothing. Participants were not routinely asked to empty their bladder before their standard clinical assessment, but a toilet was located nearby, and participants were free to take a break to attend the bathroom at any stage of the assessment.

Study III

Participants' medical history and medications were ascertained by self-report along with information about smoking and alcohol use. Height was measured with the Seca 213 stadiometer (Seca, Hamburg, Germany) to the nearest 0.001 m with the participant barefoot. Weight and BIA were measured using the TANITA DC-430 MAP device. Participants were asked to ensure they had emptied their bladder before measurement. The participant stood barefoot on the scales having removed outer clothing and contents of pockets. A standard 0.5 kg tare value was entered for all participants to account for the weight of the remaining clothing.

Muscle Function and Mass

Study I

HGS was measured with a Baseline Hydraulic Hand Dynamometer (Fabrication Enterprises Inc., New York, USA) while standing. The maximum value of two attempts on each hand was taken to the nearest 1kg. For the 5CST, the time was measured to the nearest 0.01 s for a participant to stand up from a sitting position and sit back down again five times from a standard chair (approximate seat height of 46 cm), as fast as possible, without the use of their arms.

Studies II-A and II-B

HGS was assessed using a Jamar Hydraulic Hand Dynamometer (Performance Health, Wisconsin, USA). The maximum value of two consecutive measurements taken on the left and right hands, while seated, was used. Values were rounded to the nearest 1kg, as per the precision of the device. The time taken on the 5CST was measured as the time to the nearest 0.01 s taken for a participant to stand up and sit back down again, as fast as possible, five times from a standard chair (seat height 43cm). Height was measured to the nearest 0.01m (Seca 222 Stadiometer, Seca, Birmingham, UK). BIA was performed with the TANITA DC-430 MAP Body Composition Analyser, with the procedure as reported

for weight measurement. ASMM was calculated using the Sergi equation [77] . Figure 2-3 displays the equipment used for the assessment of muscle strength and mass in Study II.

Figure 2-3: Study II FRAILMatics Clinical Sample equipment. Clockwise from top-left: Jamar Hydraulic Hand Dynamometer, TANITA DC-430 MAP Body Composition Analyser, Standard chair used (height: 43 cm) for five chair stands test.

Study III

HGS was measured to the nearest 0.1 kg, while seated, with the Jamar Plus + Digital Hand Dynamometer (Performance Health, Wisconsin, USA). The maximum value of two consecutive measures taken alternately on the left and right hands was used.

The 5CST was taken as the time to the nearest 0.01 s for the participant to stand up and sit back down again five times from a standard chair (approximate seat height 43cm).

BIA was performed with the TANITA DC-430 MAP Body Composition Analyser, with the procedure as reported for weight measurement. ASMM was calculated using the Sergi equation [77].

Given the potential limitations of BIA as discussed earlier, in Study III an emerging and alternative measure of muscle mass, muscle thickness, was measured using point of care US with the GE Vscan Air (GE HealthCare, Dublin, Ireland). The rectus femoris and vastus lateralis muscles of the right thigh were chosen given the extent of previous research involving these muscles [89]. Participants lay flat and relaxed on an examination bed with the lower limbs extended. As per the SARCopenia through UltraSound (SARCUS) guidelines [88] a point midway between the greater trochanter and the proximal boarder of the patella was marked and measurement took place at this level. A generous amount of US transmission gel was applied to the skin. The linear array transducer (3 - 12 MHz) was placed on the skin, perpendicular to the surface, with the minimum amount of pressure needed to obtain a clear image. The image was optimised with respect to depth and gain, and the medial and lateral borders of the muscle were identified. Three images of the cross section of the rectus femoris and vastus lateralis muscles in both transverse and longitudinal views were captured with the probe in the middle of the muscle. Measurements of the rectus femoris muscle thickness (RFMT) and vastus lateralis muscle thickness (VLMT) were performed offline using the Vscan Air app, with the thickness taken to be the perpendicular distance, to the nearest 0.01 cm, from upper to lower aponeurosis, at the midpoint of the muscle in the transverse plane (see Figure 2-4 and Figure 2-5). The mean of the 3 measurements was used.

Lower limb muscle strength was measured during the EMG normalisation period. For the purposes of EMG signal normalisation two maximum voluntary contractions of the right quadriceps muscle were performed [333] and force was measured using an Activforce handheld dynamometer (Activbody, San Diego, CA, USA). Participants were seated on an adjustable height chair, which was positioned so that the left foot was resting on the ground but the right foot was free to move. The dynamometer was placed resting on the right shin and attached to the chair leg via a fixed belt. The participant was asked to hold on to the bench with both hands. They were then asked to extend at the knee joint their leg as hard as they could against the dynamometer. After at least one practice knee

extension and a rest period, they were asked to perform two maximum voluntary contractions with a 30-second rest in between. The force on the handheld dynamometer to the nearest 0.1 kg was measured and the maximum of the two attempts was taken. The equipment used for the assessment of muscle strength and mass in Study III is shown in Figure 2-6.

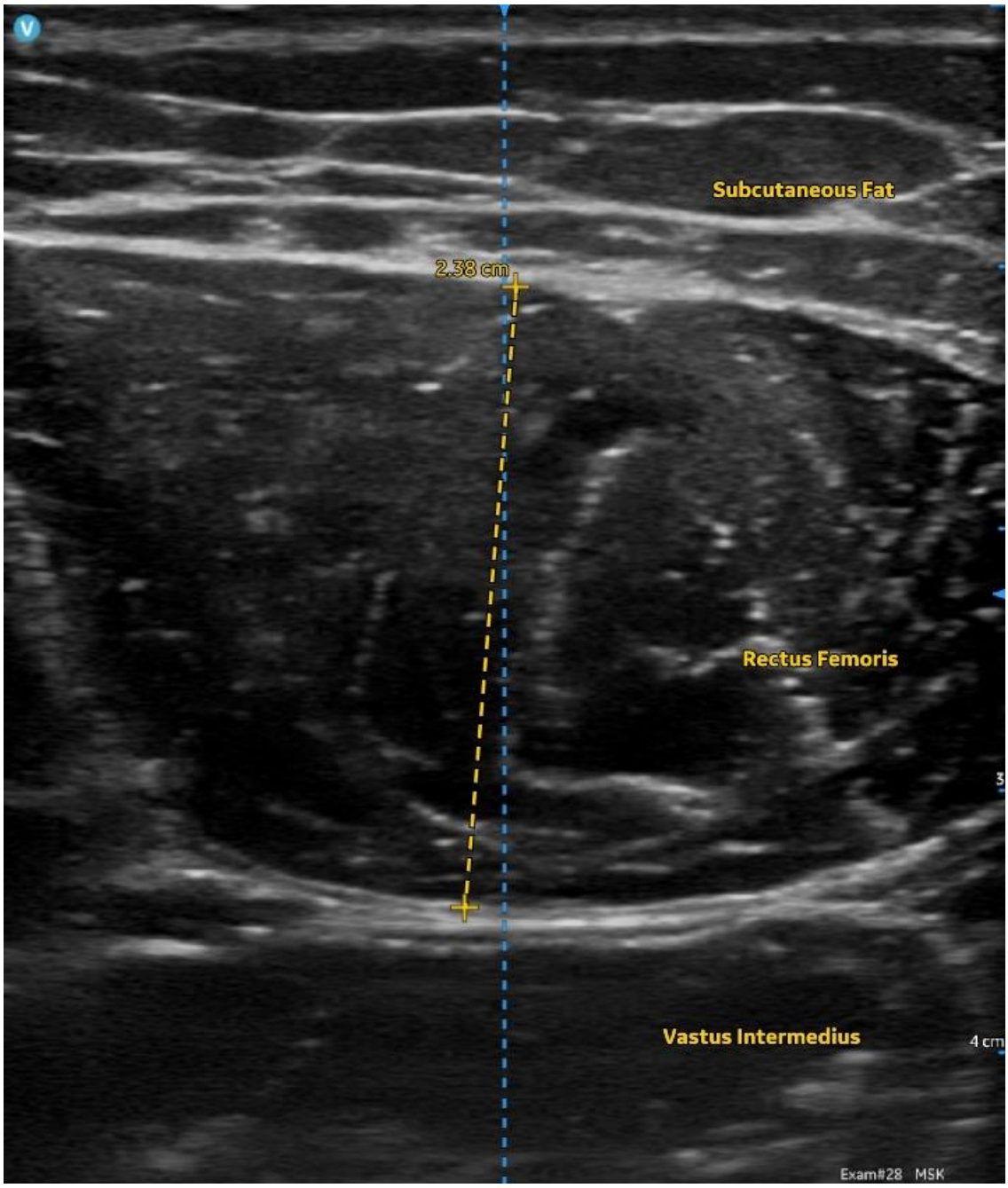

Figure 2-4: Example of ultrasound measurement of Rectus Femoris muscle thickness (RFMT) in the transverse plane.

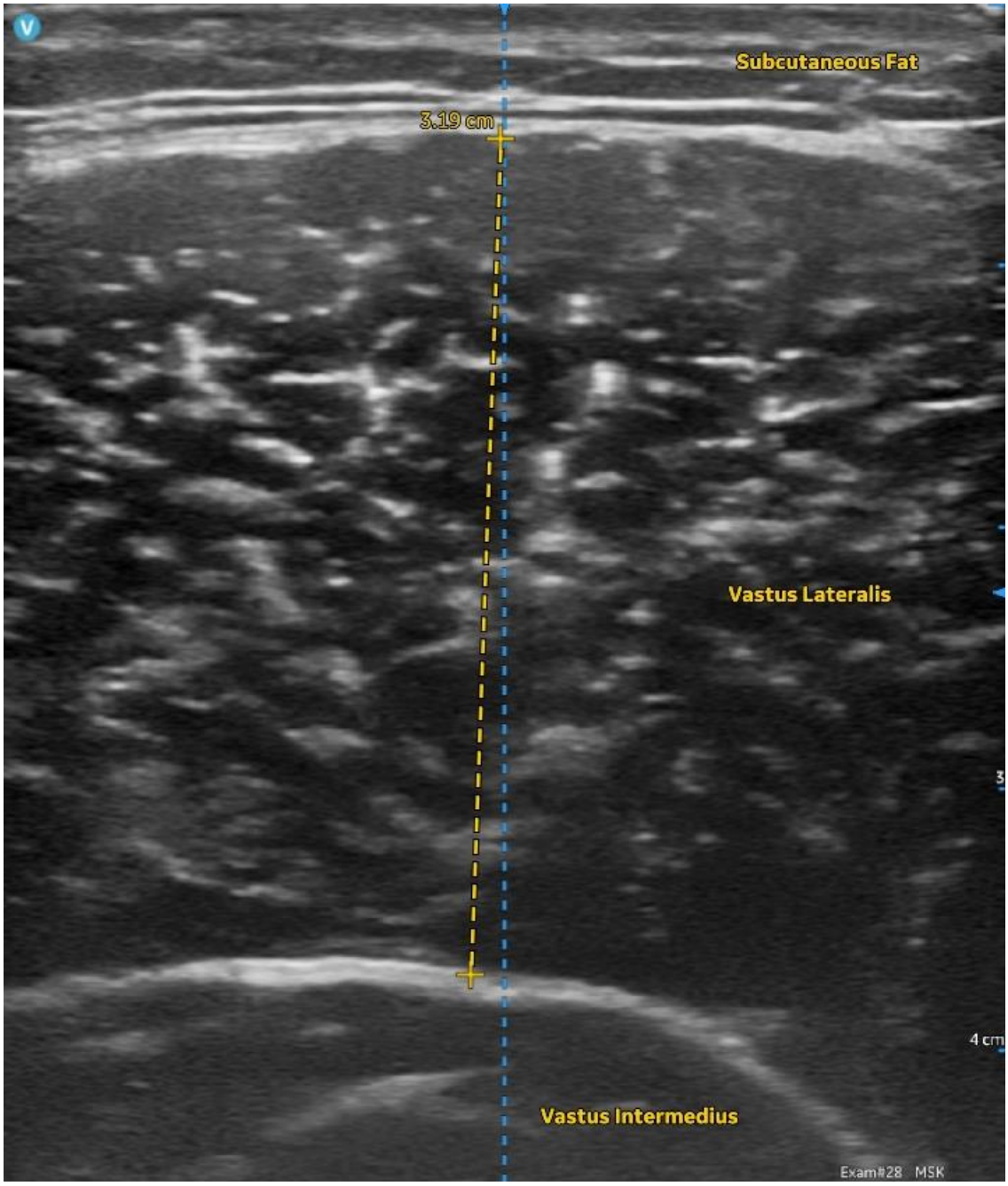

Figure 2-5: Example of ultrasound measurement of Vastus Lateralis muscle thickness (VLMT) in the transverse plane.

Figure 2-6: Study III FRAILMatics Physiological Sample equipment. Clockwise from top-left: Jamar Plus + Digital Hand Dynamometer; GE Vscan Air, linear array transducer; knee extensor strength measurement positioning; Activforce handheld dynamometer.

Sarcopenia

The EWGSOP2 guidelines [55] were used to determine sarcopenia status: robust, probable sarcopenia and sarcopenia. The EWGSOP2 guidelines were chosen because they are widely used and cited in the European region and their cut-offs have been derived in a Caucasian population, hence being applicable to the Irish population. Probable sarcopenia was defined as HGS of less than 27 kg in men and 16 kg in women and/or 5CST greater than 15 s. As no measure of muscle mass was obtained in TILDA, only probable sarcopenia could be determined. In studies II and III, low muscle mass was defined as an ASMM of less than 20 kg in men and 15 kg in women. The combination of probable sarcopenia and low muscle mass confirmed sarcopenia. Gait speed was not assessed, and so severe sarcopenia was not determined. With the focus on orthostatic haemodynamics

and participants needing independent mobility for the active stand, a gait speed of <0.8 m/s was not expected to be a feature in the vast majority of participants.

Haemodynamic Response to Standing

Study I

In the TILDA health centre assessment participants underwent an active stand test with non-invasive continuous beat-to-beat monitoring of BP and HR with digital photoplethysmography using the Finometer MIDI (Finapres Medical Systems, Amsterdam, The Netherlands). The test was performed by a TILDA research nurse at an ambient room temperature of 21–23°C. An appropriate cuff size was selected and the participant lay supine while preceding tests as part of the TILDA protocol were completed. The Finometer signals were then calibrated using brachial artery measurements. Physiocal [228] was used to keep the signals calibrated over time and the height correction unit corrected for hydrostatic pressure differences. After this supine period of between 15–20 minutes, and after ensuring the signal was stable, the participant then stood as quickly as possible (with assistance if necessary) and remained standing quietly for 3 minutes.

Studies II-A and II-B

As part of their routine clinical care, participants underwent an active stand test, performed by a specialist nurse in FASU, with continuous non-invasive beat-to-beat haemodynamic measurement using the Finapres Nova (Finapres Medical Systems, Amsterdam, The Netherlands). Ambient room temperature in the unit was maintained between 21-23°C. Before the test, participants warmed their hands under warm running water to ensure good perfusion of the digital arteries. The active stand test consisted of a supine signal calibration and resting phase of 5–10 min, followed by standing as quickly as possible and remaining standing quietly for 3 min, as per recommend guidelines [223]. Signal calibration was performed using oscillometric brachial calibration and the Physiocal function on the Finapres with the height correction unit adjusting for differences in hydrostatic pressure. The testing environment in which the active stand was performed in Study II (and Study III) is shown in Figure 2-7.

Figure 2-7: Testing Bay in the Falls and Syncope Unit, Mercer's Institute of Successful Ageing, St James's Hospital, Dublin

Study III

Instrumentation

Continuous, non-invasive, beat-to-beat haemodynamics were recorded via digital photoplethysmography with the Finapres Nova. The participant washed their hands under warm running water to ensure good perfusion of the digital arteries and a Finapres cuff of appropriate size was applied to the index finger of the left hand. Standard oscillometric BP was also measured by the Finapres with a cuff applied to the right arm. Resting signals were calibrated with brachial calibration on the Finapres device and the Physiocal function was used to keep the signal calibrated over time.

As the previous studies were limited in that they did not incorporate contemporaneous measures of muscle activation during the active stand, in Study III surface EMG and NIRS were included. Surface EMG was performed with the Shimmer3 device (Shimmer Research Ltd., Dublin, Ireland). The Shimmer3 is a wireless wearable surface EMG device that can acquire high resolution surface EMG signals to flash memory card storage and also allows for real-time monitoring via Bluetooth. Participants changed into shorts for the assessment and skin was prepared by gentle rubbing with a 70% isopropyl alcohol wipe before being allowed to dry. A pair of self-adhesive Ag/AgCl electrodes of 24 mm diameter (Kendall H124SG, Cardinal Health, Waukegan, IL, USA) were positioned over the midline of the rectus femoris muscle of the right thigh as per the Surface EMG for a Non-Invasive Assessment of Muscles (SENIAM) guidelines [334] at a point halfway between the anterior superior iliac spine and the superior patella. A second pair of electrodes were placed on the lateral gastrocnemius muscle of the right leg, at a point one-third of the distance from the head of the fibula to the heel. The inter-electrode distance, taken as the distance between the centre of the two electrodes, was minimised and was approximately 20 mm. A reference electrode was placed on the patella. A normalisation procedure was then performed. For the rectus femoris muscle, the procedure was seated knee extension as described above. For the lateral gastrocnemius, participants performed two single leg standing calf raises of 10 s duration while leaning against a wall. Participants were instructed to lift their right lower limb off the ground, stand supported by their left lower limb, leaning slightly onto the wall with both hands for support. They were then instructed to plantarflex their right ankle and rise up onto their toes as high as they could and hold that position for 10 s. They then returned to bipedal stance for a rest period of 30 s before performing one further calf raise. EMG signals were recorded using the

ConsensysPro software version 1.6 (Shimmer Research Ltd., Dublin, Ireland) at a sampling rate of 1024 Hz.

NIRS of the left rectus femoris muscle was performed using the PortaLite system (Artinis Medical Systems, Einsteinweg, The Netherlands). NIRS allows non-invasive measurement of oxygenation in muscle tissue, measuring both oxygenated and deoxygenated haemoglobin concentrations. The PortaLite device allows wireless acquisition of these signals via Bluetooth. The NIRS device was attached adhesively over the midpoint of the left rectus femoris muscle, at a matching location to that of the EMG electrodes on the right thigh, and bandage was used to secure the device to the thigh and ensure no external light reached the optodes. Data from the PortaLite was recorded at 50 Hz sampling rate using OxySoft version 3.3 (Artinis Medical Systems, Einsteinweg, The Netherlands).

Additionally, as part of the measurement protocol, cerebral frontal lobe oxygenation was acquired via a NIRS sensor on the forehead and a Shimmer3 device was used as an accelerometer placed in the midline at waist level, however these signals were not used in the current analysis. The Finapres Nova, Portalite and Shimmer3 device are shown in Figure 2-8, and Figure 2-9 gives an overview diagram of the instrumentation in Study III.

Figure 2-8: Study III FRAILMatics Physiological Sample equipment. From top: Finapres Nova front-end unit; Artinis PortaLite near-infrared spectroscopy unit; Shimmer3 surface EMG device with electrodes attached

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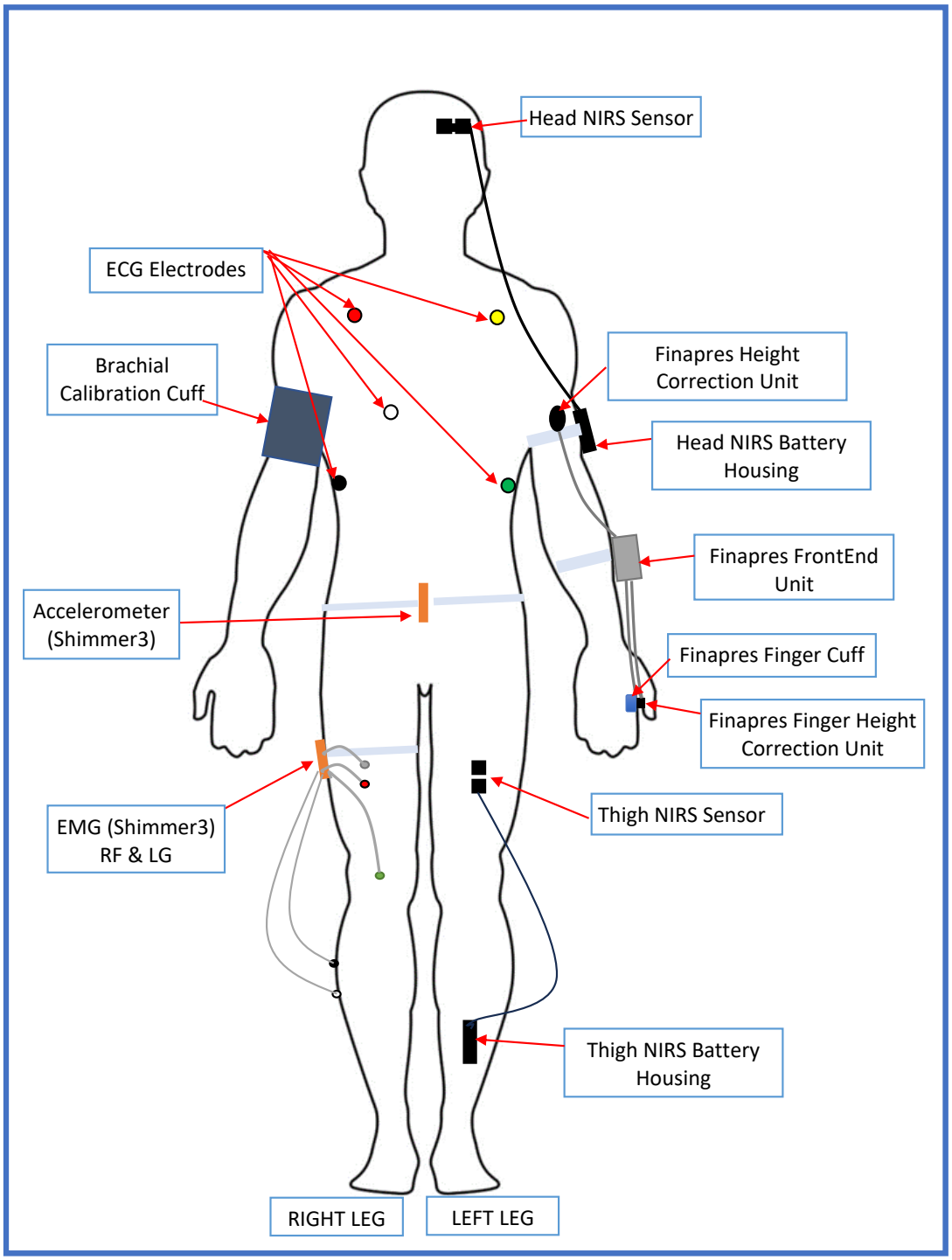

Figure 2-9: Study III FRAILMatics Physiological Sample Instrumentation Diagram. NIRS – near-infrared spectroscopy; ECG – electrocardiogram; RF – rectus femoris muscle; LG – lateral gastrocnemius muscle.

Modified Active Stand Protocol

Participants underwent a modified active stand procedure, performed by the candidate for the purposes of research, with a supine and standing lower limb muscle squeeze as a PCM, before and after standing, respectively. As per Study II, the ambient room temperature was maintained 21-23°C. During instrumentation participants lay supine and remained resting while calibration of the Finapres was performed. These two processes took between 5 to 10 minutes. Once calibrated the participants performed a bilateral lower limb muscle squeeze consisting of tensing their lower limb muscles as hard as they could for 10 s and then relaxing. After the muscle squeeze they remained supine resting for 5 minutes before standing promptly unaided and remained standing quietly for 3 minutes. After the 3 minutes had elapsed they performed another lower limb muscle tensing for 10 s before remaining standing for 1 minute further. Figure 2-10 graphical illustrates the modified active stand protocol.

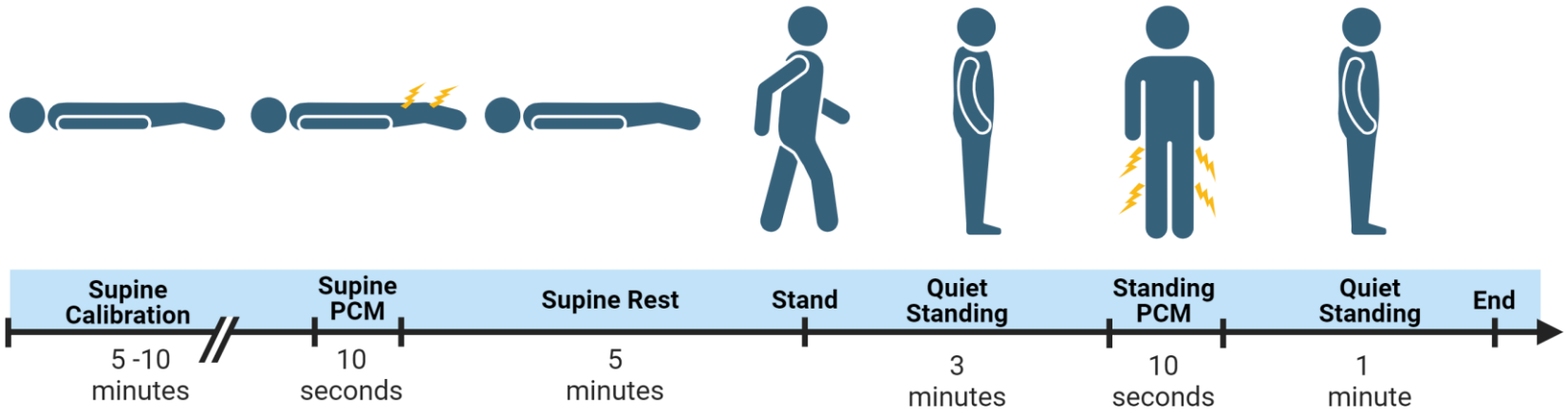

Figure 2-10: Study III FRAILMatics Physiological Sample modified active stand protocol. PCM – physical counterpressure manoeuvre.

Signal Processing

Study I

The TILDA active stand beat-to-beat BP data were available in the TILDA dataset version 3.2.2. They had undergone pre-processing by the TILDA bioengineering team to remove artefacts and ±5 s moving average filtering and feature extraction had been performed as described in a published summary [335]. Baseline supine SBP and DBP values were derived from the average of values occurring 30-60 s prior to standing. The baseline values were subtracted from the absolute values of SBP and DBP at 10 s intervals from 0 to 180 s to give relative change at these timepoints. OH30, was defined as a drop at 30 s of SBP ≥ 20 mmHg and/or DBP ≥ 10 mmHg from baseline values. Consensus OH was defined as a sustained (10 s) drop in SBP of ≥ 20 mmHg and/or DBP ≥ 10 mmHg occurring between 60 and 180 s [178]. If there was baseline hypertension (≥ 140/90 mmHg) then a drop of ≥ 30/15 mmHg was necessary.

Study II-A

I exported beat-to-beat signals for SBP, DBP and HR from the Finapres Nova software and performed pre-processing using custom written scripts in MATLAB version 9.11 (The MathWorks, Inc., Natick, MA, USA). Signals were visually inspected for poor quality and those with excess noise or artefacts were excluded. If there was a suspicion of delay between the marker for standing and actual standing, the height correction unit signal was examined and the stand time corrected. The baseline signal was taken as the mean from 60 to 30 s before standing. Ten-second averages were taken from 0 to 180 s after standing and the baseline values were subtracted from these averages to give a relative change at 10 s intervals after standing. These values were exported to Stata version 15.1 for analysis.

Study II-B

The Finapres measures the arterial pressure at the digital artery of one of the fingers, usually the index or middle finger. This arterial pressure waveform is integrated to calculate the MAP, and the reciprocal of the interval between peaks is taken as the HR. The haemodynamic parameters CO, TPR and SV are derived by the Finapres using the Modelflow algorithm. The Modelflow algorithm calculates the aortic flow waveform by simulating a non-linear three-element model of aortic input impedance [229]. This is integrated to compute SV, and from this, CO is calculated by multiplying by HR [336]. TPR is then derived from MAP by dividing by CO. These additional haemodynamic parameters were exported from the Finapres and I wrote custom scripts in MATLAB version 9.14 for pre-processing and processing. A ±5 s moving average filter was applied

to the signals and the baseline values, defined as in Study II-A, were subtracted to give relative change. The values of the haemodynamic signals at 10 s intervals from 0 to 180 s were exported to Stata version 15.1 for analysis.

Study III

I carried out signal processing using MATLAB version 9.14 and wrote custom scripts for pre-processing and processing. Data was imported from the proprietary software packages into MATLAB and signal quality was reviewed visually. Those with excessive noise or poor recording quality were excluded. Files from different modalities were aligned using the active stand markers as a common time reference point. Signals from the Finapres were smoothed using a ±5 s moving average filter (see Figure 2-11). Surface EMG signals were bandpass filtered between 20 and 500 Hz in accordance with published recommendations [337]. The surface EMG signals were normalised by dividing the signal in the active stand period by the peak root mean square (RMS) of a 100 ms window during the normalisation period [333,338]. An example of the peak RMS of an EMG signal during the normalisation period is shown in Figure 2-12, and Figure 2-13 shows an example of the filtered, normalised and RMS of an EMG signal during the modified active stand protocol. NIRS signals were zeroed by subtracting the values at the initial starting phase and then were smoothed using a ± 5 s moving average filter (Figure 2-14). The relative changes in oxyhaemoglobin and deoxyhaemoglobin values were combined to give a total haemoglobin value (THb). The changes in haemodynamic and NIRS parameters at 10 second intervals from 10 to 180 s were calculated by using the value at a timepoint t and subtracting the value at a timepoint $t - 10\ s$ from it. For EMG the RMS of the baseline period 30–60 s before standing was subtracted from the RMS of the 10 s intervals from 10–180 s. These values were exported to Stata version 15.1 for analysis.

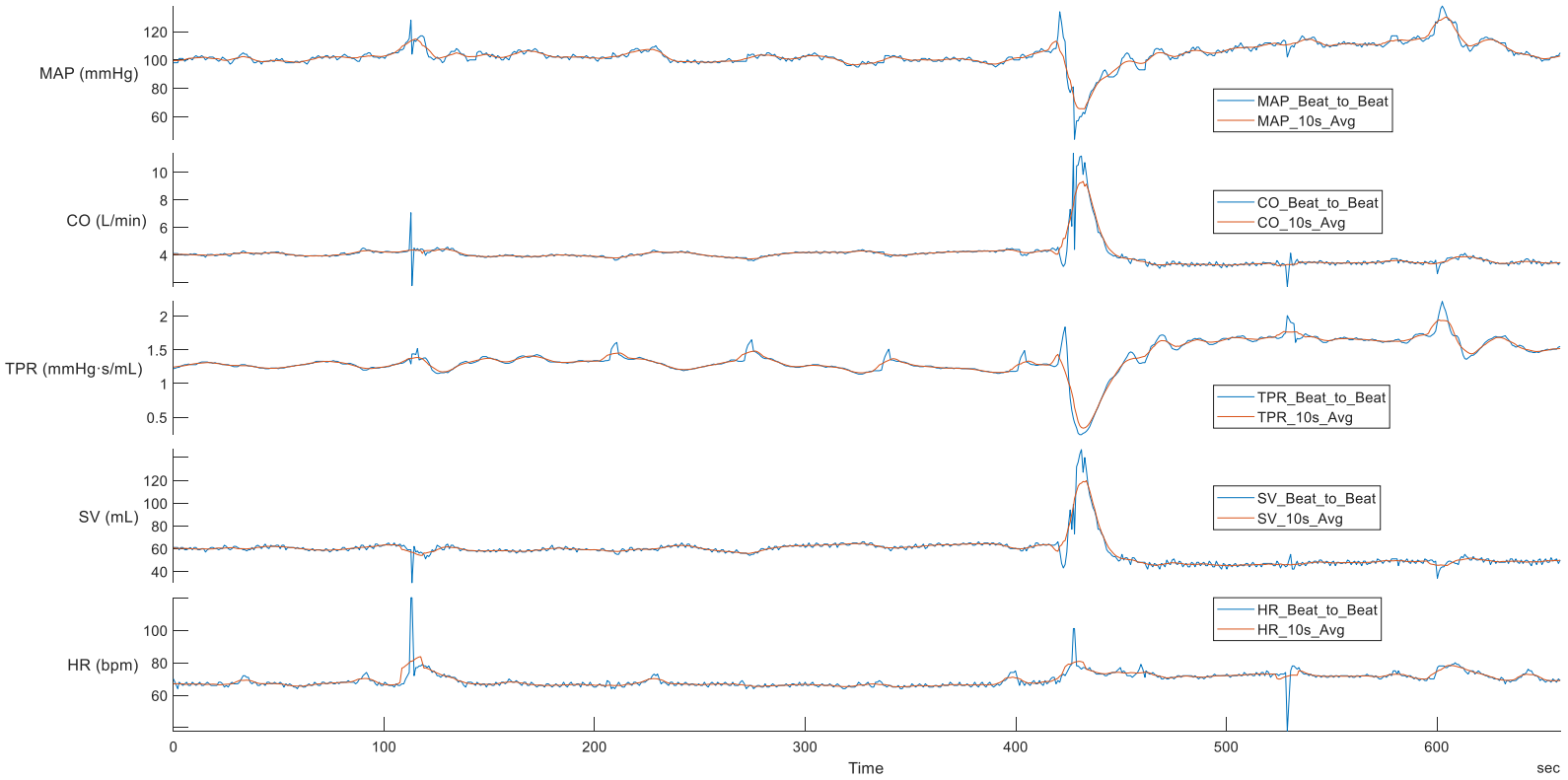

Figure 2-11: Study III FRAILMatics Physiological Sample, example of beat-to-beat haemodynamic signals (blue) vs. 10 s moving average of haemodynamic signals (red). MAP – mean arterial pressure (mmHg), CO – cardiac output (L/min), TPR – total peripheral resistance (mmHg·s/mL), SV –stroke volume (mL), HR – heart rate (bpm), Supine physical counterpressure manoeuvre (PCM) occurs at 110 s, stand at 420 s and standing PCM at 600 s

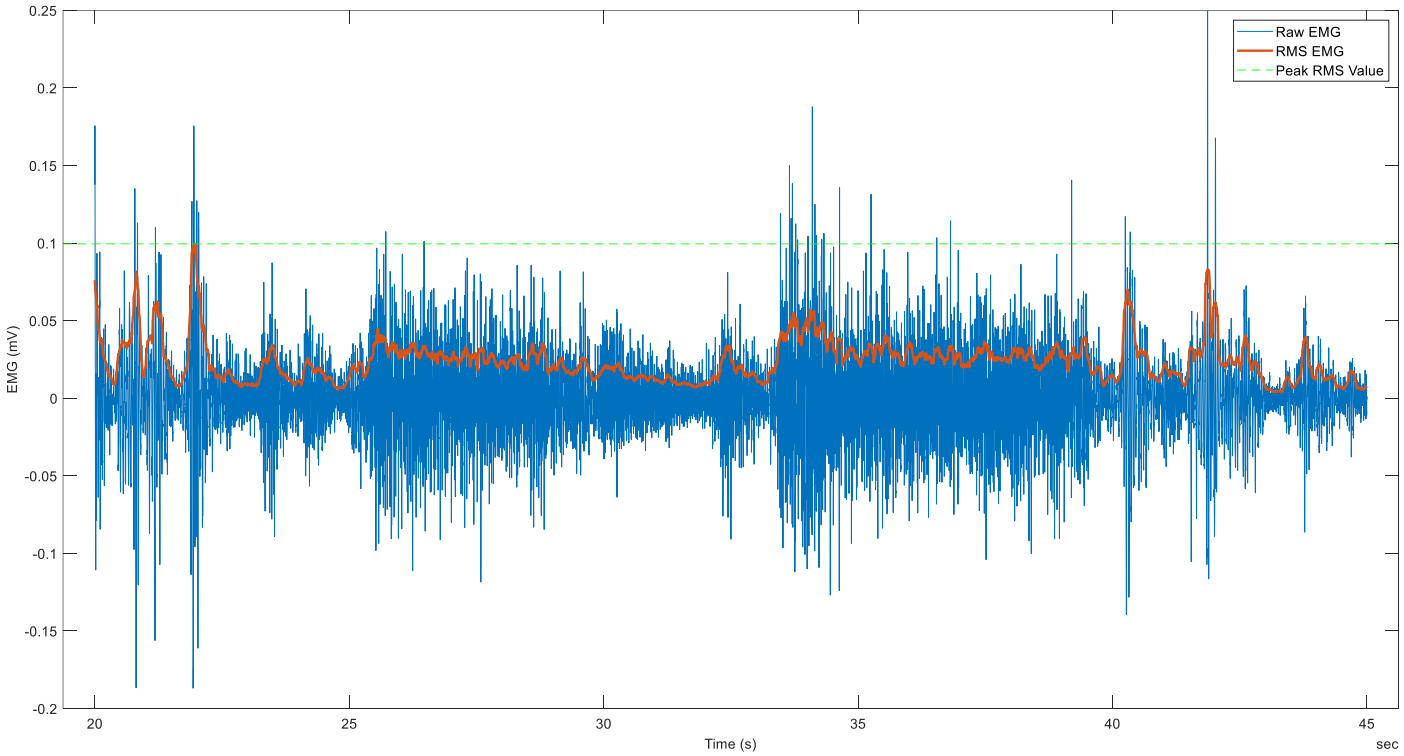

Figure 2-12: Study III FRAILMatics Physiological Sample, example of surface electromyography (EMG) of thigh, rectus femoris, normalisation period. Raw, bandpass filtered, EMG shown in blue with root mean square (RMS) tracing in red. Peak RMS value used for normalisation shown by dotted green line.

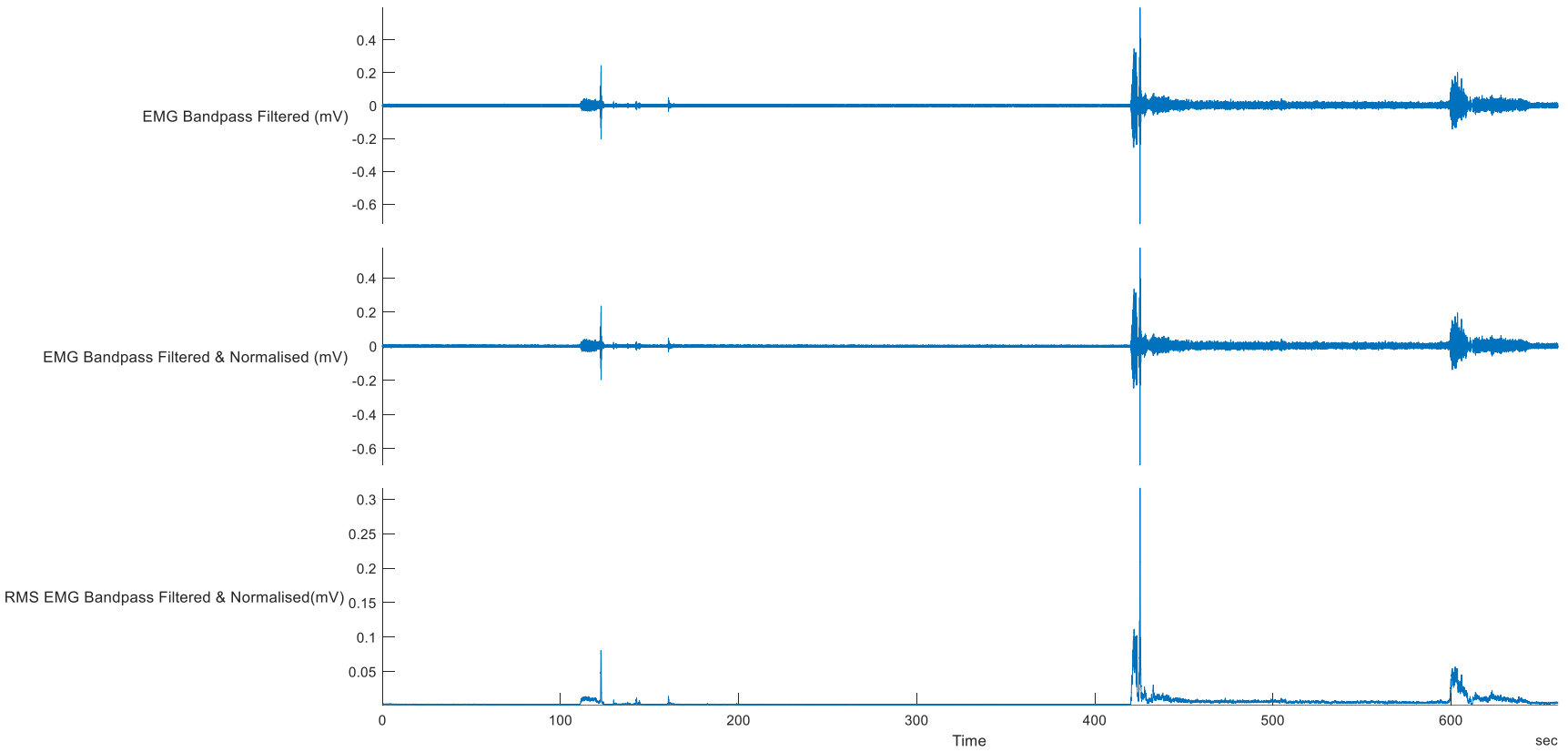

Figure 2-13: Study III FRAILMatics Physiological Sample, example of surface electromyography (EMG) of thigh, rectus femoris, during modified active stand period signals bandpass filtered, filtered and normalised, and root mean square (RMS) of filtered normalised signal. Supine physical counterpressure manoeuvre (PCM) occurs at 110 s, stand at 420 s and standing PCM at 600 s.

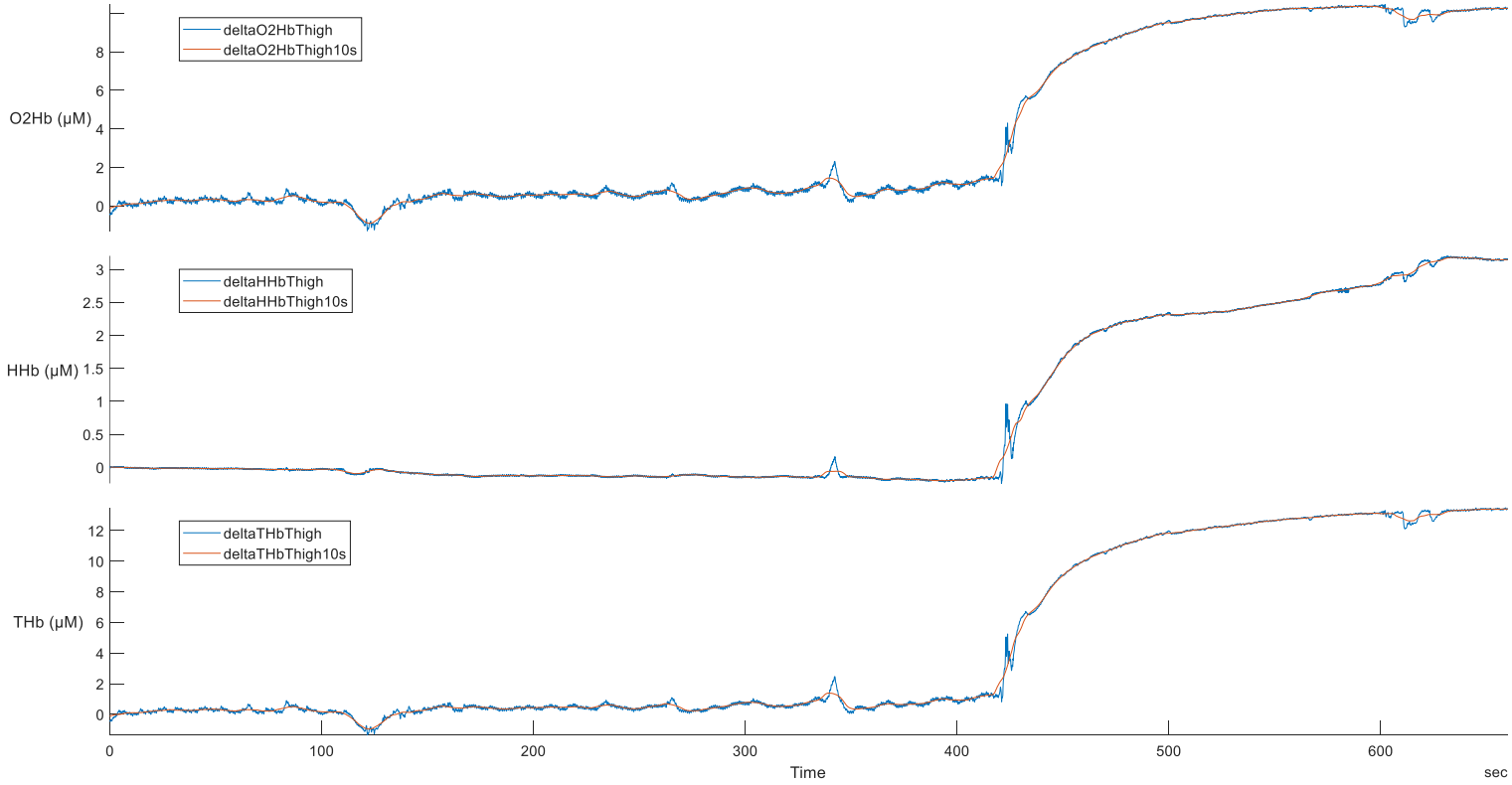

Figure 2-14: Study III FRAILMatics Physiological Sample, example of 50 Hz raw near-infrared spectroscopy signals (blue) vs. 10 s moving averages (red). O2Hb – relative concentration of oxygenated haemoglobin (µM); HHb – relative concentration of deoxygenated haemoglobin (µM); THb – relative concentration of total haemoglobin (µM). Supine physical counterpressure manoeuvre (PCM) occurs at 110 s, stand at 420 s and standing PCM at 600 s

Statistical Analysis

Statistical analysis for all studies was performed with Stata version 15.1 (StataCorp, College Station, TX, USA). The level of statistical significance was defined as $P < 0.05$ throughout.

Study I

Potential covariates were explored with a directed acyclic graph using the online package DAGitty [339] and variables that may confound the relationship between probable sarcopenia and orthostatic BP were identified and included as covariates in the model. These included: age, sex, height, weight, the presence or absence of hypertension, diabetes and heart failure, cardiovascular medications, psychotropic medications and presence or absence of fear of falling with activity limitation. Variables that mediated the relationship between sarcopenia and OH but lay on the causal pathway were not included as covariates in the model. The directed acyclic graph is shown in Figure 2-15.

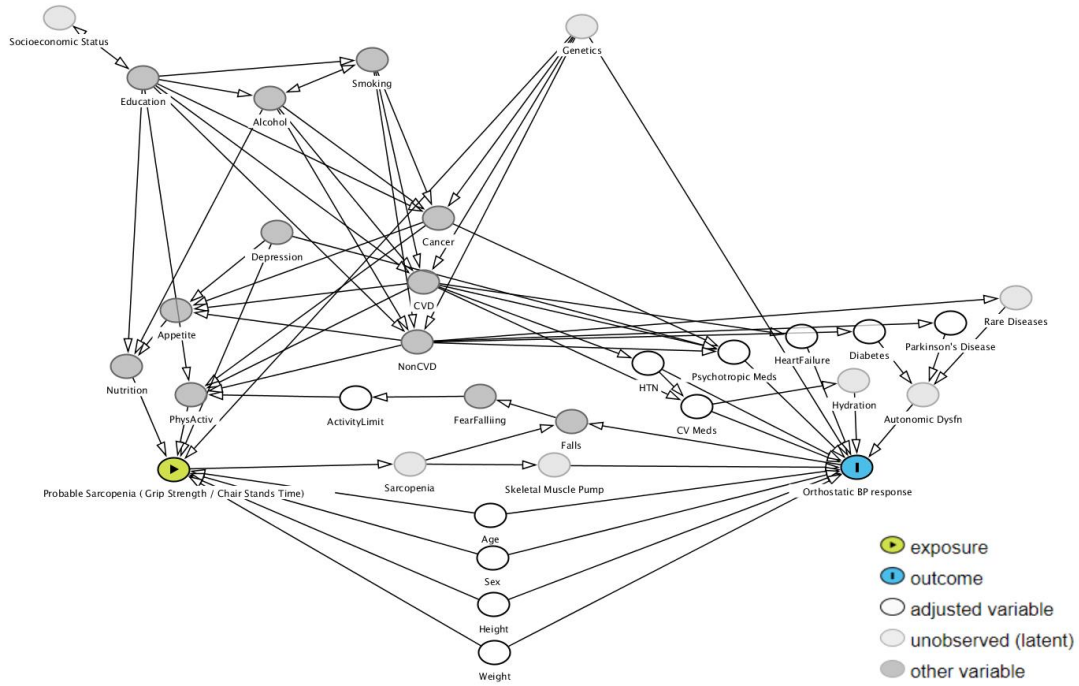

Figure 2-15: Directed acyclic graph showing the theorised relationship between probable sarcopenia and orthostatic blood pressure changes, with adjusted confounder variables in white, unobserved variables in light grey and mediator / incidental variables in dark grey. CVD – cardiovascular disease; HTN – hypertension; CV Meds – cardiovascular medications.

To examine the relationship between probable sarcopenia, OH30 and recurrent falls over longitudinal follow-up, TILDA Wave 1 was used as a baseline and probable sarcopenia was defined as per EWGSOP2 criteria for HGS (5CST was not performed at Wave 1). OH30, as defined above, was derived from the Wave 1 active stand. Participants were

categorised into a four-level variable: 0 – no probable sarcopenia, no OH30; 1 – OH30, no probable sarcopenia; 2 – probable sarcopenia, no OH30; 3 – probable sarcopenia and OH30. At each wave of follow-up from Wave 2 to 6, a 12-year period, participants were asked: "how many times have you fallen since your last interview?". The total number of falls per participant was computed and a recurrent falls variable coded: 0 – none or one fall; 1 – two or more falls. To maximise the usage of available data, an inclusive approach was taken and participants included if they had follow-up at any of the waves two to six.

The distribution of continuous variables was visually examined for normality using histograms. Descriptive statistics were presented as the mean and standard deviation of continuous variables and count and percentage of categorical variables. Differences in means and frequencies between the non-sarcopenia and probable sarcopenia groups were evaluated with the t-test and chi-squared test, respectively. The bivariate relationship of the mean SBP and DBP change after standing, grouped by probable sarcopenia cut-offs was explored graphically using the lgraph add-on package to Stata [340].

Given that multiple repeated measures of BP were taken for each participant, a statistical method that accounted for this and allowed adjustment for potentially confounding factors was needed. To assess the effect of probable sarcopenia on the change in SBP and DBP from baseline after standing, multi-level mixed-effects linear regression was used, with fixed and random effects accounting for the repeated measurements within participants. Piecewise linear splines modelling time points 0–10, 10–20, 20–30, 30–40 and 40–180 s after standing were employed as previously used in TILDA research [272,341,342]. Residual variance was modelled with a first order autoregressive process to account for the strong correlation between adjacent timepoints. The spline parameters were included as independent parameters in the mixed-effects model along with the interaction term of probable sarcopenia, 5CST criteria or HGS criteria (0 – no, 1 – yes), at each time segment. The potential confounders listed earlier were entered as covariates in the model. Where there were significant changes in terms of the interaction of the probable sarcopenia parameters on the BP response over specific time intervals, contrast analysis was used to assess differences in the mean change from baseline in BP at the relevant time points. Marginal effect plots (holding covariates at their means) were produced for the predicted mean change from baseline in SBP and DBP for those with and without probable sarcopenia by 5CST and HGS criteria.

Multivariable logistic regression models were used to investigate the prediction of OH30 by probable sarcopenia by 5CST and HGS criteria, while controlling for confounders.

Finally, difference in the odds of recurrent falls by probable sarcopenia and OH30 grouping were compared longitudinally using logistic regression. The four-level probable sarcopenia–OH30 variable was tested unadjusted in the first model, the second model adjusted for age, sex and educational attainment, and a third model also adjusted for psychotropic medication use and visual acuity.

Study II-A

The distributions of continuous variables were examined visually with histograms and distributional diagnostic plots, and tested using the skewness-kurtosis test for normality [343]. For the demographics of the sample, continuous normally distributed variables were summarised by the mean and SD, and non-normal continuous variables by the median and interquartile range (IQR). Proportions were given as count and percentage. Given that sarcopenia status could be considered a three-level ordinal variable (i.e., robust, probable sarcopenia and sarcopenia), trends in continuous variables across those three levels were examined with Kendall's rank correlation coefficient [344,345], while trends in dichotomous variables were examined using Chi-square for trend. Additionally, the effect of sarcopenia status on SBP and DBP after standing was represented graphically, from standing to 180 s, with the mean change in BP and standard error of the mean, by sarcopenia group.

As per Study I above, mixed effects models with piecewise linear splines to model time-points 0–10, 10–20, 20–30, 30–40 and 40–180 s after standing were used. The linear splines were entered into the model as independent parameters along with interaction terms with sarcopenia status (robust – 0; probable sarcopenia – 1; sarcopenia – 2) and potential confounders as covariates. The potential confounders considered were: age, sex (1– female, 2 – male), diabetes (0 – no/ 1 – yes), hypertension (0 – no/ 1 – yes), cardiovascular medications (0 – no/ 1 – yes), psychotropic medications (0 – no/ 1 – yes). In addition, in an attempt to isolate the effect of the SMP's contribution to BP response from that of the main cardiac pump, the model also controlled for HR, as an interaction term with each linear spline. Variables that theoretically lay on the causative pathway to sarcopenia, for example multimorbidity [346], were considered mediators rather than confounders and as such not controlled for in the models. As regards height and weight:

given that they are included in the Sergi equation for prediction of ASMM, the fact that height is more likely to contribute to the initial drop in BP, rather than recovery; and in order to minimise the number of covariates in the model; they were not entered as covariates in Study II. Fear of falling with activity limitation was also not assessed in Study II and so not included as a covariate.

Study II-B

In this study, for further clarity in presentation, sarcopenia status was considered as a two-level binary variable, no sarcopenia versus sarcopenia. Demographics of the sample were grouped by sarcopenia status and summarised by count and percentage. Differences between groups were tested using Pearson's chi-squared test and Fischer's exact test for those groups with an expected value of less than five. The mean, unadjusted, changes in the haemodynamic parameters MAP, CO, TPR, HR and SV, grouped by the presence or absence of sarcopenia, over the 180 s after standing, were visualised graphically.

As in studies I and II, to assess the relationship between sarcopenia and the haemodynamic parameters, mixed effects models with piecewise linear splines to model time-points 0–10, 10–20, 20–30, 30–40 and 40–180 s after standing were used. The linear splines were entered into the model as independent parameters along with interaction terms with sarcopenia status (no sarcopenia – 0; sarcopenia – 1) and potential confounders as covariates. The potential confounders considered were age, sex, diabetes, hypertension, cardiovascular medications, and psychotropic medications.

To further investigate the potentially causal haemodynamic factors in the relationship between sarcopenia, orthostatic BP recovery and falls, a structural equation model was postulated and tested in IBM SPSS Amos version 27.0 (IBM Amos Development Corporation, Wexford, PA, USA). In the model the effect of sarcopenia status on the change in TPR, HR and SV in the 10 – 20 s period was theorised to lead to impairment of MAP in the same period and subsequently to falls. Sarcopenia was also postulated to lead directly to falls. Age was included in the model as a direct path to falls and MAP change in the 10 – 20 s period, and as a covariate with sarcopenia status. Changes in haemodynamic parameters in the 10 – 20 s period were calculated as the absolute value at 20 s minus the absolute value at 10 s. The error terms on HR and the derived variables TPR and SV, were covaried, to capture the relationship between them, given the method by which they are derived, as described earlier. The overall model fit was determined with the Chi-squared test, with the null hypothesis being that the model is correct [347]. Both unstandardised

and standardised coefficients for the paths were computed using the maximum likelihood method, along with significance values. The theorised model is shown in Figure 2-16.

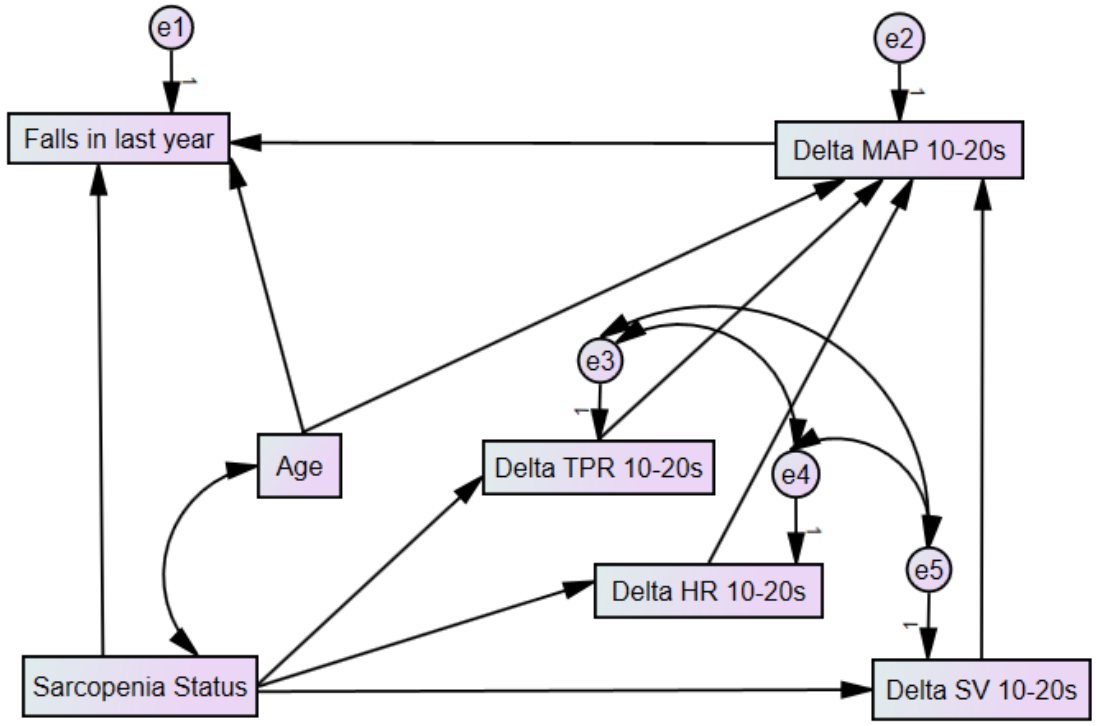

Figure 2-16: Structural equation model with postulated relationships between sarcopenia status and change in haemodynamic parameters, total peripheral resistance (TPR), stroke volume (SV), heart rate (HR), mean arterial pressure (MAP) between 10 and 20 s after standing, and the effect on falls, with age as a covariate. Straight arrows denote direct paths, curved arrows denote covariances and e1, e2, e3, etc. represent the error terms for the observed dependent variables.

Study III

The demographics of the sample were examined with histograms, box plots and the mean and standard deviation of normally distributed variables with the median and IQR of non-normally distributed variables.

In order to identify and characterise the temporal relationship between variables, a visualisation of the means and SDs of the haemodynamic, NIRS and EMG signals for the sample, for the active stand period, was generated in MATLAB.

To investigate the relationship between the different measures of muscle function and mass, pairwise Pearson correlations were performed. A heat plot of the correlations was generated using the heatplot add-on package in Stata [348].

To examine the relationship between muscle and haemodynamic parameters, the initial response in the first 30 s post stand was examined. The muscle parameters considered were maximum HGS, maximum QMS as measured during the EMG normalisation process, 5CST, BIA derived ASMM using the Sergi equation, RFMT and VLMT.

The relationship between muscle parameters and MAP was visualised using scatter plots. Linear regression analysis was used to examine further the relationship between these parameters. For the significant associations between muscle measures and MAP, these relationships were broken down into their underlying haemodynamic parameters as per the $MAP = CO \times TPR$ and $CO = SV \times HR$ equations and further analysed using linear regression.

Next thigh blood concentration as measured by rectus femoris muscle THb from NIRS, and electrical activity of the rectus femoris muscle, as measured by EMG were visualised against MAP change at 10 s intervals as before, and linear regression used to quantify associations. Again, significant relationships were explored further in terms of the underlying haemodynamics.

The maximum changes in MAP, CO, TPR, SV, HR, THb and RMS EMG were then computed for the PCM period. They were defined as the maximum values obtained, minus the steady-state values. The steady-state values were defined as the means of the 60 to 90 s period post stand. The relationships between muscle parameters and MAP change during PCMs were examined first using scatter plots and linear regression. The relationships between MAP change during PCM and CO, TPR, THb and EMG were then examined.

Chapter 3 – Study I

Published Works List

This chapter is based on my previously published paper: Duggan, E., Murphy, C. H., Knight, S. P., Davis, J. R. C., O'Halloran, A. M., Kenny, R. A., & Romero-Ortuno, R. (2022). Differential Associations Between Two Markers of Probable Sarcopenia and Continuous Orthostatic Hemodynamics in The Irish Longitudinal Study on Ageing. The Journals of Gerontology: Series A, 78(8), 1376–1382. https://doi.org/10.1093/gerona/glac243

Figure 3-1, Figure 3-4, Figure 3-5, Table 3-1, Table 3-2, and Table 3-4 from this chapter were published in the above paper.

Introduction

In this study, I examine the relationship between sarcopenia and orthostatic BP recovery and OH. The association between OH and frailty has been well established [264,274]. However, the relationship between sarcopenia and OH is less well characterized [349]. This is somewhat surprising as one might hypothesise a direct link between the two, namely via the SMP which aids venous return from the lower limbs via rhythmic muscle activity during standing [350]. The reduced muscle mass of sarcopenia might be expected to attenuate the effects of the SMP, potentially increasing the risk of OH.

One previous study found that severe sarcopenia, as classified by the EWGSOP2 definition [55], was a significant predictor of OH at 1 minute and systolic OH at 5 minutes, when compared to robust, probable sarcopenia and sarcopenia groups [200]. They however used the head-up tilt test, which gives a different hemodynamic pattern to the active stand [163] and may reduce the contribution of the SMP. Another smaller study found that EWGSOP-defined sarcopenia was an independent predictor of classical OH [263]. They utilised the active stand test but adjusted for only a small number of confounders. Both studies used oscillometric BP measurement and so were unable to study the early phase of BP recovery (i.e., the first minute post active stand).

With the limitations of the previous studies, I sought to further investigate the relationship between sarcopenia and OH using a large, well characterised sample from TILDA. I employed the EWGSOP2 cut-offs to separately examine HGS-defined and 5CST-defined probable sarcopenia. The participants from TILDA Wave 3 health assessment underwent an active stand test with continuous beat-to-beat BP measurement. I used mixed-effects models with linear splines as described in the Methods section to examine the relationship of these definitions on BP recovery and maintenance after standing.

Results

Participants

Overall, 4,266 participants aged 50 and over attended the TILDA health assessment centre in Wave 3 (Figure 3-1). Of those 3,500 underwent an active stand test and had complete data available for analysis. Details for non-performance are included in the figure. A number of participants were missing data on key variables of HGS, 5CST, weight or had a diagnosis of idiopathic Parkinson's disease and so were excluded from analysis. The final analytical sample was 2,858.

Those who attended the health assessment but either did not have active stand or were excluded tended to be: older (mean age 67.2 vs 63.9 years, P<0.001); female (58.2% vs 53.4%, P<0.01); have lower rates of third level education (38.4% vs 44.0 %, P<0.001); have higher rates of self-reported hypertension (38.6% vs 30.62%, P<0.001) and diabetes (9.7% vs 6.0%, P<0.001); and have higher rates of cardiovascular (46.5% vs 36.6%, P<0.001) and psychotropic medications (17.8% vs 11.8%, P<0.001). Those excluded also had higher rates of fear of falling with activity limitation (12.7% vs 5.1%, P<0.001), were more likely to meet EWGSOP criteria for probable sarcopenia by HGS criteria (12.1% vs 6.5%, P<0.001) but not 5CST (28.6% vs 25.3% P= 0.07).

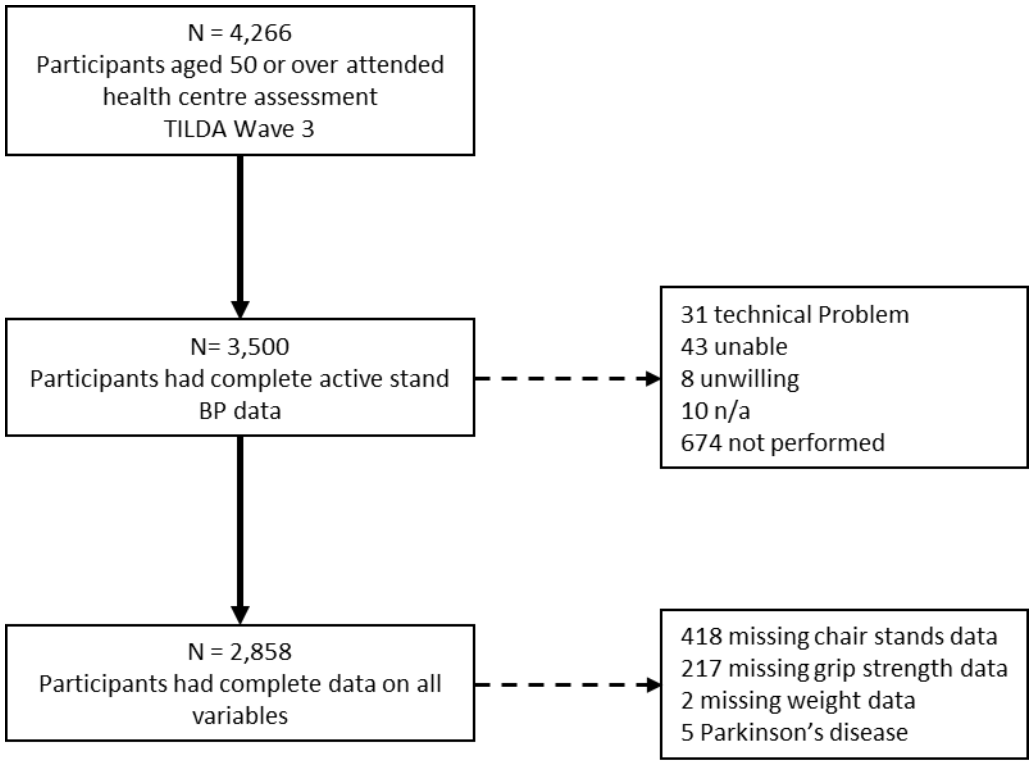

Figure 3-1: Flowchart of the participants. This figure has been published in my paper Duggan et al 2022, please see Appendix E.

Demographics

Overall, the mean age of the sample was 63.9 years, SD 7.6 years, 53.4% (n = 1,525) were women, with 25.3% (n = 723) meeting the 5CST criteria for probable sarcopenia and 6.5% (n = 187) meeting the HGS criteria. Third level education had been attained by 44.0% (n = 1,256) of the participants. The prevalence of hypertension was 30.6% (n = 875), diabetes 6.0% (n = 171), heart failure 0.5% (n = 14), cardiovascular medication use 36.6% (n =

1,045), psychotropic medication use 11.8% (n = 336) and fear of falling with activity limitation 5.1% (n = 146).

The characteristics of the sample, grouped by probable sarcopenia criteria are detailed in Table 3-1. Differences between groups were tested using t-test for continuous variables and chi-squared test for frequencies. Those who met the 5CST criteria for probable sarcopenia, when compared to the non-sarcopenic group, were older, higher weight, had a higher prevalence of hypertension and diabetes, were more likely to be on cardiovascular and psychotropic meds and had a higher prevalence of fear of falling with activity limitation.

Compared to the non-sarcopenic group, those meeting the HGS criteria for probable sarcopenia were older, with a higher proportion of women, lower rates of tertiary education, shorter stature, lower body weight, a higher prevalence of diabetes, were more likely to be on cardiovascular and psychotropic medications and had a higher prevalence of fear of falling with activity limitation and consensus OH.

Table 3-1: Characteristics of the study population grouped by probable sarcopenia cut-offs vs non-sarcopenic: 5-chair stands test (5CST) time > 15s; hand grip strength (HGS) <16kg (women) 27kg (men).

Demographics & Characteristics	5CST Criteria No		5CST Criteria Yes			HGS Criteria No		HGS Criteria Yes		
N	2135	74.7%	723	25.3%		2671	93.5%	187	6.5%	
Age (years) (mean/SD)	63.1	7.3	66.5	8.1	***	63.5	7.3	70.2	9.0	***
Female (n/%)	1138	53.3%	387	53.5%		1443	54.0%	82	43.9%	**
Tertiary Education (n/%)	962	45.1%	24	40.7%		1194	44.7%	62	33.2%	***
Height (cm) (mean/SD)	166.2	9.1	166.4	9.3		166.4	9.1	163.7	9.2	***
Weight (kg) (mean/SD)	77.7	14.9	79.1	15.4	*	78.2	15.1	75.9	15.0	*
Hypertension (n/%)	626	29.3%	249	34.4%	*	808	30.3%	67	35.8%	
Diabetes (n/%)	112	5.3%	59	8.2%	**	153	5.7%	18	9.6%	*
Heart Failure (n/%)	9	0.4%	5	0.7%		13	0.5%	1	0.5%	
Cardiovascular Meds (n/%)	737	34.5%	308	42.6%	***	955	35.8%	90	48.1%	**
Psychotropic Meds (n/%)	231	10.8%	105	14.5%	**	302	11.3%	34	18.2%	**
Fear of Falling with Activity Limitation (n/%)	86	4.0%	60	8.3%	***	129	4.8%	17	9.1%	*
Consensus OH (n/%)	154	7.2%	58	8%		191	7.2%	21	11.2%	*

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. This table has been published in my paper Duggan et al 2022, please see Appendix E.

Bivariate Visualisation

To examine the raw differences in BP response to standing between those with and without probable sarcopenia, before any statistical adjustment, the BP changes after standing were graphed. The unadjusted mean change in SBP and DBP, with 95% confidence interval, after standing grouped by 5CST and HGS probable sarcopenia criteria respectively are displayed in Figure 3-2 and Figure 3-3. On visual inspection, with overlap of the confidence intervals, there did not appear to be a significant difference between the 5CST group in either SBP or DBP. The HGS criteria group did however appeared to have a slower rate of recovery of both SBP and DBP and appeared to have a lower SBP from 20 to 40 s and DBP from 20 to 60 s after standing.

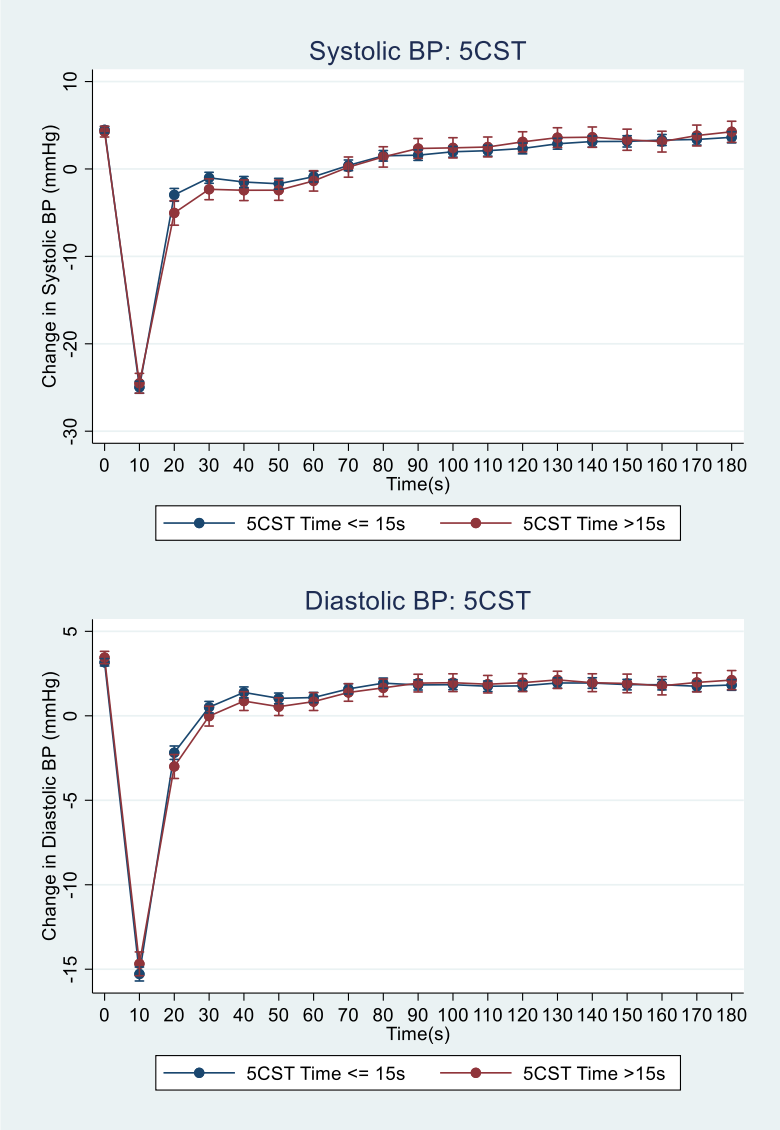

Figure 3-2: Mean change in systolic and diastolic blood pressure after standing grouped by 5 chair stands test (5CST) probable sarcopenia cut-off: 5CST time greater than 15 s.

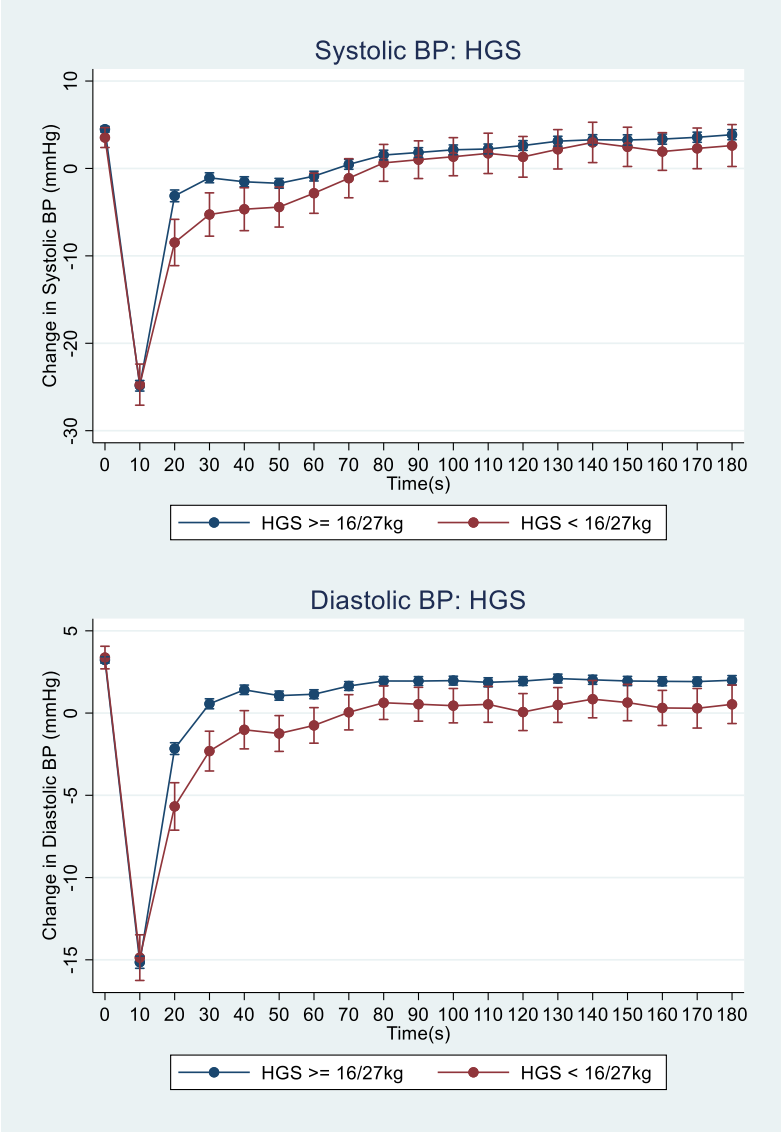

Figure 3-3: Mean change in systolic and diastolic blood pressure after standing grouped by hand grip strength (HGS) probable sarcopenia cut-offs: HGS less than 16kg (women), 27kg (men), with 95% confidence intervals.

Multivariable Analysis

Mixed-Effects Models

Mixed effects models with linear splines at time intervals at 0–10 s, 10–20 s, 20–30 s, 30–40 s and 40–180 s were used to investigate the relationship between 5CST- and HGS-defined probable sarcopenia, and SBP and DBP after standing, while controlling for potential confounders. The marginal predicted mean changes in SBP and DBP from baseline, from these models, stratified by those meeting 5CST and HGS probable sarcopenia criteria are shown in Figure 3-4 and Figure 3-5.

Table 3-2 shows the beta coefficients and 95% confidence intervals for the interaction terms of the 5CST- and HGS-defined probable sarcopenia variables with each of the five linear time splines. Examining first the 0–10 s period, the only statistically significant finding was the association of 5CST-defined probable sarcopenia with an attenuated rate of initial drop in SBP, illustrated by the positive coefficient at a time when SBP was falling. However, as apparent from the visualisation in Figure 3-4, the magnitude of the slope difference was small, and the confidence interval approached zero. Larger differences in slope were seen in the 10–20 s period where both 5CST- and HGS-defined probable sarcopenia were independently associated with an attenuated SBP and DBP recovery with a high degree of statistical certainty. The negative coefficient indicates a decrease in the rate of recovery at a time when the overall BP trend was upwards. Notably the effect size of HGS was twice that of 5CST. In the 20–30 s period of recovery 5CST- and HGS-defined probable sarcopenia groups had modestly steeper slopes of recovery compared to the non-sarcopenic groups as indicated by small positive coefficients at this time. This was similar for HGS in the 30–40 s time period. The 40–180 s time period shows small positive coefficients with a low degree of statistical certainty for the 5CST-defined probable sarcopenia group. However, the raw unadjusted visualisation in Figure 3-2 does not demonstrate such a trend.

When using contrast analysis to examine differences in predicted mean BP at key timepoints identified from the visualisation and model output: those meeting the HGS criteria had a significantly lower SBP and DBP at 20, 30 and 40 s compared to those who didn't: differences in SBP: -5.01mmHg, - 3.68mmHg, -2.32mmHg, $P < 0.05$ for all; differences in DBP: -2.68mmHg, - 1.96mmHg, -1.30 mmHg, $P < 0.05$ for all. Those meeting the 5CST criteria had a small significant difference in SBP at 20 s (-1.94mmHg, $P < 0.01$) but not at 30 s (-1.11mmHg, $P = 0.07$) or 40 s (-0.61mmHg, $P = 0.3$).

The full regression outputs from Stata are available in Appendix A:

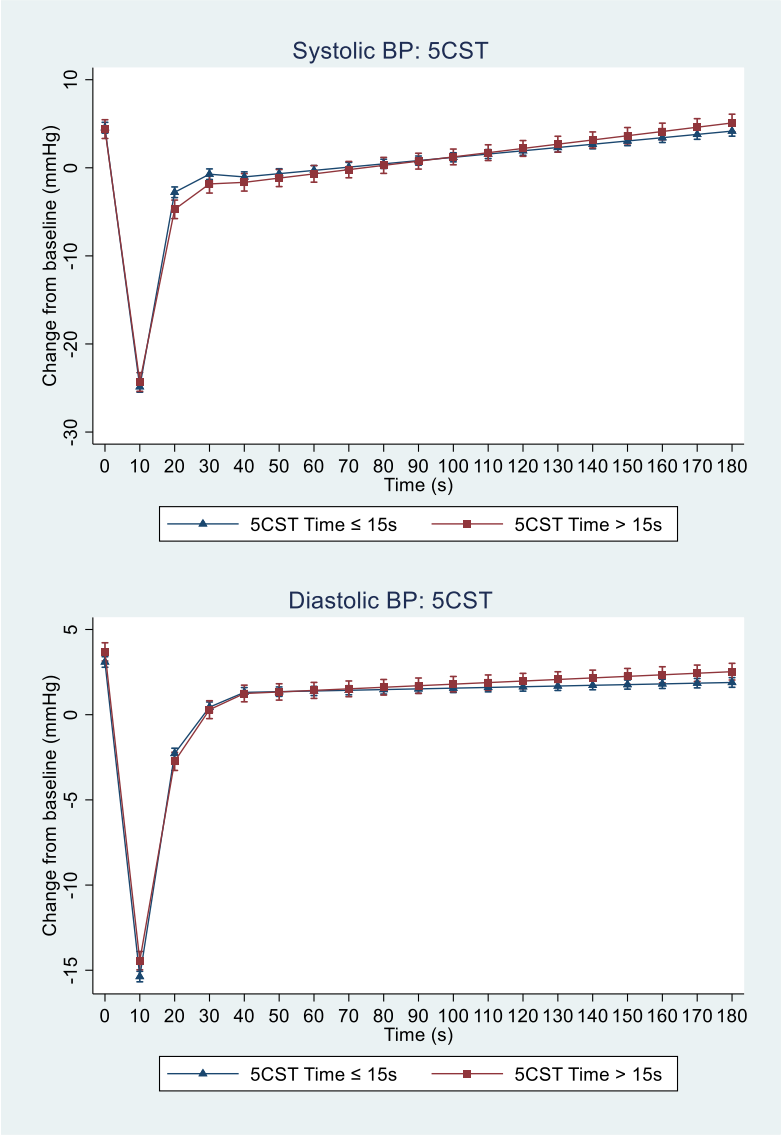

Figure 3-4: Predicted means and 95% confidence intervals, from mixed effect models, for systolic and diastolic blood pressure change (mmHg) after standing, stratified by probable sarcopenia status for 5 chair stands test (5CST) criteria (5CST > 15s). Model adjusted for age, sex, height, weight, hypertension, diabetes, heart failure, cardiovascular and psychotropic medications, and fear of falling with activity limitation. This figure has been published in my paper Duggan et al 2022, please see Appendix E.

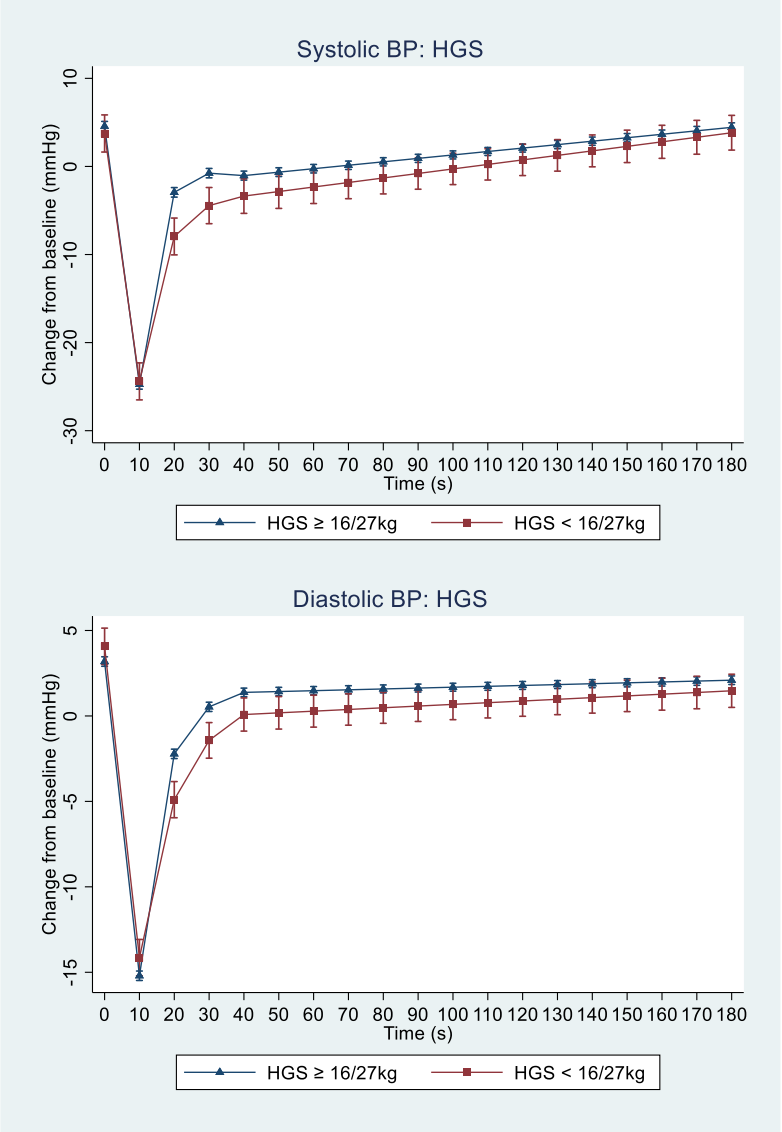

Figure 3-5: Predicted means and 95% confidence intervals, from mixed effect models, for systolic and diastolic blood pressure change (mmHg) after standing, stratified by probable sarcopenia status for hand grip strength (HGS) criteria (HGS < 16kg women / 27kg men). Model adjusted for age, sex, height, weight, hypertension, diabetes, heart failure, cardiovascular and psychotropic medications, and fear of falling with activity limitation. This figure has been published in my paper Duggan et al 2022, please see Appendix E.

Table 3-2: Coefficients and 95% confidence intervals for probable sarcopenia criteria (5 chair stands test (5CST) time > 15s, hand grip strength (HGS) < 16kg women / 27kg men) from mixed-effects models for change in systolic and diastolic blood pressure (mmHg) from baseline after standing at time intervals 0-10 s, 10-20 s, 20-30 s, 30-40 s and 40-180 s.

	0–10 s β (95% CI)	**10–20 s β (95% CI)**	**20–30 s β (95% CI)**	**30–40 s β (95% CI)**	**40–180 s β (95% CI)**
Systolic BP (mmHg)					
5CST-defined Probable Sarcopenia	0.07 (<0.01,0.14)*	-0.25 (-0.31,-0.18)***	0.08 (0.02,0.15)*	0.05 (-0.02,0.11)	0.01 (<0.01,0.02)**
HGS-defined Probable Sarcopenia	0.12 (<0.01,0.23)	-0.54 (-0.65,-0.42)***	0.13 (0.02,0.25)*	0.14 (0.02,0.25)*	0.01 (<0.01,0.02)
Diastolic BP (mmHg)					
5CST-defined Probable Sarcopenia	0.03 (<0.01,0.07)	-0.14 (-0.18,-0.10)***	0.03 (-0.01,0.07)	0.01 (-0.03,0.04)	<0.01 (<0.01,0.01)**
HGS-defined Probable Sarcopenia	0.02 (-0.05,0.08)	-0.37 (-0.44,-0.31)***	0.07 (0.01,0.14)*	0.07 (<0.01,0.13)*	<0.01 (<0.01,0.01)

Model adjusted for age, sex, height, weight, hypertension, diabetes, heart failure, cardiovascular and psychotropic medications, and fear of falling with activity limitation. * P < 0.05, ** P < 0.01, *** P < 0.001. This table has been published in my paper Duggan et al 2022, please see Appendix E.

Multivariable Logistic Regression

Next, to assess the relationship between probable sarcopenia and OH30, multivariable logistic regression models for the predication of OH30 by 5CST-defined and HGS-defined probably sarcopenia were utilised. The models were fully adjusted for confounders as before and results are shown in Table 3-3 and Table 3-4 respectively. 5CST-defined probable sarcopenia was not found to be an independent predictor of OH30 in this model. HGS-defined probable sarcopenia was an independent predictor of OH30 with age, height, and weight also significant in this model.

Table 3-3: Multivariable logistic regression for orthostatic hypotension at 30 s (OH30), for probable sarcopenia defined by 5 chair stands test (5CST) criteria (5CST > 15s).

OH30	Odds Ratio	P	95% Conf. Interval	
5CST-defined Probable Sarcopenia	0.93	0.584	0.72	1.21
Age	1.05	0.000	1.04	1.07
Female	1.17	0.379	0.83	1.65
Height	1.03	0.006	1.01	1.05
Weight	0.98	0.001	0.97	0.99
Hypertension	1.34	0.094	0.95	1.88
Diabetes	1.51	0.054	0.99	2.30
Heart Failure	1.87	0.306	0.56	6.21
Cardiovascular Meds	1.21	0.281	0.85	1.72
Psychotropic Meds	1.31	0.107	0.94	1.82
Fear of Falling with Activity Limitation	0.65	0.19	0.37	1.14

Table 3-4: Multivariable logistic regression for orthostatic hypotension at 30 s (OH30), for probable sarcopenia defined by hand grip strength (HGS) criteria (< 16kg women / 27kg men).

OH30	Odds Ratio	P	95% Conf. Interval	
HGS-defined Probable Sarcopenia	1.64	0.012	1.11	2.42
Age	1.05	0.000	1.03	1.06
Female	1.23	0.247	0.87	1.74
Height	1.03	0.003	1.01	1.05
Weight	0.98	0.001	0.97	0.99
Hypertension	1.34	0.092	0.95	1.88
Diabetes	1.49	0.063	0.98	2.27
Heart Failure	1.88	0.304	0.56	6.29
Cardiovascular Meds	1.22	0.272	0.86	1.72
Psychotropic Meds	1.28	0.140	0.92	1.78
Fear of Falling with Activity Limitation	0.63	0.106	0.36	1.10

This table has been published in my paper Duggan et al 2022, please see Appendix E.

Longitudinal Follow-Up

To examine the association between probable sarcopenia, OH30 and recurrent falls over longitudinal follow-up, data from TILDA Waves 1–6, a 12-year period was examined. Using Wave 1 as a baseline, those who had HGS-defined probable sarcopenia and OH30 were grouped into a four-level variable (see Chapter 2 – Methods for further details). Of note 5CST was not performed at Wave 1. The number of falls experienced by a participant from TILDA Waves 2–6 was calculated and those with more than 1 fall were defined as a recurrent faller. Logistic regression was used to identify the prediction of recurrent falls by HGS-defined probable sarcopenia and/or OH30 over a follow up. Data was available for 4,448 participants, mean age 61.7 years SD 8.3 years, 53.9 (n = 2,397) women. In a bivariate analysis those with either OH30 or HGS-defined probable sarcopenia were more likely have recurrent falls, with those with both conditions having the highest odds ratio for recurrent falls (Table 3-5). When controlled for age, sex and educational attainment this relationship held (Table 3-6). However, when visual acuity and psychotropic medication use were added to the model (Table 3-7) the HGS-defined probable sarcopenia and OH30 group was no longer statistically significant.

Table 3-5: Bivariate logistic regression for recurrent falls between Waves 2–6 for orthostatic hypotension at 30 s (OH30) and/or for probable sarcopenia defined by hand grip strength (HGS) criteria (< 16kg women / 27kg men).

Recurrent Falls	Odds ratio	P	95% Conf. interval	
No Probable Sarcopenia or OH30				
OH30, No Probable Sarcopenia	1.36	0.001	1.14	1.62
Probable Sarcopenia, No OH30	1.51	0.000	1.23	1.84
Probable Sarcopenia & OH30	1.88	0.000	1.36	2.61

Table 3-6: Multivariable logistic regression for recurrent falls between Waves 2–6 for orthostatic hypotension at 30 s (OH30) and/or for probable sarcopenia defined by hand grip strength (HGS) criteria (< 16kg women / 27kg men), controlled for basic confounders.

Recurrent Falls	Odds ratio	P	95% Conf. interval	
No Probable Sarcopenia or OH30				
OH30, No Probable Sarcopenia	1.19	0.061	0.99	1.43
Probable Sarcopenia, No OH30	1.30	0.011	1.06	1.60
Probable Sarcopenia & OH30	1.44	0.035	1.03	2.01
Age	1.03	0.000	1.02	1.03
Female	1.38	0.000	1.22	1.57
Education				
Secondary	0.87	0.115	0.73	1.03
Third/higher	1.01	0.920	0.85	1.20

Table 3-7: Multivariable logistic regression for recurrent falls between Waves 2–6 for orthostatic hypotension at 30 s (OH30) and/or for probable sarcopenia defined by hand grip strength (HGS) criteria (< 16kg women / 27kg men), controlled for further confounders.

Recurrent Falls	Odds ratio	P	95% Conf. interval	
No Probable Sarcopenia or OH30				
OH30, No Probable Sarcopenia	1.17	0.096	0.97	1.40
Probable Sarcopenia, No OH30	1.28	0.018	1.04	1.58
Probable Sarcopenia & OH30	1.36	0.078	0.97	1.92
Age	1.03	0.000	1.02	1.04
Female	1.36	0.000	1.19	1.55
Education				
Secondary	0.89	0.186	0.75	1.06
Third/higher	1.04	0.683	0.87	1.24
Visual Acuity	0.68	0.040	0.47	0.98
Psychotropic Meds	1.93	0.000	1.56	2.39

Discussion

Main Findings and Strengths

In this study I aimed to investigate the relationship between probable sarcopenia and orthostatic BP recovery and maintenance in a large, population-based sample from TILDA. The main finding was that probable sarcopenia was associated with a significantly attenuated BP recovery from nadir after standing. HGS-defined probable sarcopenia had an effect twice as strong as that of 5CST-defined probable sarcopenia. Those with HGS-defined probable sarcopenia had significantly lower SBP and DBP at 20, 30 and 40 s after standing, and HGS-defined probable sarcopenia was an independent predictor of OH30. The longitudinal examination of participations with HGS-defined probable sarcopenia and OH30, from Wave 1 to Wave 6 of TILDA show that this group is at a higher risk of recurrent falls.

This is the first study to examine the association between probable sarcopenia and orthostatic haemodynamics with continuous beat-to-beat BP measurements allowing precise characterisation of BP phenotype. The results are further strengthened by a large

and well characterised sample allowing adjustment for potential confounders, and longitudinal follow-up over 12 years.

Upper Limb vs Lower Limb Measures

These results point to possible subtle differences in the underlying pathophysiology of the effects of probable sarcopenia on BP recovery after standing and are interesting in that the upper limb measures of probable sarcopenia seemed to predict orthostatic haemodynamics better than lower limb measures. This is somewhat surprising as *a priori* one might expect the lower limb to have a greater effect on BP, via the SMP, than the upper limb. There are two main possibilities for this result. The upper limbs may be more important in terms of the SMP than the lower limbs, or 5CST may not be as good a measure of lower limb muscle strength. Indeed, others have raised the fact that 5CST tests not only strength but balance, proprioception, mobility and endurance [351]. To the best of my knowledge there is no literature examining the relative contributions of the upper and lower limbs to the SMP in orthostatic BP recovery. Given that HGS correlates better with muscle mass than 5CST time [352,353], it may be a better proxy for lower limb strength and correlate better with orthostatic BP recovery.

The Initial Drop in BP

Probable sarcopenia as defined by 5CST criteria had a weak but positive association with SBP in the initial 10 s period. However, as SBP was dropping at this time, this positive association means that those meeting the 5CST criteria had a less steep fall in their SBP after standing. This differs from findings by Mol et al [276] who found that the rate of SBP decline but not the magnitude was associated with 5CST time. However, there were significant differences in methodology: Mol et al used 5-second averaging of BP and examined the first 15 s period whereas this study used 10-second averaging and looked at the first 10 s period, which may account for the differences. Furthermore, the mechanisms behind the initial drop in BP are not fully elucidated [354] and recent evidence has found better outcomes in those with initial OH [181,186], suggesting that a larger initial drop is physiological rather than pathological.

BP Recovery from Nadir

What is clearer however is the importance of BP recovery from nadir [213,355]. The strongest and most consistent associations in the present study were found in the BP recovery phase. Both 5CST- and HGS-defined probable sarcopenia were negatively associated with SBP and DBP recovery in the 10–20 s phase, with a high degree of

statistical significance. This means that those with probable sarcopenia had a slower rate of BP recovery. The strength of the effect for HGS was more than twice that of 5CST. Furthermore, those with HGS-defined probable sarcopenia had significantly lower SBP and DBP at 20, 30 and 40 s. Lower SBP recovery at 30 s has been found previously to be associated with a greater proportion of orthostatic intolerance symptoms [356]. The reduced BP recovery in those with HGS-defined probable sarcopenia could increase the risk of falls with resultant risk of fracture [218] and subsequent morbidity and mortality [357]. The results also fit with a conceptual model of the SMP which aids BP recovery and maintenance [350].

The majority of existing studies that investigated HGS and OH [200,263,264,268,273] used oscillometric BP and therefore they were unable to consider the BP recovery phase. Romero-Ortuno et al [274] assessed the relationship between frailty and OH with continuous BP and did not find a difference in HGS in those with delayed BP recovery, however they used a morphological clustering approach rather than a strict OH definition and had a smaller sample (n= 442). In terms of 5CST and BP recovery, Mol et al [278] found, using continuous BP measurement, that slower DBP recovery in the 15–30 and 30–60 s periods post stand, but not SBP recovery, was associated with longer 5CST time in older adults after adjustment for relevant confounders.

In the 20–30 s and 30–40 s phases, those with HGS-defined probable sarcopenia had a small but significant positive association with SBP and DBP, suggesting faster BP recovery during these phases. However, given that those participants had, on average, entered those time periods with a lower BP, it is physiologically plausible that their rate of recovery would be greater during these phases.

Steady-State Post Recovery

In the steady state period, post recovery (40–180 s), probable sarcopenia had little (5CST) or no (HGS) association with SBP or DBP. Studies looking at classically measured (oscillometric) OH at 3 minutes have found it to be associated with weak HGS [268,273] and confirmed sarcopenia [263], they however adjusted for limited confounders, and recruited in outpatient [263,273] or hospital inpatient [268] setting, where the demographics and prevalence of OH, sarcopenia and severe sarcopenia may be different. Soysal et al [200] did not find a significant relationship between OH at 3 minutes and either probable or confirmed sarcopenia. As regards those studies using beat-to-beat BP, Mol et al [278] did not find an independent association between 5CST time and SBP or

DBP from 60–180 s. Meanwhile, de Bruïne et al [267] found that participants with the worst performance on the 5CST had significantly higher odds of OH between 15–180 s compared to those with the best or intermediate performance. The discrepant findings in the published literature may have much to do with the heterogeneity in the methods used and the definitions employed.

Longitudinal Follow-Up

Over longitudinal follow-up from a baseline at TILDA Wave 1 to a maximum of Wave 6 (12 years), those with both HGS-defined probable sarcopenia and OH30 has a significantly increased odds of recurrent falls compared to those with one disorder or none. This suggests that OH30 mediated by probable sarcopenia may be an independent risk factor for falls. This relationship held after for controlling for potential confounders of age, sex and educational status. However, when visual acuity and psychotropic medications, other risk factors for falls, the probable sarcopenia-OH30 group was no longer significant. This suggests other risk factors may be stronger in their relationship with falls. There may also be mediation effects as psychotropic medication use is related to both sarcopenia [358] and OH [205].

Clinical Importance of Results

The results of the present study are important as they highlight that probable sarcopenia is a potentially modifiable risk factor for OH. They add to the importance of assessing probable sarcopenia; in addition to its well-known direct risk of falls and adverse outcomes [138], a second pathway is emerging, namely the effects of sarcopenia on the SMP with attendant risk of delayed BP recovery from standing and overt OH, adding further to falls risk. The recently published World Falls Guidelines [359] advise consideration of muscle strength assessment with 5CST or HGS as part of a multifactorial falls assessment but do not include it as a graded recommendation in their guidelines from the working groups, nor do they recommend the diagnosis or treatment of probable sarcopenia as routine in their falls work-up. The results from the current study suggest that given its direct risk of falls, and the OH-mediated falls pathway, research is needed on the role of identifying probable sarcopenia and sarcopenia in falls risk assessment clinics, and subsequently on the efficacy of interventions to ameliorate sarcopenia.

Effect Size

It must be stated however that the size of the effects reported have been modest. This is in keeping with the likely relatively small contribution of the SMP (vis-à-vis the main cardiac

pump) to BP regulation on standing. Although to the best of my knowledge there exist no published quantitative data on the exact numerical contribution of the SMP to orthostatic BP, a study looking at muscle pumping manoeuvres (tip-toeing), in healthy subjects, found an average increase of 17± 9 mmHg SBP [251]. It is likely that the BP rise from quiet standing is significantly less than this and closer to the non-significant 4±7 mmHg found with leg crossing in the study. Indeed, baroreflex mediated HR increases and splanchnic vasoconstriction likely contribute to the bulk of BP recovery and maintenance during quiet standing [350].

Limitations

There are a number of limitations to this study which must be considered. Most significantly, as no measure of muscle mass was obtained in the TILDA study, it was not possible to differentiate between participants with probable and confirmed sarcopenia. Therefore, there is the possibility that weak HGS reflected pathological processes other than sarcopenia such as rheumatological or neurological causes. However, this is tempered by the fact that in clinical practice HGS assessment is significantly easier to implement than direct measurement of muscle mass with DXA or BIA, perhaps therefore making the results more generalisable. This was also an observational study and unmeasured confounding remains a possibility although every effort was taken to minimise this. Diseases and medications were self-reported and therefore subject to recall bias. In addition, while beat-to-beat BP measurement is the state of the art in terms of assessment of orthostatic BP response, there do exist limitations and challenges with its employment. Previous research has shown low to moderate intra-person reliability of absolute measures, however not on relative measures of changes from baseline [360] as were used in the current study. Furthermore, patterns of haemodynamic response to standing have been found to vary over time [361]. Factors such as hydration status, meal timing and caffeine intake can affect results [223], none of which it was possible to control for. Co-morbidities and medications can also influence BP response and were controlled for in the current study, although not the timing of medications in relation to testing.

Finally, a significant number of the participants did not undergo or did not have data available for the active stand test. The reasons are detailed in Figure 3-1 however for the majority it was not possible to ascertain the reason. There were also missing data on the 5CST and HGS tests. Analysis of these participants show that they were older, higher proportion of females, lower levels of tertiary education as well as higher rates of

hypertension, diabetes, cardiovascular and psychotropic medications and fear of falling with activity limitation. It is known that frailty is associated with missing data in longitudinal studies [362] and indeed the higher proportion of those fitting the criteria for probable sarcopenia by HGS criteria in the excluded group agree with this. The exclusion of those participants with missing data may have reduced population representativeness and also reduced the size of the effect seen in the relationship between probable sarcopenia and OH.

Conclusion

In summary, probable sarcopenia had a significant association with delayed BP recovery, with HGS-defined probable sarcopenia having a greater effect than 5CST-defined probable sarcopenia. HGS-defined probable sarcopenia was also an independent predictor of OH30. Those with HGS-defined probable sarcopenia and OH30 had a significantly increased odds of recurrent falls over longitudinal follow-up.

Chapter 4 –Study II-A

Published Works List

This chapter is based on my previously published paper: Duggan, E., Knight, S. P., & Romero-Ortuno, R. (2023). Relationship between sarcopenia and orthostatic blood pressure recovery in older falls clinic attendees. European Geriatric Medicine, 14, 439–446. https://doi.org/10.1007/s41999-023-00775-0

Figure 4-2, Figure 4-3, Table 4-1 and Table 4-2 from this chapter were published in the above paper

Introduction

In the previous chapter, probable sarcopenia, especially that defined by the HGS criteria was associated with an impaired recovery of BP in the early stages after standing. In general, delayed BP recovery on standing has previously been under-recognised in comparison to the classic syndrome of OH, and is now emerging as an important driver of falls and adverse clinical outcomes in older adults [363,213,218]. Whereas previously OH was defined in terms of a sustained drop in BP (≥20 mmHg systolic and/or ≥10 mmHg diastolic) at 3 minutes after standing, the prevalence of delayed BP recovery has been identified through the use of beat-to-beat orthostatic BP measurement in a number of population cohort studies [181,186].

Sarcopenia has emerged as one of the major age-associated health challenges of the 21st century [325]. Accumulating evidence suggests that sarcopenia is one of the central pathological processes driving physical frailty [109] and it is implicated in a wide range of adverse health outcomes in older adults [134,135]. Additionally, sarcopenia is associated with cardiovascular diseases including coronary artery disease, atrial fibrillation, and heart failure [364,365].

As discussed earlier, there may be reason to suspect a pathophysiological link between sarcopenia and both delayed BP recovery and OH, given the role of the SMP in BP recovery and maintenance. The SMP is thought to aid venous return to the heart during exercise and standing, via rhythmic activity of the muscles of the lower limbs [350]. Loss of muscle strength and mass in sarcopenia could affect SMP function, leading to slower BP recovery and OH. This could then lead to falls, fractures, increased morbidity and even subsequent mortality. The clinical importance here is that unlike many other causes of OH, sarcopenia is potentially preventable and/or reversible through physical exercise and nutrition interventions [366].

Two previous studies found significant association between sarcopenia and OH measured with intermittent oscillometric devices [200,263]; however, the relationship between sarcopenia and beat-to-beat orthostatic BP recovery is less well known. Given the limitations of Study I in only being able to consider probable sarcopenia, I went on to investigate confirmed sarcopenia. I recruited a clinical sample from new attendees to the Falls and Syncope Unit at St James's Hospital, Dublin. Participants underwent an active stand test with beat-to-beat BP monitoring as per usual care in the clinic. I assessed muscle strength by HGS and 5CST, and measured muscle mass with BIA. The EWGSOP criteria

were used to classify participants into robust, probable sarcopenia and sarcopenia groups. Mixed-effects models with piecewise linear splines were used, as in Study I, to investigate the BP response to standing while controlling for potential confounders and the effect of HR.

Results

Participants

Over the recruitment period, 123 patients consented to participate in the study. As outlined in Figure 4-1, 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.

Those excluded were more likely to meet OH30 criteria (66.7% vs 31.2%, P < 0.05) and have polypharmacy (78.6% vs 48.6%, P < 0.05). There were no statistically significant differences in: mean age (73.5 years vs 70.1years, P = 0.251), sex (35.7% female vs 57.8, P = 0.18), sarcopenia prevalence (18.2% vs 14.7%, P = 0.559), physical frailty as per SHARE-FI (21.4% vs 15.6%, P = 0.578), hypertension (28.6% vs 48.6%, P), diabetes (28.6% vs 14.7%, P = 0.185), cardiovascular medications (64.3% vs 50.5%, P = 0.330) or psychotropic medications (50.0% vs 33.0%, P = 0.210).

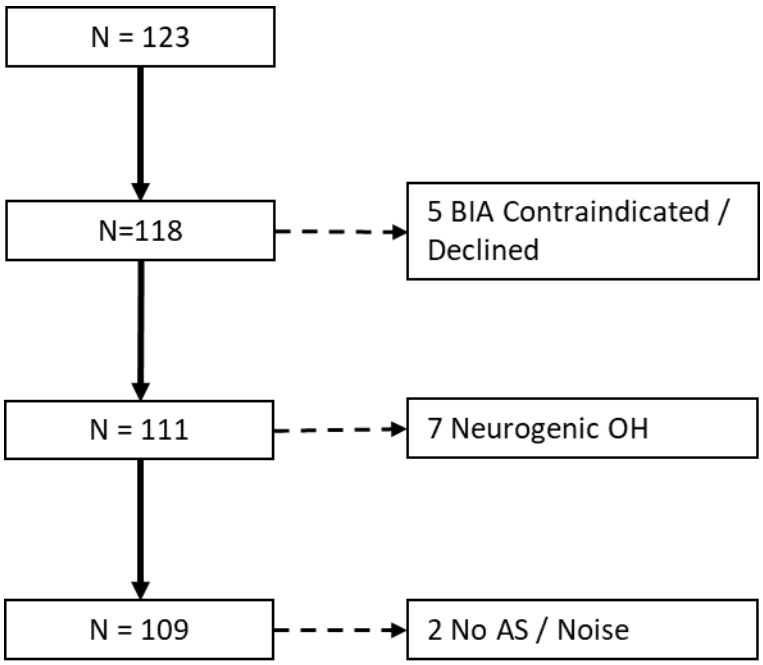

Figure 4-1: Flowchart of participants. BIA: bioelectrical impedance analysis; OH: orthostatic hypotension; AS: active stand.

General Demographics of the Sample

Overall, of the 109 included participants, the mean age of the included sample was 70.0 years (SD 10.5, range 50 to 93), and 57.8% (n = 63) were women. The median body mass index was 25.8 kg/m^2 (IQR 4.9 kg/m^2), with median max HGS 24.0 kg (IQR 13.0 kg), median 5CST time 13.5 s (IQR 6.6 s) and median ASMM as per Sergi equation 18.5 kg (IQR 6.6 kg). The median number of chronic diseases per participant was 3 (IQR 2), median number of medications was 4 (IQR 4). The prevalence of physical frailty, as per SHARE-FI was 15.6% (n = 17), 5.9% (n = 6) were malnourished as per the MNA-SF, 10.2% (n = 11) were current smokers overall and 16.5% (n= 18) exceeded the recommend weekly maximum intake of alcohol. In terms of falls, 54.1% (n = 59) had experienced a fall in the last year and 19.3% (n = 21) had recurrent falls in the last year. The prevalence of consensus OH was 5.9% (n = 6).

Demographics by Sarcopenia Status

The demographics of the sample were examined in relation to sarcopenia status: robust, probable sarcopenia and sarcopenia (Table 4-1). Sarcopenia status was statistically treated as an ordinal variable and trends in continuous variables were tested with Kendall's rank correlation coefficient and trends in dichotomous variable with Chi-square for trend. Statistically significant trends across sarcopenia status were identified for increasing age and presence of multimorbidity, physical frailty, polypharmacy, psychotropic medications, and increasing 5CST. Max HGS and ASMM significantly decreased as sarcopenia status increased. The differences in sex, BMI, prevalence of OH30, hypertension, diabetes and cardiovascular medication use across sarcopenia status did not meet statistical significance.

Table 4-1: Characteristics of the sample grouped by sarcopenia status.

	Robust (58 / 53.2%)	Probable Sarcopenia (35 / 32.1%)	Sarcopenia (16 / 14.7%)	P
Age (years) (mean/SD)	66.1 (9.8)	73.8 (8.8)	76.0 (11.2)	<0.001
Female (n / %)	30 (51.7)	24 (68.6)	9 (56.3)	0.383
BMI (kg/m²) (median/ IQR)	25.5 (4.8)	27.8 (4.3)	23.0 (5.8)	0.502
5CST (s) (median/ IQR)	12.0 (2.8)	19.7 (6.2)	18.7 (11.1)	<0.001
HGS (kg) (median/ IQR)	29.0 (14.0)	20.0 (11.0)	16.5 (9.0)	<0.001
ASMM (kg) (median/ IQR)	19.2 (6.9)	18.6 (6.5)	14.5 (6.3)	0.034
Frail (n / %)	1 (1.7)	10 (28.6)	6 (37.5)	<0.001
Multimorbidity (n / %)	41 (70.7)	31 (88.6)	15 (93.8)	0.014
Polypharmacy (n / %)	21 (36.2)	21 (60.0)	11 (68.8)	0.006
Hypertension (n / %)	26 (44.8)	18 (51.4)	9 (56.3)	0.368
Diabetes (n / %)	8 (13.8)	7 (20.0)	1 (6.3)	0.756
Cardiovascular Meds (n/%)	29 (50.0)	16 (45.7)	10 (62.5)	0.564
Psychotropic Meds (n / %)	11 (19.0)	18 (51.4)	7 (43.8)	0.006
OH30 (n / %)	14 (24.1)	13 (37.1)	7 (43.8)	0.083

BMI: body mass index; 5CST: five chair stands test; HGS: hand grip strength; ASMM: appendicular skeletal muscle mass; OH30: orthostatic hypotension at 30 s after standing; Meds: medications; SD: standard deviation; n: number; IQR: interquartile range. This table has been published in my paper Duggan et al 2023, please see Appendix E.

Bivariate Visualisation

To gain insight into the overall changes in BP and HR after standing, before complex statistical modelling was performed, the raw unadjusted mean changes at 10-second intervals from 0 to 180 s were graphed. Those raw data-based mean changes in SBP, DBP and HR after standing, grouped by sarcopenia status, are displayed in Figure 4-2. Visually, the probable sarcopenia and sarcopenia groups appeared to have slower recoveries from the SBP nadir, especially in the 10–20 s period. In the steady state period from 60–180 s there did not appear to be significant differences between the groups. In terms of DBP, in the 10–20 s period the sarcopenia group continued to fall while the probable sarcopenia and robust group had begun to recover. The HR response in the initial 0–10 s appeared

less pronounced in the sarcopenia and probable sarcopenia groups compared with the robust, and the recovery from peak in the 10–20 s period for those groups also appeared slower. In the 60–180 s period the HR for the sarcopenia group appeared to be lower on average than the other two groups.

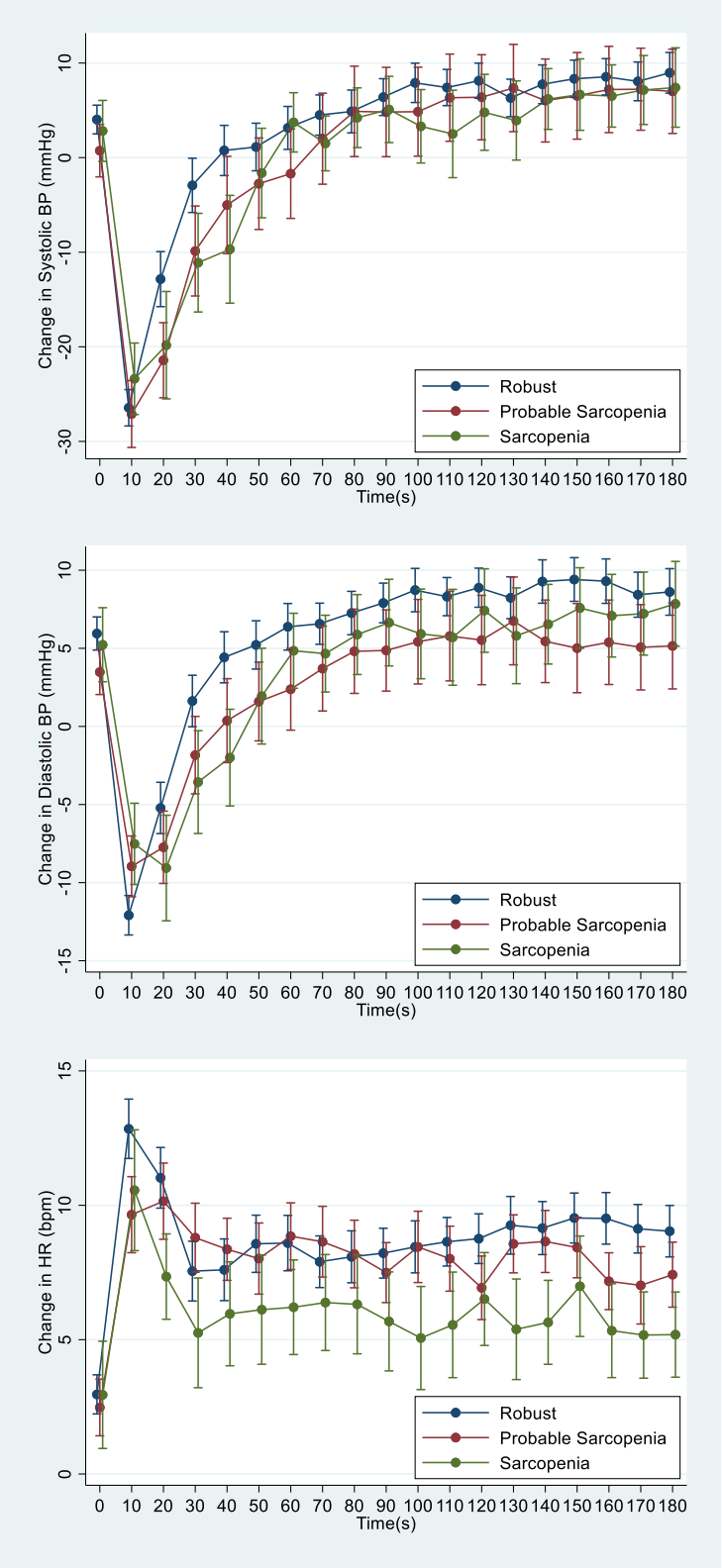

Figure 4-2: Mean change in systolic blood pressure, diastolic blood pressure (mmHg) and heart rate (beats per minute – bpm) after standing grouped by sarcopenia status. Unadjusted. Error bars: standard error of the mean. This figure has been published in my paper Duggan et al 2023, please see Appendix E.

Multivariable Analysis

To investigate the relationship between sarcopenia status and BP after standing, while controlling for confounders, as in Study I, mixed-effects models with linear splines at time intervals 0–10 s, 10–20 s, 20–30 s, 30–40 s, 40–180 s were employed. Given the potential differences in HR between the groups, in an attempt to control for the effects of the *cardiac pump*, HR was entered as an interaction term across each of the splines. The β coefficients and CI for each of the five time intervals from the mixed-effects models are presented in Table 4-2. To aid interpretation, the predicted marginal means for change from baseline in SBP and DBP, grouped by sarcopenia status, are shown in Figure 4-3.

In the initial 0–10 s period, there was a reduced rate of initial drop in DBP for the probable sarcopenia and sarcopenia group, as evidenced by the significant moderate positive coefficients at a time when the overall BP trend was downwards. There was significantly attenuated recovery of both SBP and DBP during the 10-20 s period post standing for both the probable sarcopenia and sarcopenia groups when compared to the robust group, demonstrated by the negative coefficients during a period where the overall BP trend was positive. For both SBP and DBP, the sarcopenia group had a more attenuated recovery than the probable sarcopenia group. In the 20–30 s, 30–40 s and 40–180 s periods, no significant difference in the slope of recovery / change in SBP or DBP was seen.

Examining the predicted change in SBP from baseline at the 30 s timepoint post standing, from the model: for the robust group it was -3.38 mmHg (95% CI -8.39, 1.62); probable sarcopenia group -6.85mmHg (95% CI -13.28, -0.41); and sarcopenia group -6.30 mmHg (95% CI -15.62, 3.03). Contrast analysis between the sarcopenia and robust groups showed the difference -2.91 mmHg, was not statistically significant, P = 0.597. At 180 s the predicted means were 8.45 mmHg (95% CI 3.51, 13.38), 10.08 mmHg (95% CI 3.75, 16.42) and 11.34 mmHg (95% CI 2.16, 20.51) for robust, probable sarcopenia and sarcopenia groups respectively. The 2.89 mmHg difference between the sarcopenia and robust groups was not statistically significant when tested with contrast analysis, P = 0.594.

The full mixed-effects regression models' outputs are included in Appendix B:

Table 4-2: Beta-coefficients and 95% confidence intervals for the effect of sarcopenia status on the change in systolic and diastolic blood pressure (mmHg) from baseline at time intervals 0-10 s, 10-20 s, 20-30 s, 30-40 s and 40-180 s after standing.

	0-10 s β (95% CI)	**10-20 s β (95% CI)**	**20-30 s β (95% CI)**	**30-40 s β (95% CI)**	**40-180 s β (95% CI)**
Systolic BP					
Probable Sarcopenia	0.10 (-0.28,0.48)	-0.59 (-0.97, -0.21)**	0.20 (-0.18, 0.58)	0.13 (-0.24, 0.51)	0.03 (-0.03, 0.08)
Sarcopenia	0.32 (-0.18, 0.83)	-0.85 (-1.35, -0.34)**	-0.07 (-0.57, 0.44)	-0.15 (-0.64, 0.35)	0.05 (-0.02, 0.13)
Diastolic BP					
Probable Sarcopenia	0.48 (0.26, 0.71)***	-0.45 (-0.68, -0.23)***	-0.15 (-0.37, 0.07)	-0.04 (-0.26, 0.18)	0.01 (-0.02, 0.04)
Sarcopenia	0.49 (0.20, 0.78)**	-0.65 (-0.95, -0.36)***	-0.16 (-0.45, 0.14)	-0.10 (-0.39, 0.19)	0.04 (< -0.01, 0.08)

Models were adjusted for age, sex, diabetes, hypertension, cardiovascular and psychotropic medications, and heart rate. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. This table has been published in my paper Duggan et al 2023, please see Appendix E.

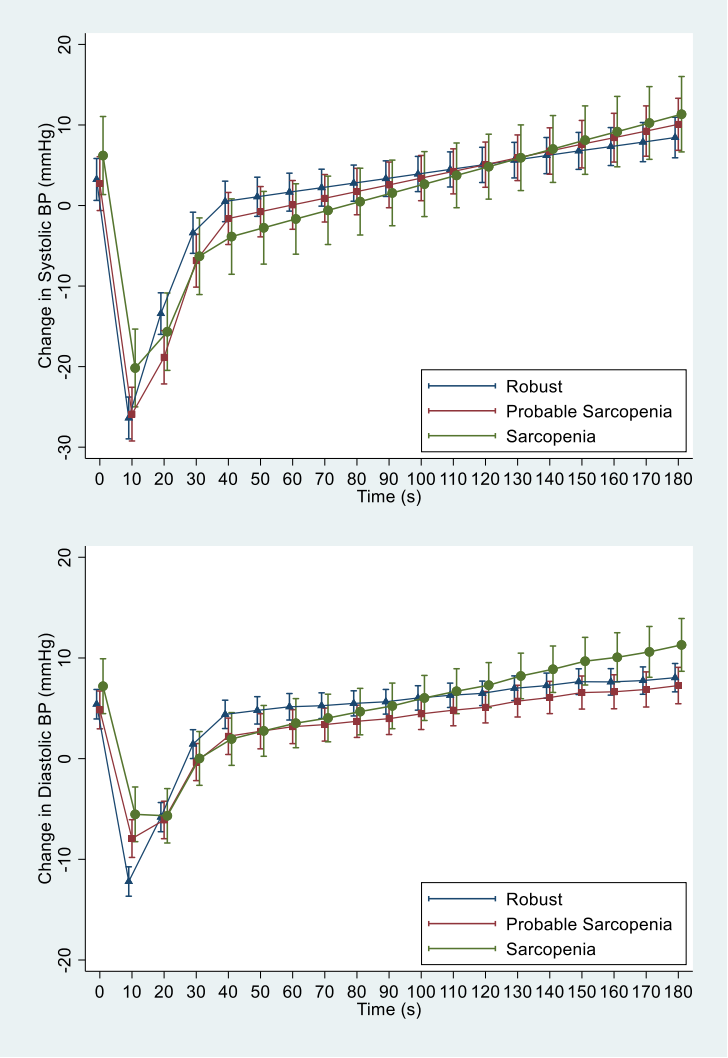

Figure 4-3: Predicted means and standard error of the mean from mixed effects models for change in systolic and diastolic blood pressure (mmHg) after standing, grouped by sarcopenia status. Models were adjusted for age, sex, diabetes, hypertension, cardiovascular and psychotropic medications, and heart rate. This figure has been published in my paper Duggan et al 2023, please see Appendix E.

Discussion

Key Findings and Strengths

This study sought to confirm the findings of Study I for the association between probable sarcopenia and BP recovery from standing, and to investigate whether BIA confirmed sarcopenia was associated with BP recovery. It was observed that both probable sarcopenia and sarcopenia were associated with an attenuated rate of recovery of both SBP and DBP in the 10–20 s period after standing, with a larger attenuation for the sarcopenia group compared to the probable sarcopenia group. These effects were independent of age, sex, diabetes, hypertension, cardiovascular and psychotropic medications, and HR response, supporting the hypothesis that they may represent the effect of the SMP of the lower limbs in supporting early post-standing haemodynamic stabilisation.

The results were strengthened by the comprehensive characterisation of participants allowing robust statistical control for potential confounding, the use of continuous beat-to-beat BP measurements allowing detailed analysis of the BP response to standing and the use of the consensus EWGSOP2 guidelines for sarcopenia.

The Initial Drop in BP

In this study, an attenuated fall in DBP in the initial 10 s after standing was found for the probable sarcopenia and sarcopenia groups compared to the robust group, as demonstrated by the significant positive β coefficients during a time when the overall BP was falling. It has been argued that the initial drop in BP on active standing, which is not seen on passive tilting [172], may be more physiological than pathological and mostly related to the speed of standing [164]. As applied to the current results, this is plausible as those with sarcopenia would be expected to have a lower standing speed with a slower initial fall in BP and a less pronounced nadir.

BP Recovery from Nadir

As in Study I, the strongest and most consistent findings in this study were in the 10–20 s period after standing with the relatively large negative beta-coefficients indicating a slower rate of SBP and DBP recovery in this period, with a high degree of statistical certainty. Indeed, as is apparent from Figure 4-3 the sarcopenia group on average continues to fall in DBP while the other 2 groups have begun to recover. This slower recovery could expose individuals to an increased risk of cerebral hypoperfusion and increase orthostatic intolerance [356]. Few studies have examined continuous BP recovery and muscle measures, however in agreement with my findings Mol et al [278] found DBP recovery, as

measured with beat-to-beat BP, in the 15–30 s and 30–60 s periods post-standing was associated with worse 5CST performance. De Bruine et al [267] found that participants with the worst performance on 5CST, compared to intermediate and best groups, had significantly higher odds of OH measured with beat-to-beat BP. However, neither study measured muscle mass to determine sarcopenia.

Steady-State Post Recovery

The current study found no significant differences between the groups in the 40–180 s time period. This fits with the low rate of consensus OH, which is not surprising given that those with presumed or confirmed neurogenic OH were excluded from the study. Similar to the current study Kobayashi and Yamada [269] did not find a significant difference in HGS and leg extensor strength between those with and without OH measured continuously; however, they used the head-up tilt test, which would be expected to reduce the role of the SMP compared to active standing. In contrast, a number of studies have found a higher prevalence of oscillometric-determined OH in older participants with sarcopenia when measured lying and standing [263,264], and using a head-up tilt test [200]. Benton et al. [279] found greater drops in BP measured oscillometrically on standing, in a low muscle mass group compared to a normal muscle mass group, both before and after overnight fast. Chen et al [268] found significantly increased odds of OH with auscultatory BP measurements for those with weak HGS, while Roca et al [273] reported similar results with oscillometric measurement of BP. Differences in sample characteristics may explain some of the results — the current sample had relatively low rates of sarcopenia (14.7%) and physical frailty (15.6%) compared to 42.2% with severe sarcopenia in the study by Soysal et al [200]. Higher prevalence and more severe sarcopenia may lead to larger deficits in BP recovery and maintenance than were seen in the current study. The consensus OH definition used in the current study accounted for hypertension which is not consistently applied and may partly explain the lower rate of OH in the study compared to expected prevalence of up to 30% [367].

Clinical Importance

These results extend Study I and to the best of my knowledge, show for the first time an association between confirmed sarcopenia and delayed BP recovery using continuous non-invasive orthostatic haemodynamic measurements. The findings are clinically important as even in the absence of OH at 30 s, delayed BP recovery in the early post-standing phase

could contribute to reduced cerebral perfusion and increase the risk of falls and syncope [213,278,354], which in turn can lead to fractures, hospital admissions, loss of functional independence, and risk of institutionalisation [218,368]. Although sarcopenia can directly lead to falls [21], the current results suggest the existence of an indirect mechanism whereby sarcopenia could also contribute to falls by impairing early post-standing BP recovery. The importance here is that sarcopenia is a potentially reversible risk factor. Recent evidence from the SPRINTT trial found that a multicomponent intervention could reduce sarcopenia and mobility disability in older adults [123]. Similar interventions could target lower limb strength to optimise the SMP and BP recovery, reducing the risk of falls where sarcopenia-mediated impaired orthostatic BP recovery is a contributory factor.

Potential Mechanisms

Despite the theory of its existence being nearly 100 years old [289], the SMP remains understudied and its precise contribution to orthostatic haemodynamics in older adults is largely unknown [369]. Based on the current results, one could hypothesise that sarcopenia may lead to reduced activity of the SMP during early orthostasis, and hence reduced venous return from the lower limbs resulting in a slower or incomplete recovery of BP. While it is not possible to claim causality from the current cross-sectional design, physiologically the sarcopenia → reduced SMP activity → delayed orthostatic BP recovery pathway is more plausible than the reverse pathway (i.e., delayed BP recovery causing sarcopenia). However, there is a theoretical possibility of a feedback loop in that those with delayed BP recovery resulting in OH and subsequent falls could develop fear of falling with reduced activity leading to sarcopenia and potentially worsening their OH [370].

Differences from Study I

The present study did not replicate a finding of Study I, namely the statistical significance of the association between probable sarcopenia and OH30. This may have been due to the imprecision of the estimates, given the small sample size in the present study and the higher variability in the data as evidenced by the wider standard errors shown in the data visualisations. This suggests that the magnitude of the SMP effect is at best modest, and this is in keeping with known physiology. Indeed, the predominant mechanisms known to be involved in BP recovery after standing are the baroreflex-mediated splanchnic and peripheral vasoconstriction and the increased CO via vagal withdrawal causing an increase in heart rate [173]. Yet, even if the SMP contribution is modest, it is one that is potentially

more modifiable, via physical training to improve muscle mass and strength, than other autonomic nervous system mechanisms.

Limitations

As well as the relatively small sample size, limitations of the present study include the known limitations of BIA for determination of muscle mass [80], and also that patients were not required to fast before measurements. Although medication records were collected, no information was available in relation to timing of medication ingestion in relation to the active stand test routinely performed in the clinic. The sample was collected from attendees to a falls and syncope unit and so unsurprisingly the prevalence of falls is high. This may limit generalisability to the general older population. The lower rates of sarcopenia as compared to previous studies may have reduced the magnitude of the differences seen in the study.

Conclusion

In this study it was found that older falls clinic patients with sarcopenia had a slower rate of recovery of BP early after standing, as measured by continuous non-invasive haemodynamics. This may put them at risk of OH, falls and fractures. The potential mechanisms underlying this relationship remain unclear and warrant further investigation.

Chapter 5 – Study II-B

Published Works List

This chapter is based on my previously published paper: Duggan, E., Knight, S. P., Xue, F., & Romero-Ortuno, R. (2023). Haemodynamic Parameters Underlying the Relationship between Sarcopenia and Blood Pressure Recovery on Standing. Journal of Clinical Medicine, 13(1), 18. https://doi.org/10.3390/jcm13010018

Figure 5-2, Table 5-1 and Table 5-2 from this chapter were published in the above paper.

Introduction

Study II-A focused on the relationship between sarcopenia and BP recovery after standing. Given that humans stand on average 60 times per day [371] and one of the key challenges associated with orthostasis is the maintenance of BP in the upright position, this issue is not insignificant. Gravity leads to a pooling of blood in the lower limbs and below the level of the heart and therefore a reduction in intrathoracic blood volume [155]. As a consequence, this leads to a decrease in central venous pressure and therefore SV, resulting in a decline in CO [175]. Without counter-regulatory measures, a precipitous fall in MAP would occur [372].

A number of mechanisms are involved in the recovery of BP on standing. Carotid and cardiopulmonary baroreceptors detect a fall in BP triggering a reduction in cardiac vagal activity and increase in sympathetic activity leading to an increase in HR which limits the fall in CO (caused by the drop in SV) [162]. TPR increases via sympathetic mediated vasoconstriction in splanchnic and peripheral blood vessels [163]. Finally, the rhythmic activity of the SMP of the lower limbs may also improve venous return and subsequent SV and CO, thus helping maintain MAP [350].

Impairment of these mechanisms with ageing or disease may result in a delayed recovery of BP or a failure of BP to recover — OH [234]. In general, a 'classic' non-recovery OH pattern observed at three minutes post-standing, especially when accompanied by a reduced or absent HR increase, is more likely to be neurogenic, largely caused by either primary or secondary autonomic failure [373]. However, the importance of causes such as heart failure, medications and hypovolaemia is increasingly recognised in non-neurogenic presentations [374].

A potential contributor to OH is sarcopenia, a clinical condition of low muscle mass and function [375] that is prevalent in older people [28] and has been associated with many adverse outcomes [135]. Previous research has demonstrated an association between classic OH, assessed with intermittent BP measurement, and sarcopenia [200,263]. In the two previous studies, I found an association between beat-to-beat orthostatic BP recovery and both probable sarcopenia in a population study and sarcopenia in a clinical setting.

However, the potential haemodynamic mechanisms underlying these associations have not been investigated and remain unclear. Departing from the well-established physiology equations: $MAP = CO \times TPR$ and $CO = SV \times HR$ [376], the aim of this study was to

explore how the relationship between orthostatic BP recovery and sarcopenia may be mediated in haemodynamic terms.

Using the Finapres Modelflow derived parameters for CO, TPR and SV along with the measured MAP and HR, I again employed mixed-effects models to investigate the relationship between sarcopenia, this time as a dichotomous variable: present or absent; and haemodynamic parameters in the same sample as in Study II-A.

Results

Participants and Demographics

The same sample as in Study II-A was used, maintaining the same exclusion criteria; however, an additional 2 participants were excluded due to poor signal quality of the derived haemodynamic parameters. This left a final analytical sample size of 107 with a mean age of 69.7 years (SD 10.4 years), with 61 (57%) being women. Further characteristics of this sample, grouped by sarcopenia status, are presented in Table 5-1. No significant differences were seen across age, sex, prevalence of hypertension or diabetes, or cardiovascular or psychotropic medication use.

Table 5-1: Characteristics of the sample grouped by sarcopenia status.

	No Sarcopenia (91/85%)	**Sarcopenia (16/15%)**	**P**
Age Group (n /%)			0.143
50–64 years	30 (90.9)	3 (9.1)	
65–74 years	34 (89.5)	4 (10.5)	
75+ years	27 (75.0)	9 (25.0)	
Women (n/%)	52 (57.1)	9 (56.3)	0.947
Hypertension (n/%)	42 (46.2)	9 (56.3)	0.456
Diabetes (n/%)	15 (16.5)	1 (6.3)	0.457
Cardiovascular Meds (n/%)	44 (48.4)	10 (62.5)	0.297
Psychotropic Meds (n/%)	27 (29.7)	7 (43.8)	0.265

Meds: medications This table has been published in my paper Duggan et al 2023, please see Appendix E.

Bivariate Visualisation

As in the previous two studies, the mean changes in MAP, CO, TPR, SV and HR were visualised using unadjusted raw data. These changes are graphed in Figure 5-1, with error bars representing the standard error of the mean.

Visually, the sarcopenia group appeared to have slower MAP recovery from nadir at 10 s, with a less pronounced peak in CO and a slower recovery of TPR from nadir at 10 s. In terms of the constituents of CO, SV appeared to have a less pronounced peak and appeared to remain at a higher level post peak for the sarcopenia group; for HR, the groups did not differ for peak at the 10 s timepoint but HR appeared to return to a lower level post peak for the sarcopenia group.

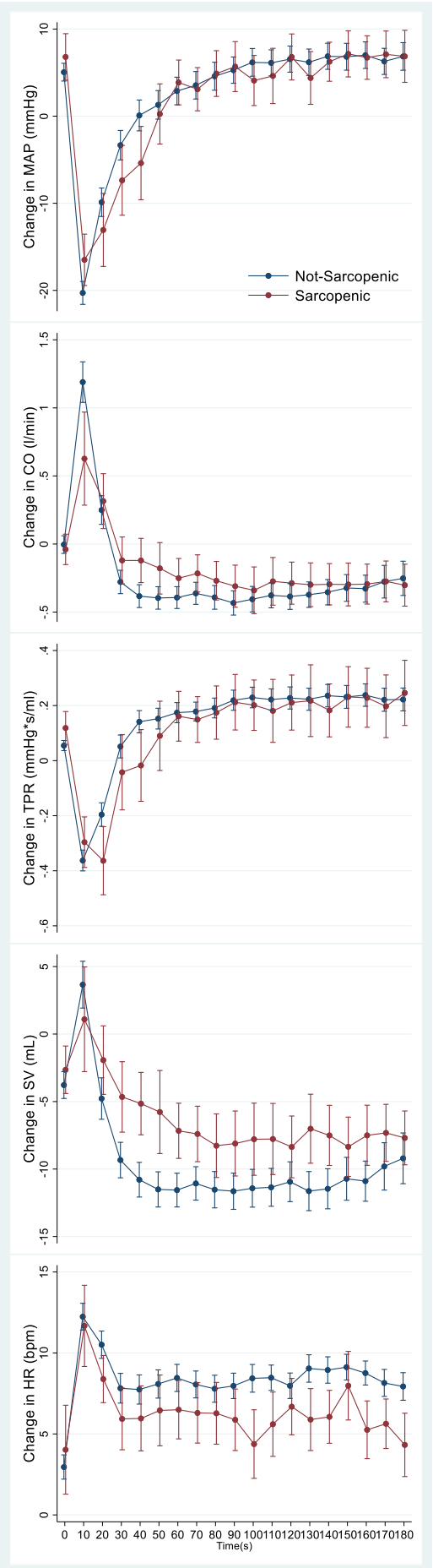

Figure 5-1: 1 Mean change in mean arterial pressure (MAP; mmHg), cardiac output (CO; L/min), total peripheral resistance (TPR; mmHg·s/mL), stroke volume (SV; mL) and heart rate (HR, beats per minute) after standing grouped by sarcopenia status. Unadjusted. Error bars: standard error of the mean.

Multivariable Analysis

To investigate the relationship between sarcopenia and the five haemodynamic parameters, as in the previous two studies, mixed-effects models with linear splines at time intervals 0–10 s, 10–20 s, 20–30 s, 30–40 s and 40–180 s were used. Models were adjusted for age, sex, hypertension, diabetes, cardiovascular and psychotropic medication use. The beta coefficients with confidence intervals and p-values, at each of the five time segments, from the models for the relationship are shown in Table 5-2. Plots of the marginal effects of the means for the two groups is shown in Figure 5-2 for each of the haemodynamic parameters.

For MAP in the 0–10 s periods, no significant difference was seen between the groups. The recovery in MAP in the 10–20 s post-stand period was significantly attenuated in the sarcopenia group compared to the no sarcopenia group as evidenced by the highly statistically significant negative beta coefficient, at a time when the overall MAP trend was upwards. No significant differences between the groups were seen in MAP in the 20–30 s, 30–40 s or 40–180 s periods.

CO for the sarcopenia group had an attenuated initial rise to peak in the 0–10 s period, shown by the significant negative coefficients when overall CO was rising. This was followed by an attenuated recovery of CO from peak, for the sarcopenia group, in the 10–20 s period, demonstrated by the significant positive beta coefficient at a time when CO was returning to baseline. In the 20–30 s, 30–40 s and 40–180 s periods no significant difference in CO was seen between the groups.

In the 0–10 s initial period, no significant difference in TPR was seen between the groups. However, TPR showed a significantly attenuated recovery in the 10–20 s period after standing for the sarcopenia group compared with no sarcopenia, again as indicated by a significant negative coefficient at a time when overall TPR was recovering. Again, in the 20–30 s, 30–40 s and 40–180 s time periods no significant differences were seen between the groups.

For SV in the 0–10 s period, the sarcopenia group had a significantly diminished rate of increase to peak, illustrated by the negative coefficient at a time when SV was rising. This was followed in the 10–20 s period by a slower recovery from peak in SV for the sarcopenia group, demonstrated by a significant positive coefficient. No significant differences were seen in SV at the later 20–30 s, 30–40 s and 40–180 s periods.

For HR, no significant differences were seen between the two groups at any of the time intervals. The full mixed-effects regression outputs are included in Appendix C:

Table 5-2: Beta-coefficients (β) and 95% confidence intervals (CI) for the effect of sarcopenia status on the change in mean arterial pressure (MAP; mmHg), cardiac output (CO; L/min), total peripheral resistance (TPR; mmHg·s/mL), stroke volume (SV; mL) and heart rate (HR; beats per minute) from baseline at time intervals 0–10 s, 10–20 s, 20–30 s, 30–40 s and 40–180 s after standing.

	0–10 s β (95% CI)	**10–20 s β (95% CI)**	**20–30 s β (95% CI)**	**30–40 s β (95% CI)**	**40–180 s β (95% CI)**
MAP	0.23 (-0.13,0.59)	-0.67 (-1.03,-0.31)***	-0.05 (-0.41,0.31)	-0.10 (-0.45,0.31)	0.03 (-0.02,0.08)
CO	-0.05 (-0.08,-0.03)***	0.06 (0.03,0.09)***	0.01 (-0.02,0.04)	0.01 (-0.02,0.04)	<-0.01 (<-0.01,<0.01)
TPR	<0.01 (-0.01,0.01)	-0.02 (-0.03,-0.01)***	0.01 (<-0.01,0.02)	-0.01 (-0.02,<0.01)	<0.01 (<-0.01,<0.01)
SV	-0.37 (-0.72,-0.02)	0.54 (0.19,0.88)***	0.18 (-0.17,0.52)	0.09 (-0.25,0.43)	-0.02 (-0.06,0.02)
HR	-0.16 (-0.40,0.08)	-0.15 (-0.39,0.09)	0.03 (-0.21,0.26)	0.02 (-0.22,0.25)	-0.01 (-0.04,0.01)

Models were adjusted for age, sex, diabetes, hypertension, cardiovascular and psychotropic medications. *P < 0.05, **P < 0.01, ***P < 0.001. This table has been published in my paper Duggan et al 2023, please see Appendix E.

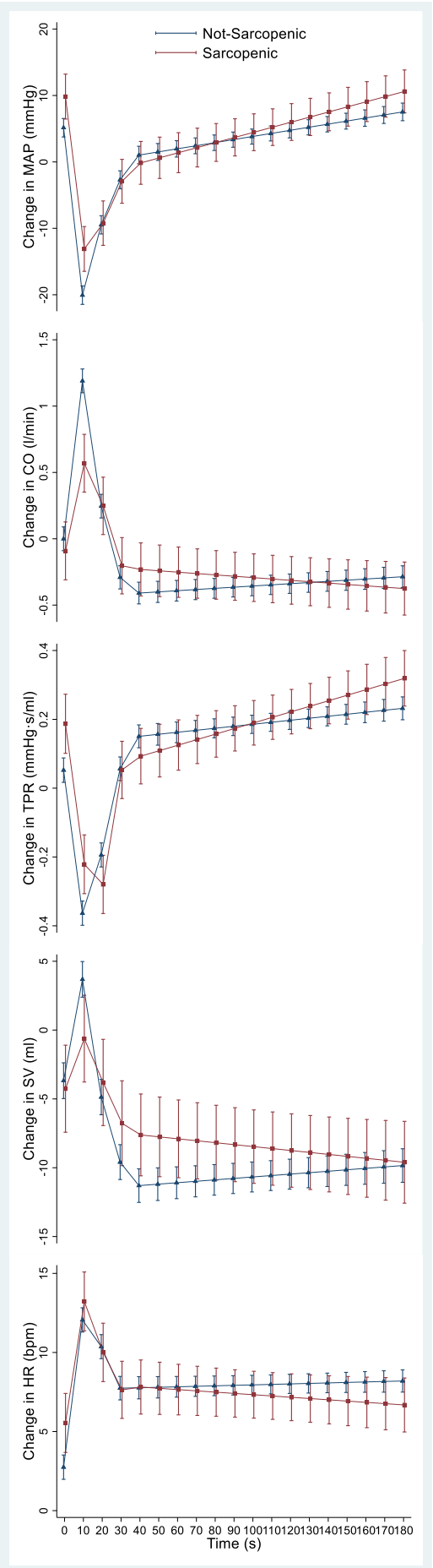

Figure 5-2: Predicted means and standard error of the mean from mixed-effects models for change in mean arterial pressure (MAP; mmHg), cardiac output (CO; L/min), total peripheral resistance (TPR; mmHg·s/mL), stroke volume (SV; mL) and heart rate (HR; beats per minute) from baseline after standing grouped by sarcopenia status. Models were adjusted for age, sex, diabetes, hypertension, cardiovascular and psychotropic medications. This figure has been published in my paper Duggan et al 2023, please see Appendix E

Structural Equation Modelling

To further investigate the potential casual associations in the relationship between sarcopenia, orthostatic haemodynamics and falls, a SEM was postulated and tested in IBM SPSS Amos. In the model, the effect of sarcopenia status on the change in TPR, HR and SV in the 10–20 s period after standing was theorised to lead to impairment in MAP recovery in the 10–20 s period and this subsequently to falls. Sarcopenia was also postulated to lead directly to falls. Age was added to the model as a direct path to both falls and MAP recovery as well as a covariate with sarcopenia status. Covariances were also added between the error terms of the derived parameters to account for their close relationship given the method by which they are estimated. The model is shown in Figure 5-3 with standardised regression coefficients on the paths. The full model output with both unstandardised and standardised regression coefficients is presented in Table 5-3.

Overall, the hypothesised SEM was supported by the data, $\chi^2 = 8.41$ with 7 degrees of freedom and $P = 0.298$. Significant coefficients were seen in the paths: sarcopenia → SV, sarcopenia → TPR and sarcopenia → falls. The TPR → MAP path was also significant. The paths sarcopenia → HR and MAP → falls were not significant. The paths age → falls, age → MAP, SV → MAP and HR → MAP were also not significant. When TPR was removed from the model the path SV → MAP was significant, $\beta = -0.33$, β standardised = -0.34, $P < 0.001$.

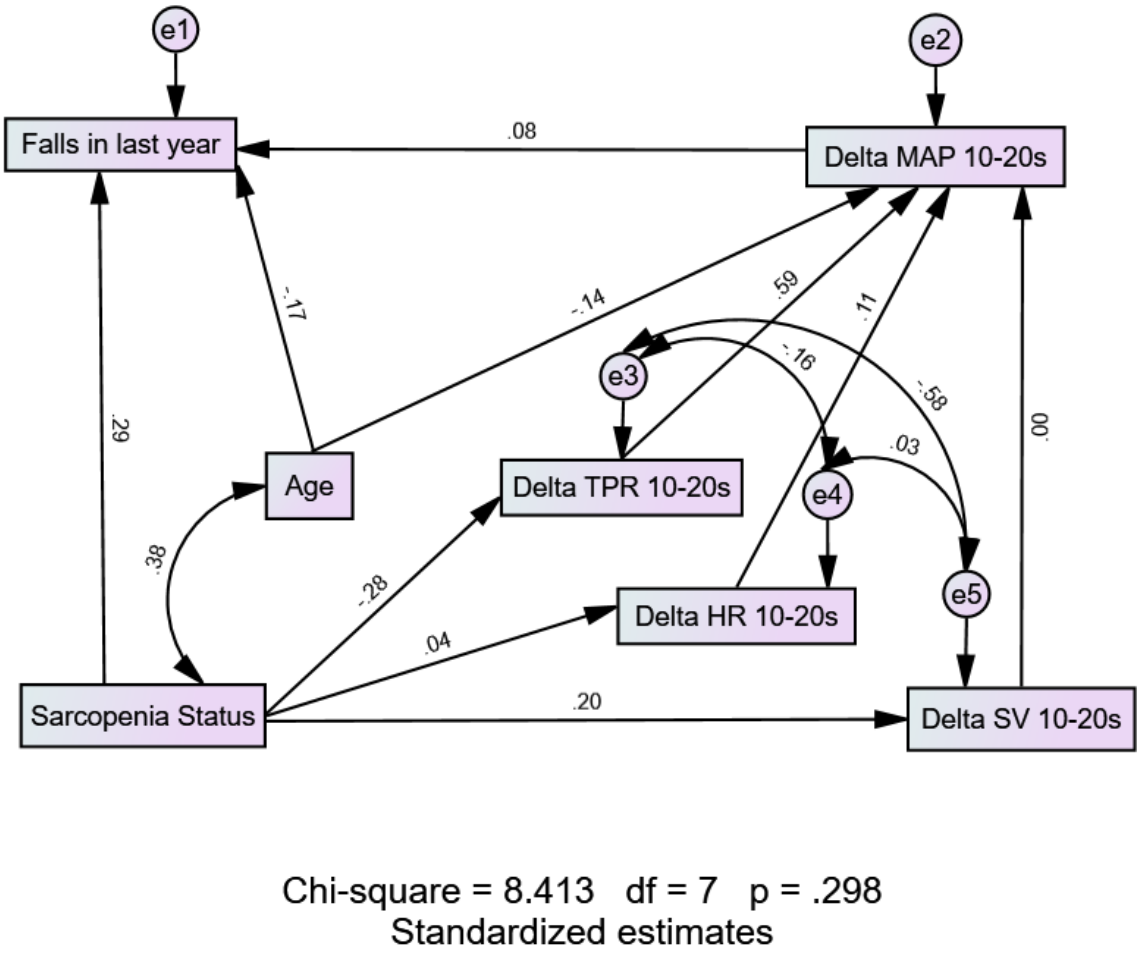

Figure 5-3: Structural equation model with postulated relationships between sarcopenia status and change in haemodynamic parameters, total peripheral resistance (TPR), stroke volume (SV), heart rate (HR), mean arterial pressure (MAP) between 10 and 20 s after standing, and the effect on falls, with age as a covariate. Straight arrows denote direct paths, curved arrows denote covariances and e represents error terms.

Table 5-3: Regression coefficients, unstandardised (β) and standardised (β Std) from structural equation model shown in Figure 5-3.

Path			β	S.E.	β Std	P
Delta HR 10–20 s	←	Sarcopenia Status	0.50	1.15	0.42	0.662
Delta SV 10–20 s	←	Sarcopenia Status	4.68	2.19	0.20	0.033
Delta TPR 10–20 s	←	Sarcopenia Status	-0.21	0.07	-0.28	0.003
Delta MAP 10–20 s	←	Age	-0.22	0.12	-0.14	0.075
Delta MAP 10–20 s	←	Delta HR 10–20 s	0.21	0.15	0.11	0.156
Delta MAP 10–20 s	←	Delta TPR 10–20 s	17.57	2.91	0.59	<0.001
Delta MAP 10–20 s	←	Delta SV 10–20 s	-0.001	0.09	-0.001	0.992
Falls in Last Year	←	Delta MAP 10–20 s	0.02	0.02	0.08	0.435
Falls in Last Year	←	Sarcopenia Status	1.27	0.45	0.29	0.005
Falls in Last Year	←	Age	-0.05	0.03	-0.17	0.104

S.E. – standard Error. MAP – mean arterial pressure. TPR – total peripheral resistance. SV – stroke volume. HR – heart rate.

Discussion

Key Findings and Strengths

In this study, I explored the relationship between the presence or absence of sarcopenia and the haemodynamic response to standing. I found that sarcopenia was associated with an attenuated recovery of MAP during the 10–20 s period after standing, in keeping with the findings in Study II-A regarding SBP and DBP. I expanded upon my previous findings by examining the components of MAP, namely CO and TPR, demonstrating early post-standing changes in both, factors that may drive the alterations observed in MAP. Furthermore, CO is determined by SV and HR and I observed significant changes in SV in the 0–10 s and 10–20 s period after standing, but no significant difference in HR between sarcopenia and non-sarcopenia groups. The findings were supported by a SEM which postulated potentially causal relationships between sarcopenia status, orthostatic haemodynamics and falls. These results are important as they provide insights into the possible underlying pathophysiology of delayed BP recovery in older adults with sarcopenia and this may have implications for the clinical management of this condition. My findings are strengthened by a well-characterised participant sample, enabling adjustments for potential confounders. Additionally, the use of continuous beat-to-beat hemodynamic measurements allows for a non-invasive and precise characterisation of the hemodynamic response to orthostasis.

MAP

The finding of an attenuated rate of recovery of MAP in the 10–20 s period after standing is in keeping with Study II-A, which also found an attenuated rate of SBP and DBP recovery in both probable and confirmed cases of sarcopenia during the same timeframe. To my knowledge, no previous studies had examined the relationship between sarcopenia and the early BP response to standing. However, one study [278] found an association between 5CST time (a component of the EWGSOP2 criteria for probable sarcopenia) and DBP recovery, 30 to 60 s after standing, with a longer 5CST time being associated with worse DBP recovery. Another study [267] found that those in the slowest category for 5CST had significantly higher odds of initial OH in the first 15s after standing. Together with the current study, they add weight to the hypothesis that muscle function and mass may be linked to BP recovery early after standing.

CO

CO showed a significantly attenuated initial increase in the sarcopenic group when compared to the non-sarcopenic. The sarcopenic group also showed an attenuated recovery from peak CO in the 10–20 s period. Thus, one can surmise that the changes in MAP were related to the attenuated CO response in the initial 10 s contributing to subsequent slower MAP recovery in the 10–20 s period. The initial increase in CO on standing followed by prompt recovery seen in the non-sarcopenic group has been previously established in healthy participants [172,377]. Whilst no previous data had been reported in subjects with sarcopenia, Wieling et al. [378] found that older participants had a less pronounced rise in CO to peak after standing when compared to younger participants, similar to the current finding in CO in the same period. The effects of ageing on skeletal muscle may have played a role in these findings. On the other hand, Van Wijnen and colleagues [379] found that in a group with delayed BP recovery there was no significant difference on average in CO compared to a normal BP recovery group but there was a large interparticipant variation in the delayed BP recovery group. Muscle mass or strength was not assessed in this study, but since the participants were 18 years and older, the likelihood of sarcopenia within this sample is low.

TPR

Examining the TPR response, it is known that in healthy adults TPR falls initially due to a number of mechanisms related to the muscular effort of standing, before recovering from nadir [179]. The attenuated recovery of TPR in the sarcopenia group in the 10–20 s period is similar to that of MAP, suggesting that the attenuated MAP recovery is driven at least partially by TPR [163]. Indeed, Van Wijnen et al. [379] found that TPR recovery was impaired in those with delayed BP recovery compared to normal BP recovery while changes in CO were not different, suggesting that TPR was the primary driver of delayed BP recovery in that group. Decreased TPR leading to OH has been reported previously in diabetics [380] and Pérez-Denia et al. [282] found impaired TPR recovery in those with multimorbidity and suggested that this might drive impairments in BP recovery. Again in these two studies muscle parameters were not examined but it is known that both multimorbidity [346] and diabetes [381] are related to sarcopenia and so it may be one of the factors involved.

SV and HR

When breaking down CO into its constituents, SV and HR, SV showed an attenuated rise to peak in the 0–10 s period and recovery from peak in the 10–20 s period while there were no significant differences in HR. This suggests that CO changes were driven by SV rather than HR. At first this finding is somewhat unexpected, as one might anticipate an increase in HR in individuals with sarcopenia to compensate for the potential reduction in venous return due to impaired SMP function, which could result in decreased SV. The other possibility is that the sarcopenia individuals were unable to mount an increase HR response, perhaps due to chronotropic incompetence [382], and the reduced SV is a manifestation of sarcopenia on the SMP. The association between sarcopenia and SV/HR after standing has not previously been investigated but the response of SV to standing has been show previously to differ between younger and older subjects. Wieling et al. [378] demonstrated a stable SV with large increase in HR in the initial 7s after standing in the younger group while in the older group there was less of a HR increase with initial fall in SV followed by transient recovery and subsequent further fall. As before, although muscle factors were not included, it is possible that they played a role in the differential response seen in older people.

Structural Equation Modelling

Structural equation modelling allows the postulation and testing of models with potentially causal pathways. Importantly SEM alone cannot prove causality which much be based on factors such as theoretical knowledge, study design and temporal nature of associations [383]. The SEM in this study supports the hypothesis that sarcopenia may affect TPR and SV in the early post stand period leading to impaired MAP recovery. This was demonstrated by the significant sarcopenia → TPR and sarcopenia → SV pathways. This was followed by the significant TPR → MAP pathway, and while the SV → MAP pathway was not significant in the main model, when TPR was removed, SV was highly statistically significant. This suggests that the effects of SV are overshadowed by TPR when both are in the same model. The path sarcopenia → HR was not significant which fits with the results of the mixed-effects models. The change in MAP from 10–20 s was not significantly associated with falls, while sarcopenia status was. This suggests that the direct pathway to falls from sarcopenia is stronger and more significant and the indirect sarcopenia to BP recovery pathway may be a weaker, less important one. However, as these data are cross-sectional in nature any causal inferences must be treated with caution.

Potential Mechanisms

There are several potential mechanisms underlying the findings. Specifically, in this sample, the effects on CO seemed primarily driven by SV rather than HR. It is established that SV is determined by preload, contractility and afterload [384]. Afterload is largely determined by MAP itself, thereby acting as a negative feedback mechanism [385]. Contractility is determined in part through preload via the Frank-Starling mechanism, as well as intrinsic factors [386]. It is here that the influences of sarcopenia on the heart muscle might act. Cardio-sarcopenia is a relatively novel concept [387], especially as traditionally hypertrophy rather than wasting of the heart is seen with ageing. However, a small number of studies have shown reductions in left ventricular mass in sarcopenia [388,389]. If correct, one might hypothesise that cardio-sarcopenia could lead to decreased contractility, leading to decreased SV, in turn impacting CO and subsequently leading to delayed recovery of MAP as seen in this study. When examining preload, it is influenced by end-diastolic volume, which is determined largely by venous return [385]. It is in this aspect that the SMP may play a role [350], potentially contributing to the effects of sarcopenia. An impaired SMP in sarcopenia might reduce venous return thus decreasing preload and subsequently affecting SV, consequently leading to impaired MAP recovery as described in the pathway above. With regards TPR, this may be an effect of sarcopenia on the autonomic nervous system. It has been shown that general MSNA is proportional to the muscle mass involved [253]. Therefore, those with sarcopenia might have reduced MSNA leading to impaired recovery of TPR and resultant delayed recovery of MAP.

Limitations

Of course, there may be other mechanisms at play. Other syndromes such as frailty may be involved although the underlying pathophysiology between sarcopenia and physical frailty are increasingly recognised as likely being common [104]. Impairment of the exercise pressor reflex [390] may be involved although this is less likely as no significant differences in HR were found. In a cross-sectional analysis, one cannot assert causality. However, it is more plausible that the pathway from sarcopenia to impaired BP recovery is the causal direction rather than the reverse pathway from impaired BP recovery to sarcopenia. There is the possibility of a positive feedback loop in that those with impaired BP recovery leading to falls may restrict activity due to fear of falling, which could lead to sarcopenia. I was unable to adjust for this pathway in this analysis and so acknowledge it as a limitation. Other limitations include the inherent limitations of BIA in the estimation of muscle mass [391], the relatively small sample size, and the lack of information on timing of

medications in respect to the active stand test. Furthermore, the use of Modelflow derived haemodynamics has inherent limitations [392]. Whilst the gold standard would be invasive measurement [393], conducting such procedures would be neither practical nor ethical in this population. Doppler echocardiography could be used, however Modelflow has been shown to be an acceptable alternative [394] especially when relative haemodynamic changes are required rather than absolute [395], as in the current design.

Importance of Findings

The results of the current study are important for a number of reasons. Firstly, from a pure pathophysiological and scientific point of view, they are novel. To the best of my knowledge, no previous study has utilised this methodology to address the question as to how sarcopenia could contribute to delayed BP recovery in older individuals. Secondly, the results are of clinical importance. Through the use of beat-to-beat BP monitoring, impaired BP recovery has become increasingly recognised [181,396] and has been shown to independently predict falls, fractures and mortality [213,218,363]. The current results link sarcopenia with impaired BP recovery and this, in turn, could potentially be implicated in subsequent falls and fractures. Importantly, sarcopenia is potentially reversible and multicomponent interventions that improve sarcopenia [123] could also be used to ameliorate delayed BP recovery. This of course underlines the importance of identifying sarcopenia in the falls and syncope unit in the first place [21]. Pressor agents such as fludrocortisone and midodrine are routinely prescribed for OH and delayed BP recovery [214] despite their off-label use and potential side effects [171]. Perhaps increasing use of multicomponent intervention as well as training in PCMs [256] would lessen the use of these medications and also benefit cases of combined supine hypertension and OH [397], where physical interventions could help both.

Conclusion

In conclusion, sarcopenia was observed to be associated with an attenuated rate of recovery of MAP early after standing. This appeared to be driven by initial blunted peak of CO followed by attenuated recovery of CO from peak and TPR from nadir. The CO finding appeared to be driven by SV rather than HR. There are a number of potential mechanisms implicated including: cardio-sarcopenia, the effects of sarcopenia on the autonomic nervous system and the SMP, and further research is needed to clarify the mechanisms involved and their relative contributions.

Chapter 6 – Study III

Introduction

The previous three chapters addressed the relationship between sarcopenia and BP recovery and how it may be mediated in terms of the underlying haemodynamics. Taking a broader view, muscle mass and muscle strength are key factors involved in healthy ageing [398,399]. Even in the absence of disease, the role of muscle has been shown to predict outcomes in later life [400]. The role of muscle strength, in particular HGS and 5CST, and BP recovery, has been previously studied in attendees to geriatric outpatient clinics [267,278]. In a Malaysian population, the MELoR study examined OH definitions and HGS [186]. However, these studies did not include muscle mass, BP recovery was not examined as a continuous variable, and alternate measures of lower limb muscle strength were not considered. In Studies I and II-A of this thesis, BP was examined continuously but in the setting of sarcopenia status. The potential mechanisms involved in the relationship were introduced in Study II-B but the role of the SMP remains poorly understood [401].

In terms of the management of OH and vasovagal syncope, PCMs are recommended in both US and European guidelines [214,257]. PCMs consist of various exercises and muscle tensing manoeuvres of the lower limbs to augment BP and prevent symptoms of light-headedness and reduce the risk of syncope [249]. The roles of muscle mass and function in the effectiveness of PCMs are not well-known [402], but is had been speculated that decreased muscle mass and strength with ageing may reduce the effectiveness of PCMs [403].

It is on this backdrop and with these issues in the previous literature in mind, that the aims of Study III are framed:

1. To investigate the association between existing and emerging measures of muscle mass and strength.
2. To inspect the relationship between muscle parameters and BP recovery in healthy ageing.
3. To explore the haemodynamics underlying this relationship and investigate if there is evidence for the role of the SMP.
4. To study the role of muscle strength and mass in the efficacy of PCMs.
5. To examine the haemodynamics underlying PCMs and look for evidence of the role of the SMP.

To achieve these aims, I recruited a sample of healthy, community-dwelling, functionally independent, adults over the age of 50 from a local healthy ageing group. I measured HGS, 5CST, QMS, ASMM with BIA, and RFMT and VLMT with US. Participants underwent a modified active stand test with PCM pre- and post-stand while measuring continuous haemodynamics, NIRS of the thigh, and surface EMG of the thigh and calf. Signals were aligned and pre-processed, and linear regressions were used to assess the relationship between muscle parameters and active stand signals.

Results

Participants

Thirty-one participants were recruited to the study (Figure 6-1). Full data on demographics, health characteristics, HGS, BIA, muscle US and haemodynamics were available for all 31 participants. One participant was unable to complete the 5CST. For thigh NIRS, in eight participants there were issues with signal quality with a fit factor below 98% and those signals were excluded. For EMG, one participant's data was corrupted due to software issues, for thigh EMG a further participant's data could not be used due to signal quality issues during the normalisation period. For calf EMG, five participants had signal loss on standing likely due to loss of electrode contact. For this reason, calf EMG was not used in the analysis. To maximise power in the analyses, full available data were used, and the number included in each analysis is stated therein.

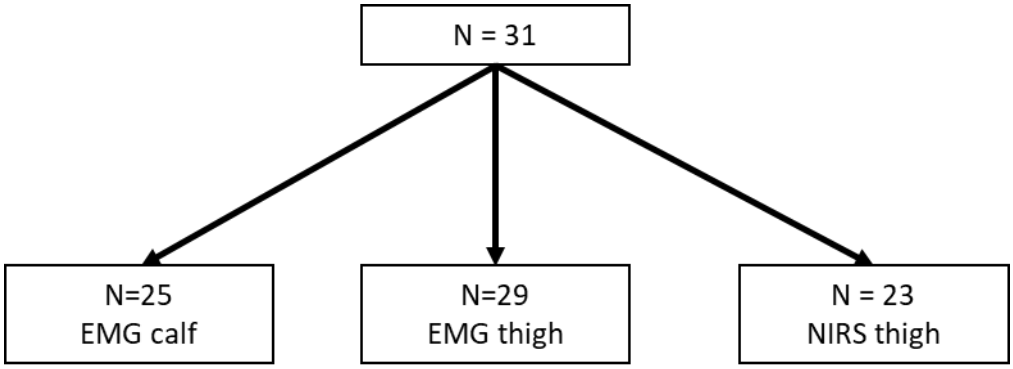

Figure 6-1: Flowchart of the participants in Study III

Demographics

The demographics, health characteristics and muscle measures for the sample are shown in Table 6-1. Normally distributed variables are given as mean and SD, non-normally distributed variables as median and IQR. The age in the study ranged from 59 – 82 years.

Table 6-1: Demographics and characteristics of the sample.

Age (years) (mean, SD)	70.5 (5.0)
Female (n, %)	25 (80.7)
No. of chronic diseases (med, IQR)	2.0 (2.0)
No. of medications (med, IQR)	2.0 (3.0)
Polypharmacy (n, %)	5 (16.1)
Smoking (n, %)	
Never	23 (74.2)
Past	8 (25.8)
Current	0 (0)
Alcohol above guidelines (n, %)	8 (25.8)
Max HGS (kg) (mean, SD)	24.2 (7.1)
5CST (s) (med, IQR)	10.6 (2.5)
Max QMS (kg) (mean, SD)	24.2 (8.6)
ASMM (kg) (med, IQR)	16.5 (6.0)
RFMT (cm) (mean, SD)	1.6 (0.3)
VLMT (cm) (mean, SD)	1.7 (0.3)

HGS – hand grip strength; 5CST – 5 chair stands time; QMS – quadriceps muscle strength; ASMM – appendicular skeletal muscle mass; RFMT – rectus femoris muscle thickness; VLMT – vastus lateralis muscle thickness. SD – standard deviation; med – median; IQR – interquartile range

Relationship Between Measures of Muscle Strength and Mass

To investigate the relationship between the various measures of muscle mass and function in the study, pairwise correlations were performed, and the heat plot shown in Figure 6-2 was generated. Strong correlations were present between maximum HGS and maximum QMS and ASMM. RFMT and VLMT were moderately correlated. 5CST was weakly correlated or uncorrelated with all the measures. Given that RFMT and VLMT are similar measures and are highly correlated, RFMT was used in the analyses that follow, in order to reduce duplication.

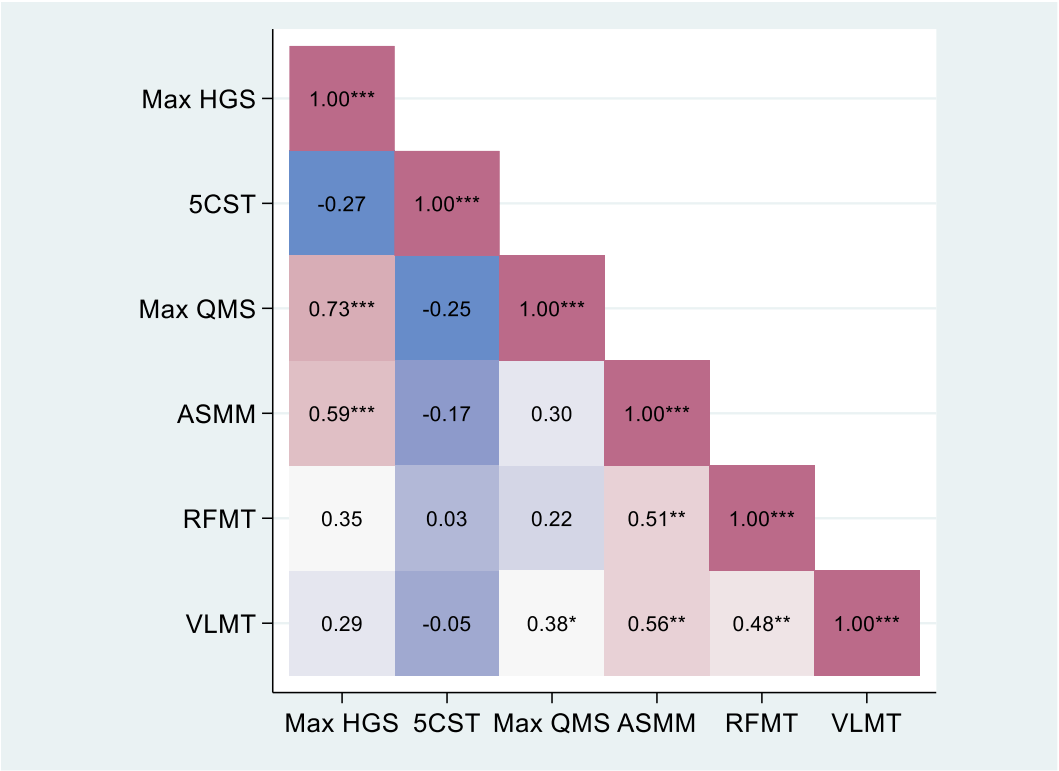

*Figure 6-2: Heat plot of the pairwise correlations between the muscle parameters. HGS – hand grip strength; 5CST – 5 chair stands time; QMS – quadriceps muscle strength; ASMM – appendicular skeletal muscle mass; RFMT – rectus femoris muscle thickness; VLMT – vastus lateralis muscle thickness. * P < 0.05, ** P < 0.01, *** P < 0.001*

Visualisation of the Signals

To identify and visually assess temporal relationships between acquired signals, a visualisation of the mean and standard deviation of the signals from the 21 participants with complete data was generated in MATLAB and is presented in Figure 6-3. The supine PCM occurred at 120 s, the stand at 420 s and the standing PCM at 600 s. The raw signals are plotted in Appendix D: . Visually, it was apparent that EMG activity increased during both PCMs and also during quiet standing compared to supine rest. THb dipped initially on standing followed by a gradual increase during the standing period. As expected, MAP increased during the PCMs. There was an initial MAP rise during the act of standing, followed by a large drop and prompt recovery, and it remained steady until the standing PCM.

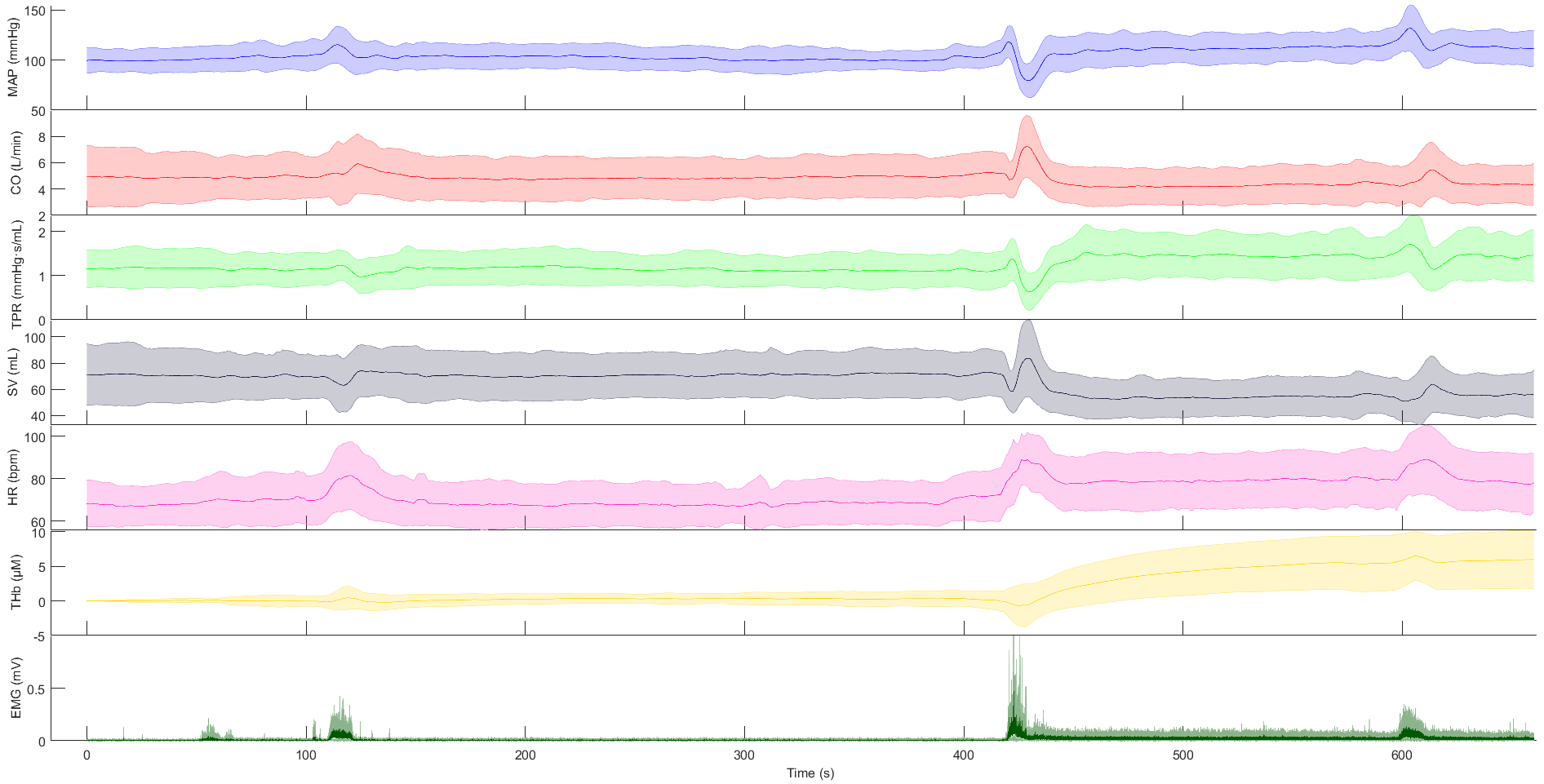

Figure 6-3: Mean and standard deviation of mean arterial pressure (MAP) (mmHg), cardiac output (CO) (L/min), total peripheral resistance (TPR) (mmHg·s/mL), stroke volume (SV) (mL), heart rate (HR) (bpm), change in total haemoglobin concentration from thigh NIRS (THb) (μM), rectified EMG signal from thigh (mV).

Muscle Parameters and MAP Recovery in the First 30 s After Standing

To investigate the relationships between muscle mass and function, and MAP change after standing, the first 30 s of MAP post-standing was examined in 10 s intervals and the changes in MAP from 0 – 10 s, 10 – 20 s and 20 – 30 s were calculated. Scatterplots were used to visualise the relationship between change in MAP at each of these timepoints and the following muscle parameters: maximum HGS, 5CST, maximum QMS, ASMM and RFMT. Linear regression was used to quantify the relationship between variables.

Change in MAP 0 – 10 s

For the 0 – 10 s period, scatterplots of the muscle measures against change in MAP are displayed in Figure 6-4. The regression outputs are shown in Table 6-2. From these, it can be seen that there was no significant relationship between any of the muscle measures and MAP change in the 0 – 10 s period.

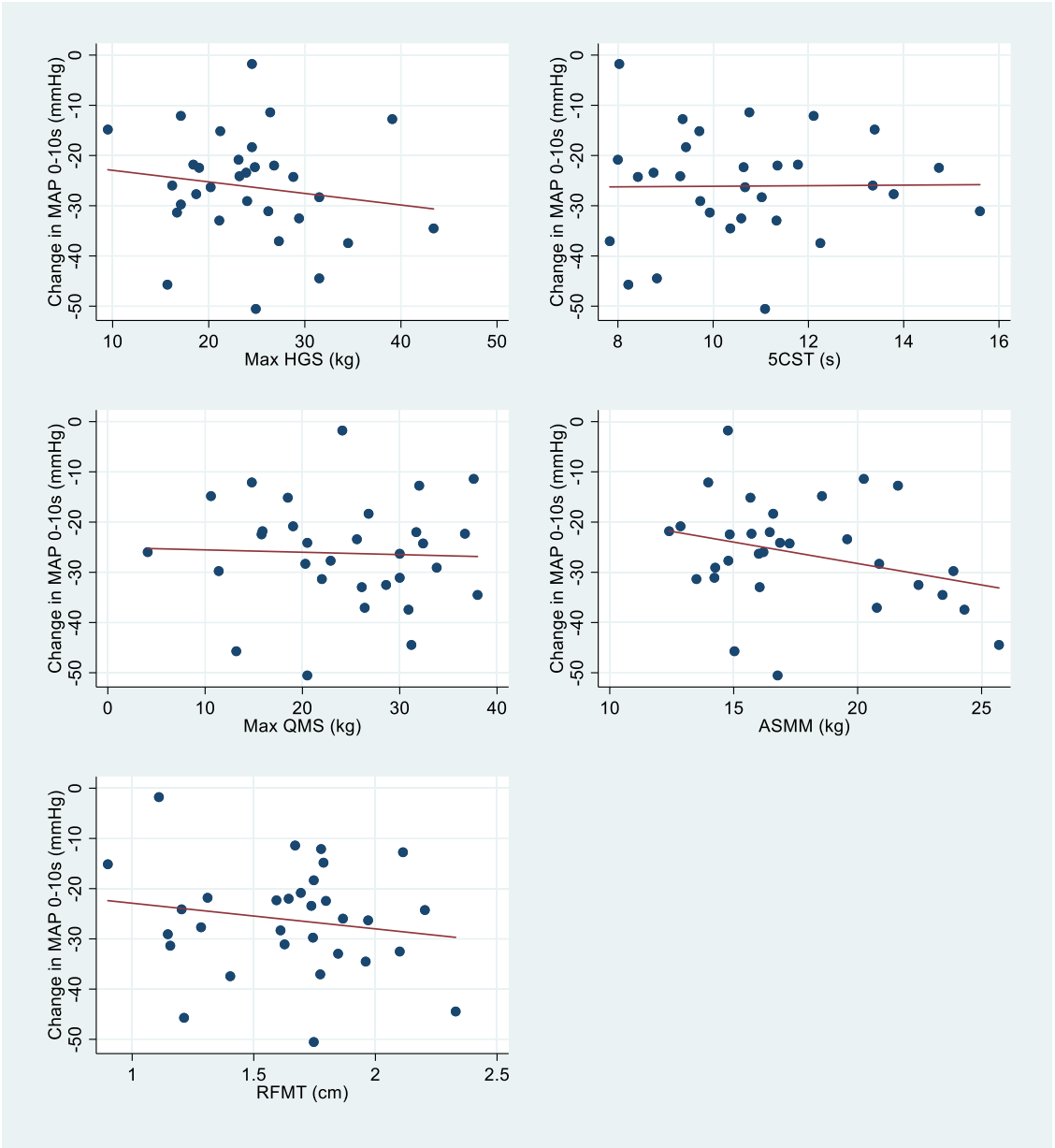

Figure 6-4: Scatterplots with fitted regression lines for the change in MAP 0 – 10 s time period (mmHg) vs. maximum hand grip strength (HGS) (kg), 5 chair stands time (5CST) (s), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Table 6-2: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in MAP 0 – 10 s time period (mmHg) vs. maximum hand grip strength (HGS) (kg), 5 chair stands time (5CST) (s), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Change in MAP 0 – 10 s	β	S.E.	β Std	P	R^2	N
Max HGS	-0.23	0.28	-0.15	0.409	0.02	31
5CST	0.06	1.00	0.01	0.956	0.00	30
Max QMS	-0.05	0.23	-0.04	0.839	0.00	31
ASMM	-0.85	0.51	-0.29	0.108	0.09	31
RFMT	-5.11	5.6	-0.17	0.369	0.03	31

Change in MAP 10 – 20 s

For the 10 – 20 s period after standing, scatterplots of the muscle measures against change in MAP are displayed in Figure 6-5. The regression outputs are shown in Table 6-3. From these, it can be seen that maximum HGS, ASMM and RFMT were significantly and positively associated with change in MAP, with RFMT having the strongest effect size in terms of magnitude of standardised regression coefficients and coefficient of determination. Neither 5CST nor maximum QMS were significantly associated with MAP change at this time interval.

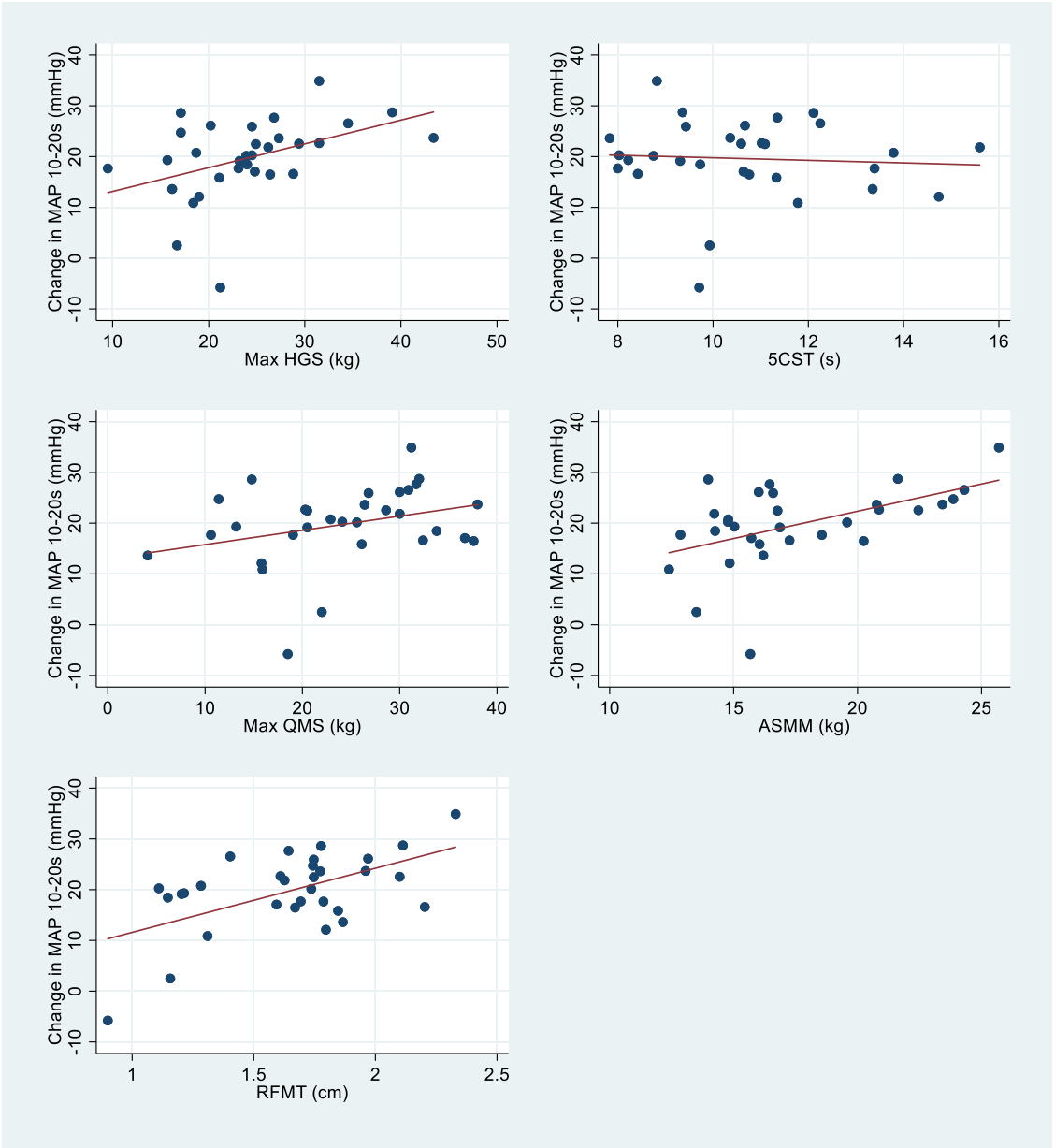

Figure 6-5: Scatterplots with fitted regression lines for the change in MAP 10 – 20s time period (mmHg) vs. maximum hand grip strength (HGS) (kg), 5 chair stands time (5CST) (s), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Table 6-3: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in MAP 10 – 20 s time period (mmHg) vs. maximum hand grip strength (HGS) (kg), 5 chair stands time (5CST) (s), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Change in MAP 10 – 20 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Max HGS	0.47	0.19	0.43	0.017	0.18	31
5CST	-0.25	0.73	-0.07	0.733	0.00	30
Max QMS	0.28	0.16	0.31	0.093	0.09	31
ASMM	1.07	0.34	0.51	0.004	0.26	31
RFMT	12.63	3.46	0.56	0.001	0.32	31

Change in MAP 20 – 30 s

For the 20 – 30 s period, scatterplots of the muscle measures against change in MAP are displayed in Figure 6-6. The regression outputs are shown in Table 6-4. From these, it can be seen that there were significant negative associations between maximum HGS, maximum QMS, ASMM and RFMT, and change in MAP. Those with higher values tended to have lower change in MAP, and from Figure 6-3 one can see that some participants would have recovered MAP at this stage, with regression outputs suggesting that they were those with higher values of HGS, QMS, ASMM and RFMT. ASMM had the strongest association in terms of standardised β coefficients and R^2. 5CST was not significantly associated with MAP change at this time interval.

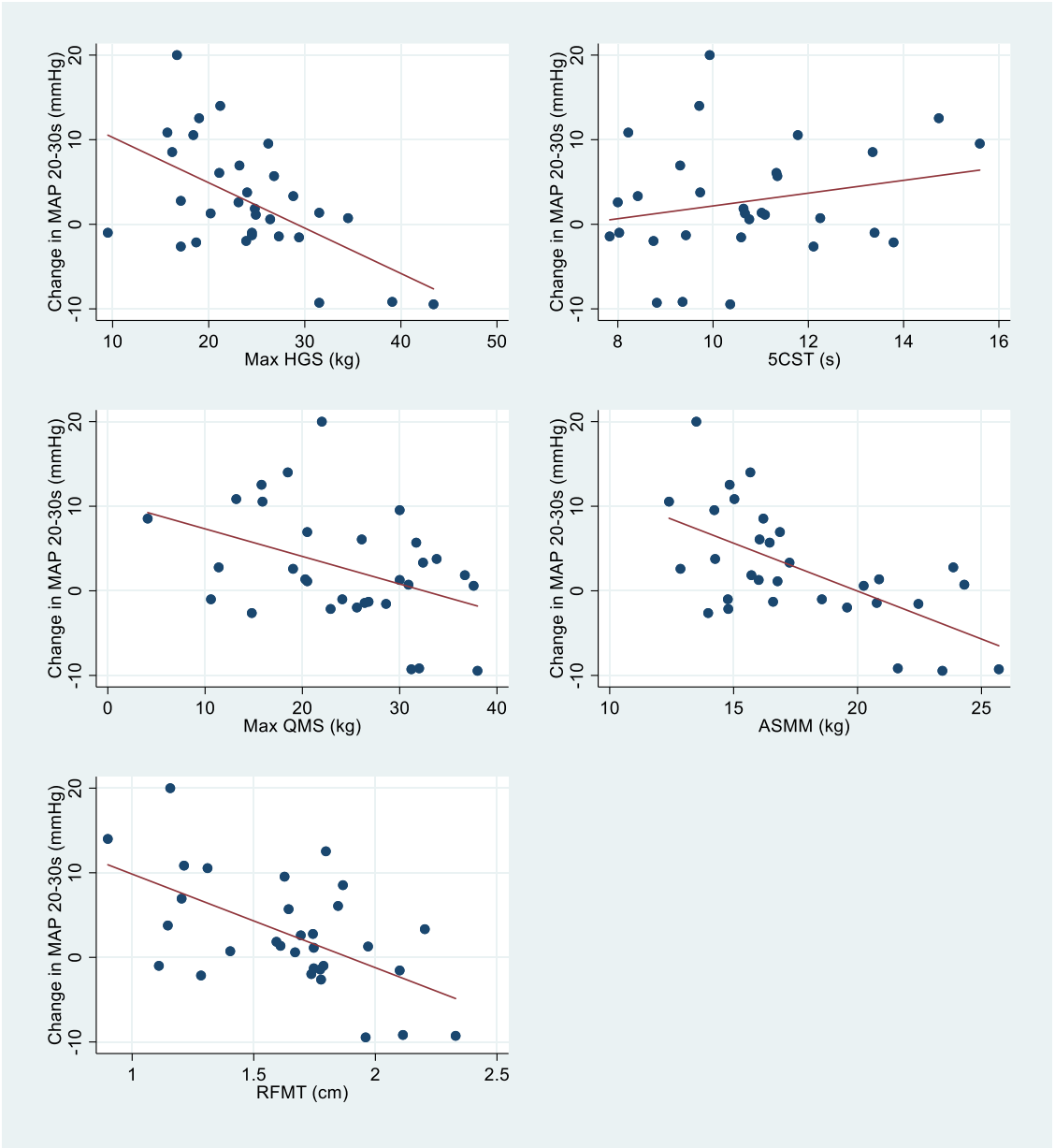

Figure 6-6: Scatterplots with fitted regression lines for the change in MAP 10 – 20s time period (mmHg) vs. maximum hand grip strength (HGS) (kg), 5 chair stands time (5CST) (s), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Table 6-4: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in MAP 20 – 30 s time period (mmHg) vs. maximum hand grip strength (HGS) (kg), 5 chair stands time (5CST) (s), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Change in MAP 20 – 30 s	β	S.E.	β Std	P	R^2	N
Max HGS	-0.54	0.15	-0.56	0.001	0.32	31
5CST	0.76	0.62	0.22	0.235	0.05	30
Max QMS	-0.33	0.13	-0.41	0.021	0.17	31
ASMM	-1.13	0.27	-0.62	<0.001	0.38	31
RFMT	-11.06	2.97	-0.57	0.001	0.32	31

Muscle Parameters and Haemodynamic Measures in the First 30 s After Standing

To examine the haemodynamic parameters underlying MAP and their associations with the various muscle measures, CO and TPR were examined. Subsequently, CO was broken down into SV and HR. Measures and timepoints that had been significantly associated with MAP recovery in the first 30 s after standing were examined using linear regression.

Change in CO 10 – 20 s

Beginning with CO in the 10 – 20 s period, scatterplots against maximum HGS, ASMM and RFMT are shown in Figure 6-7, with the corresponding regression outputs in Table 6-5. From these, it can be seen that the change in CO in the 10 – 20 s period, which subsequently drives the change in MAP, was significantly and negatively associated with maximum HGS, but not with ASMM or RFMT. This suggests that those with higher maximum HGS had a greater recovery from peak of CO.

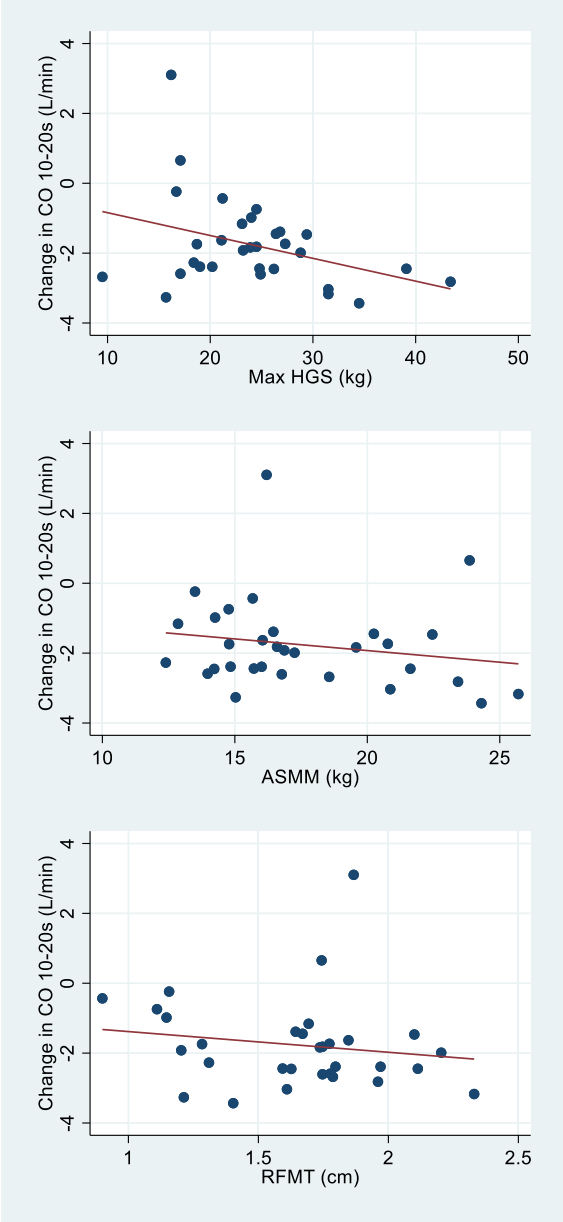

Figure 6-7: Scatterplots with fitted regression lines for the change in CO 10 – 20s time period (L/min) vs. maximum hand grip strength (HGS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Table 6-5: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in CO 10 – 20 s time period (L/min) vs. maximum hand grip strength (HGS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Change in CO 10 – 20 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Max HGS	-0.07	0.03	-0.36	0.048	0.13	31
ASMM	-0.07	0.06	-0.19	0.308	0.04	31
RFMT	-0.59	0.68	-0.16	0.393	0.03	31

Change in CO 20 – 30 s

In terms of the change in CO in the 20 –30 s period, which drives the change in MAP, Figure 6-8 shows scatterplots against maximum HGS, maximum QMS, ASMM and RFMT, with Table 6-6 providing the regression outputs. Change in CO in the 20 – 30 s period was significantly and positively associated with maximum QMS but not with maximum HGS, ASMM or RFMT. The majority of changes in CO were close to or less than zero, suggesting that those with higher maximum QMS had more stable CO during this period.

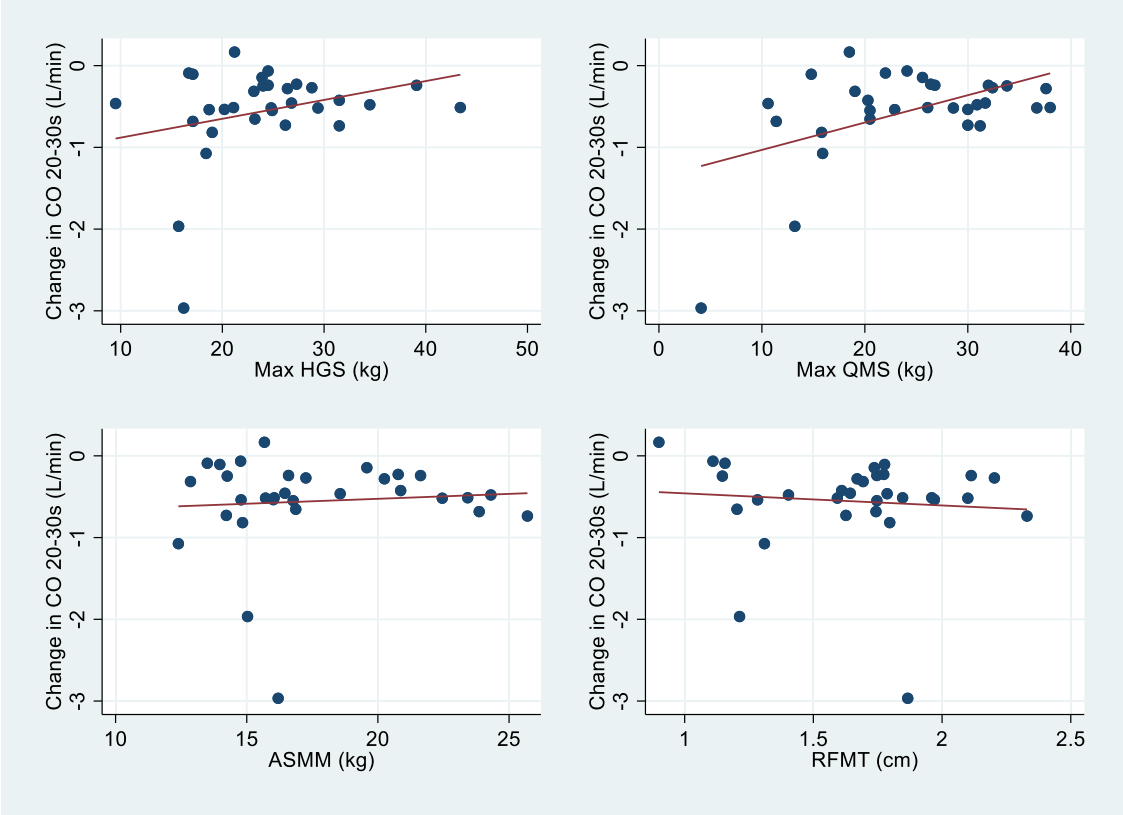

Figure 6-8: Scatterplots with fitted regression lines for the change in CO 20 – 30s time period (L/min) vs. maximum hand grip strength (HGS) (kg), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Table 6-6: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in CO 20 – 30 s time period (L/min) vs. maximum hand grip strength (HGS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Change in CO 20 – 30 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Max HGS	0.02	0.01	0.28	0.126	0.08	31
Max QMS	0.03	0.01	0.49	0.005	0.24	31
ASMM	0.01	0.03	0.08	0.685	0.01	31
RFMT	-0.15	0.31	-0.09	0.637	0.01	31

Change in TPR 10 – 20 s

As regards the second component of MAP in the 10 – 20 s period, TPR, scatterplots of change in the 10 – 20 s period against maximum HGS, ASMM and RFMT are shown in Figure 6-9, and regression outputs in Table 6-7. None of the three muscle measures were significantly associated with TPR change in this time period.

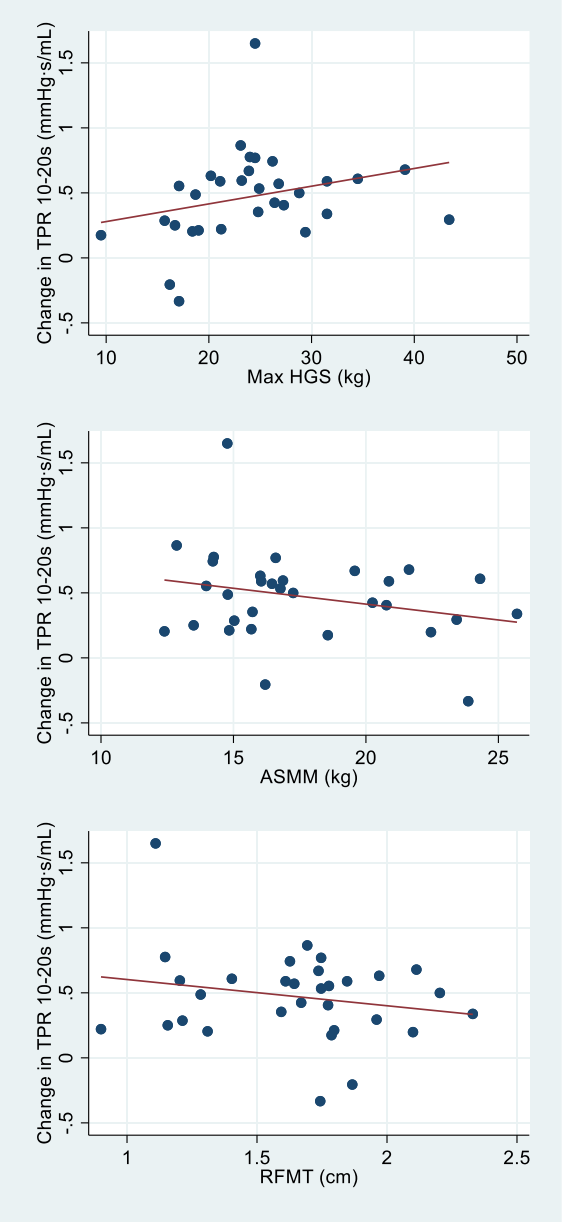

Figure 6-9: Scatterplots with fitted regression lines for the change in TPR 10 – 20s time period (mmHg·s/mL) vs. maximum hand grip strength (HGS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Table 6-7: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in TPR 10 – 20 s time period (mmHg·s/mL) vs. maximum hand grip strength (HGS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Change in TPR 10 – 20 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Max HGS	0.01	0.01	0.28	0.129	0.08	31
ASMM	-0.02	0.02	-0.26	0.160	0.07	31
RFMT	-0.20	0.18	-0.20	0.275	0.04	31

Change in TPR 20 – 30 s

As regards TPR in the 20 – 30 s time interval, scatterplots against maximum HGS, maximum QMS, ASMM and RFMT are shown in Figure 6-10, and outputs from the regressions in Table 6-8. Change in TPR in this period was significantly and negatively associated with maximum HGS, ASMM and RFMT, with ASMM having the strongest effect size in terms of standardised coefficient and coefficient of determination. Those with higher values on the three significant parameters had less change in TPR, which fits with the MAP changes in the same period.

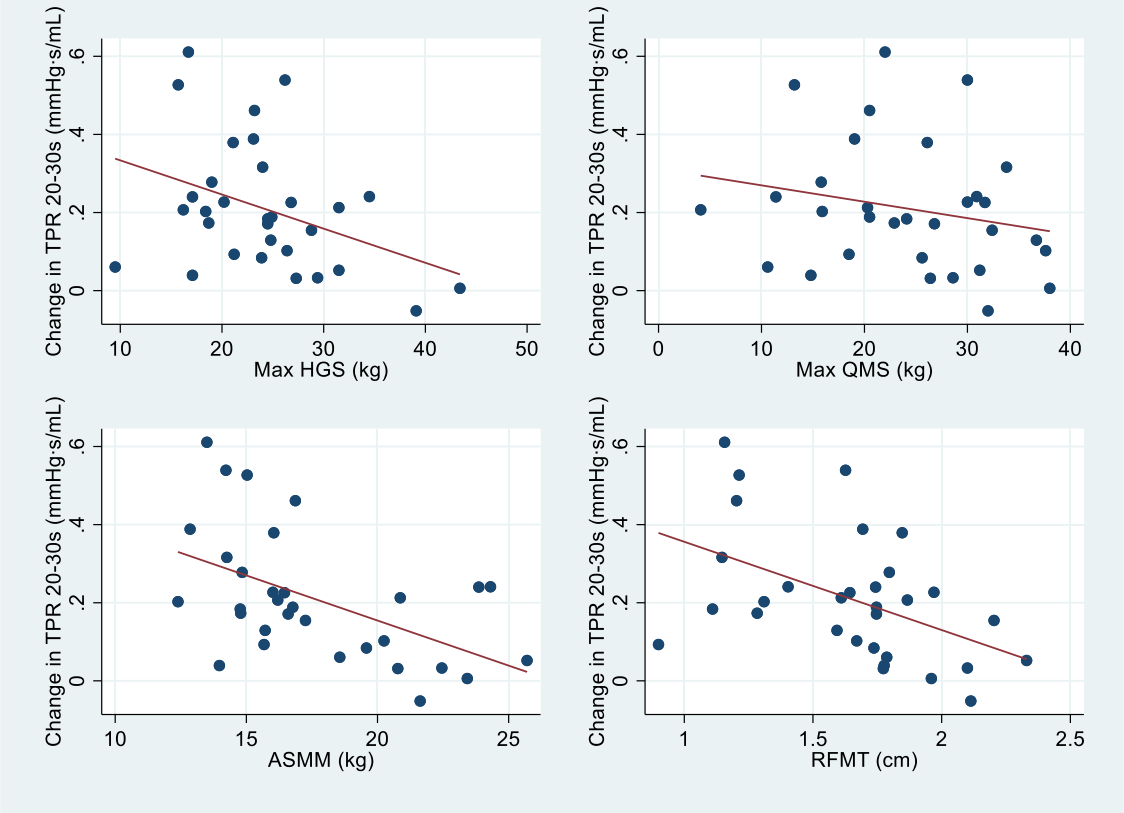

Figure 6-10: Scatterplots with fitted regression lines for the change in TPR 20 – 30s time period (mmHg·s/mL) vs. maximum hand grip strength (HGS) (kg), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Table 6-8: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in TPR 20 – 30 s time period (mmHg·s/mL) vs. maximum hand grip strength (HGS) (kg), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Change in TPR 20 – 30 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Max HGS	-0.01	0.00	-0.38	0.037	0.14	31
Max QMS	-0.00	0.00	-0.22	0.238	0.05	31
ASMM	-0.02	0.01	-0.52	0.003	0.27	31
RFMT	-0.23	0.08	-0.48	0.007	0.23	31

Change in SV and HR 10 – 20 s

Examining the components of CO: SV and HR, in the 10 – 20 s period, scatterplots against the muscle parameter found to be significantly associated with CO in this time period, maximum HGS, are shown in Figure 6-11. Linear regression outputs are shown in Table 6-9. Change in SV, but not HR, was found to be significantly and negatively associated with maximum HGS. Participants with higher HGS had a greater recovery from peak SV.

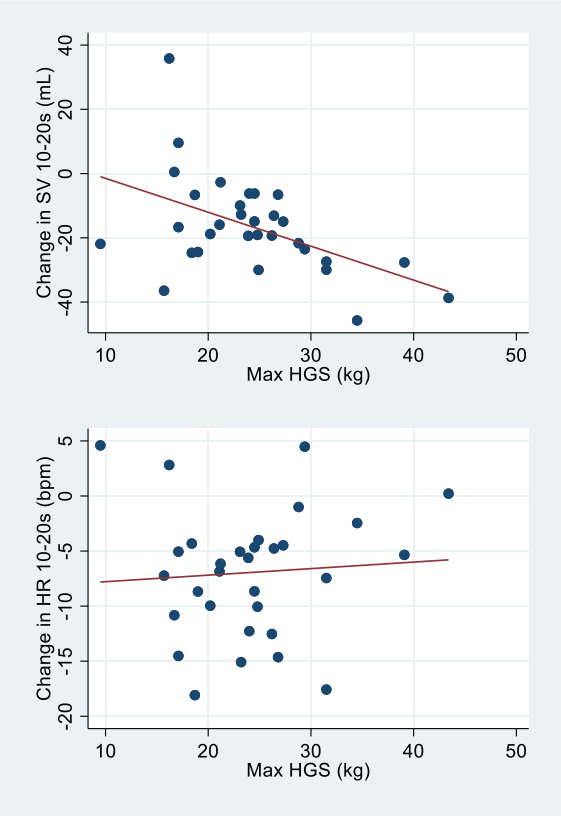

Figure 6-11: Scatterplots with fitted regression lines for the change in SV (mL) and HR (bpm) in the 10 – 20 s time period vs. maximum hand grip strength (HGS) (kg).

Table 6-9: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in SV (mL) and HR (bpm) in the 10 – 20 s time period vs. maximum hand grip strength (HGS) (kg).

Change in SV 10 – 20 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Max HGS	-1.06	0.35	-0.49	0.005	0.24	31
Change in HR 10 – 20 s						
Max HGS	0.06	0.15	0.07	0.700	0.01	31

Change in SV and HR 20 – 30 s

In the 20 – 30 s period, again starting with the muscle parameter found to be significantly associated with CO, maximum QMS, scatterplots against change in SV and HR in the 20 – 30 s period are shown in Figure 6-12, and regression outputs in Table 6-10. SV but not HR was significantly associated with maximum QMS in this time period. Those with higher maximum QMS had less change in this period as they were closer to zero.

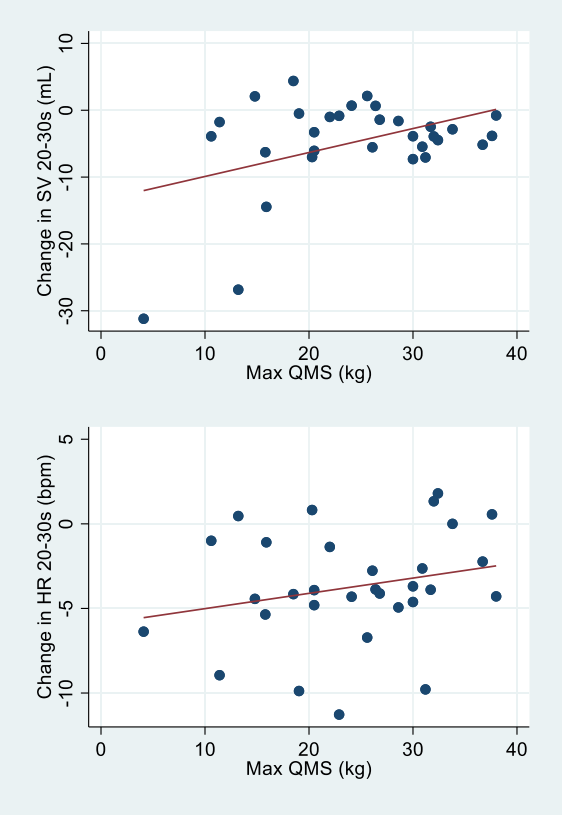

Figure 6-12: Scatterplots with fitted regression lines for the change in SV (mL) and HR (bpm) in the 20 – 30 s time period vs. maximum quadriceps muscle strength (QMS) (kg).

Table 6-10: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in SV (mL) & HR (bpm) in the 20 – 30 s time period vs. maximum quadriceps muscle strength (QMS) (kg).

Change in SV 20 – 30 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Max QMS	-0.36	0.15	0.42	0.020	0.17	31
Change in HR 20 – 30 s						
Max QMS	0.09	0.07	0.23	0.208	0.05	31

NIRS, EMG and Haemodynamic Measures in the First 30 s After Standing

Next, the relationship between thigh haemoglobin concentration, as measured by NIRS, electrical activity of the thigh muscles, as measured by surface EMG, and MAP change after standing were examined using linear regression. As before, parameters found to be significantly associated were broken down into the underlying haemodynamic components.

NIRS and MAP 0–30 s

First, THb of the thigh (rectus femoris muscle) as measured by NIRS and change in MAP within 30 s after standing were examined. Scatterplots of the change in MAP at time intervals 0 – 10 s, 10 – 20 s and 20 – 30 s against change in THb concentration at the same time intervals are shown in Figure 6-13, and outputs of the respective regressions in Table 6-11. A significant, positive association was seen between change in THb and change in MAP in the 10 – 20 s period. Those with greater changes in THb had greater recovery of MAP in this time period. Changes during the 0 – 10 s and 20 – 30 s periods were not significant.

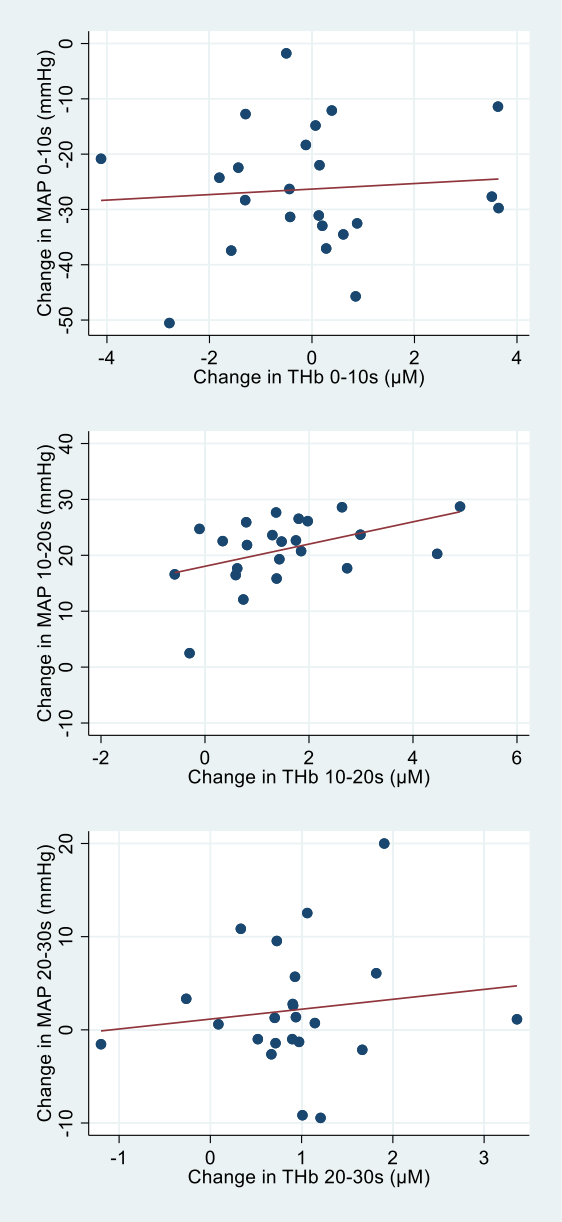

Figure 6-13: Scatterplots with fitted regression lines for: the change in MAP (mmHg) vs. change in THb thigh (μM) over the 0 – 10 s time period; the change in MAP (mmHg) vs. change in THb thigh (μM) over the 10 – 20 s time period; and the change in MAP (mmHg) vs. change in THb thigh (μM) over the 20 – 30 s time period.

Table 6-11: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in MAP (mmHg) vs. change in THb thigh (μM) over the 0 – 10 s time period; the change in MAP (mmHg) vs. change in THb thigh (μM) over the 10 – 20 s time period; and the change in MAP (mmHg) vs. change in THb thigh (μM) over the 20 – 30 s time period.

Change in MAP 0 – 10 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Change in THb 0 –10 s	0.50	1.33	0.08	0.711	0.01	23
Change in MAP 10 – 20 s						
Change in THb 10 – 20 s	1.99	0.86	0.45	0.031	0.20	23
Change in MAP 20 – 30 s						
Change in THb 20 – 30 s	1.06	1.69	0.14	0.535	0.12	23

NIRS, CO and TPR 10 – 20 s

The MAP findings were decomposed into its constituent CO and TPR changes in the same time period and examined against THb. Scatterplots are shown in Figure 6-14 and regression outputs in Table 6-12. Change in TPR but not CO, was significantly and positively, associated with change in THb. Those with greater changes in THb had greater changes in TPR during this time interval.

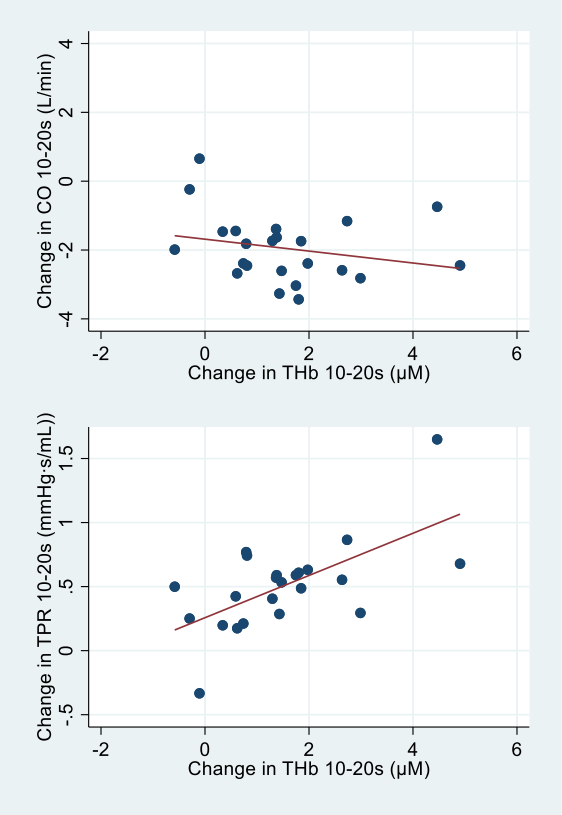

Figure 6-14: Scatterplots with fitted regression lines for: the change in CO (L/min) vs. change in THb thigh (µM) over the 10 – 20s time period; and the change in TPR (mmHg·s/mL) vs. change in THb thigh (µM) over the 10 – 20s time period.

Table 6-12: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in CO (L/min) vs. change in THb thigh (µM) over the 10 – 20 s time period; and the change in TPR (mmHg·s/mL) vs. change in THb thigh (µM) over the 10 – 20 s time period.

Change in CO 10 – 20 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Change in THb 10 –20 s	-0.17	0.15	-0.24	0.268	0.06	23
Change in TPR 10 – 20 s						
Change in THb 10 – 20 s	0.16	0.04	0.63	0.001	0.39	23

EMG and MAP 0 – 30 s

The change in RMS EMG from baseline at 10-second intervals during the first 30 s after standing was compared to changes in MAP at the same intervals. Scatterplots are shown in Figure 6-15 and regression outputs in Table 6-13. No significant relationships were seen between MAP and RMS EMG at any of the time intervals.

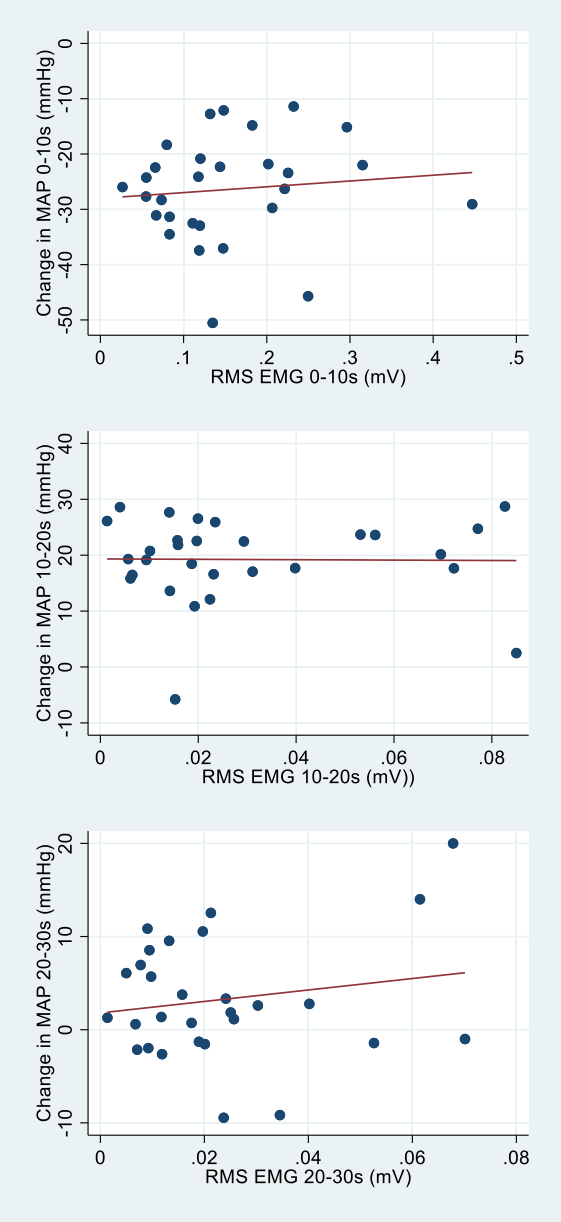

Figure 6-15: Scatterplots with fitted regression lines for: the change in MAP (mmHg) vs. RMS EMG (mV) over the 0 – 10 s time period; the change in MAP (mmHg) vs. RMS EMG (mV) over the 10 – 20 s time period; and the change in MAP (mmHg) vs. RMS EMG (mV) over the 20 – 30 s time period.

Table 6-13: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in MAP (mmHg) vs. RMS EMG (mV) over the 0 – 10 s time period; the change in MAP (mmHg) vs. RMS EMG (mV) over the 10 – 20 s time period; and the change in MAP (mmHg) vs. RMS EMG (mV) over the 20 – 30 s time period.

Change in MAP 0 – 10 s	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
RMS EMG 0 –10 s	10.50	19.27	0.10	0.54	0.01	29
Change in MAP 10 – 20 s						
RMS EMG 10 – 20 s	-3.42	56.72	-0.01	0.952	0.00	29
Change in MAP 20 – 30 s						
RMS EMG 20 – 30 s	61.55	66.36	0.18	0.362	0.03	29

MAP and Muscle Parameters During PCM

The maximum change in MAP during the standing PCM was examined against measures of muscle mass and function. Overall, the mean maximum change in MAP across the sample was 19.2 (SD 9.6) mmHg. Scatterplots with fitted regression lines for the maximum change in MAP during PCM vs. each of the muscle parameters are shown in Figure 6-16, and regression outputs in Table 6-14. Among the muscle parameters, only 5CST was significantly and negatively associated with change in MAP during PCM. Those with faster time on the 5CST had a greater gain in their MAP during PCM.

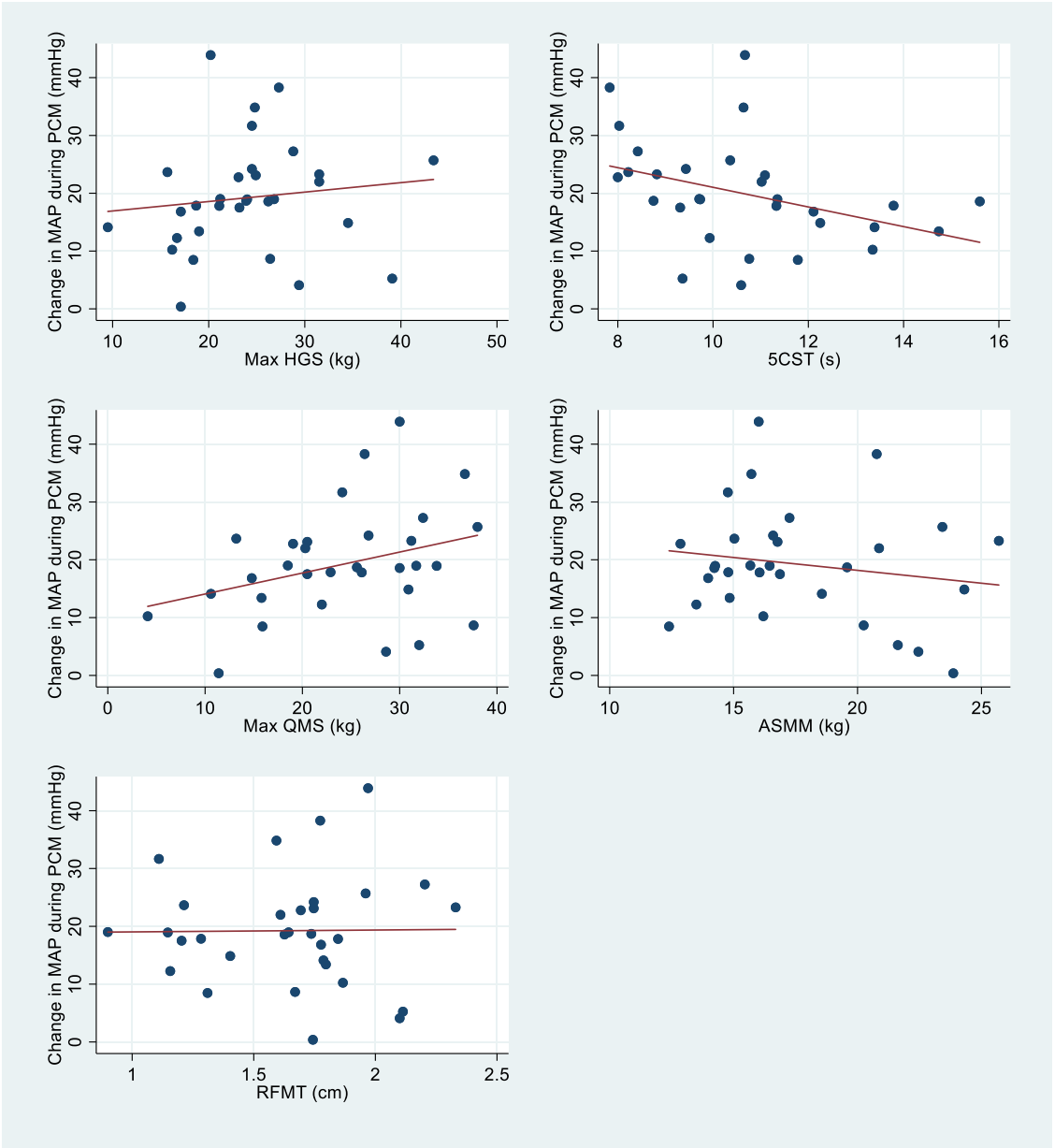

Figure 6-16: Scatterplots with fitted regression lines for the change in MAP during PCM (mmHg) vs. maximum hand grip strength (HGS) (kg), 5 chair stands time (5CST) (s), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Table 6-14: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the change in MAP during PCM (mmHg) vs. maximum hand grip strength (HGS) (kg), 5 chair stands time (5CST) (s), maximum quadriceps muscle strength (QMS) (kg), appendicular skeletal muscle mass (ASMM) (kg), and rectus femoris muscle thickness (RFMT) (cm).

Change in MAP during PCM	β	S.E.	β Std	P	R^2	N
Max HGS	0.16	0.25	0.12	0.520	0.01	31
5CST	-1.70	0.79	-0.38	0.040	0.14	30
Max QMS	0.36	0.20	0.32	0.077	0.10	31
ASMM	-0.45	0.48	-0.17	0.362	0.03	31
RFMT	0.32	5.15	0.01	0.950	0.00	31

NIRS, EMG and Haemodynamic Measures During PCM

Change in MAP during PCM, NIRS and EMG

The relationships between THb, RMS EMG and MAP change during PCM were then examined. Scatterplots are shown in Figure 6-17 and regression outputs in Table 6-15. Neither change in THb nor RMS EMG during PCM were significantly associated with change in MAP during PCM.

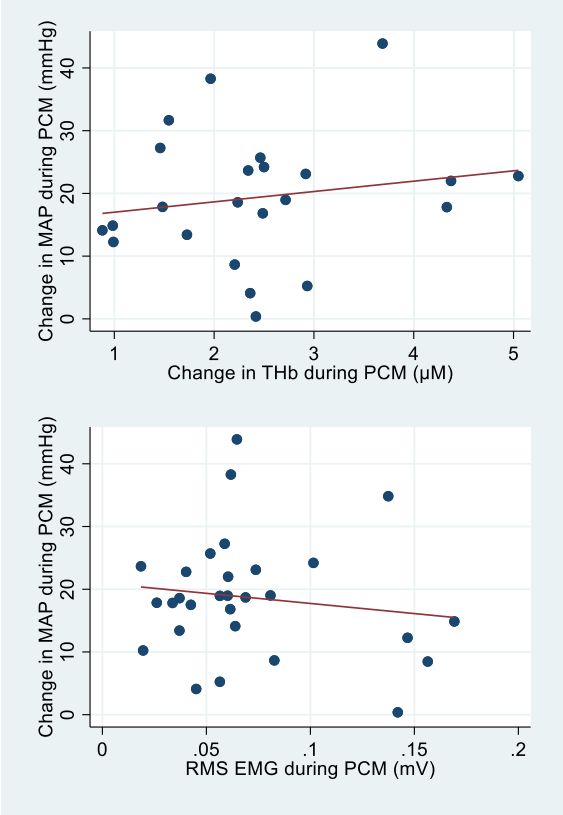

Figure 6-17: Scatterplots with fitted regression lines for: the change in MAP during PCM (mmHg) vs. change in THb during PCM (μM); and the change in MAP during PCM (mmHg) vs. RMS EMG during PCM (mV).

Table 6-15: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the: change in MAP during PCM (mmHg) vs. change in THb during PCM (μM); and the change in MAP during PCM (mmHg) vs. RMS EMG during PCM (mV).

Change in MAP during PCM	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Change in THb during PCM	1.65	2.02	0.18	0.424	0.03	23
Change in MAP during PCM						
RMS EMG during PCM	-32.29	44.41	-0.14	0.473	0.02	29

Change in MAP and Haemodynamics During PCM

CO and TPR were examined against MAP during the standing PCM. The means of the maximum change in CO and TPR during PCM were 1.0 (SD 1.0) L/min and 0.3 (SD 0.4) mmHg·s/mL, respectively. From the scatterplots shown in Figure 6-18 and the regression outputs in Table 6-16, it can be seen that change in TPR but not CO was significantly and positively associated with change in MAP during the PCM. Those with the greatest change in TPR had the greatest change in MAP.

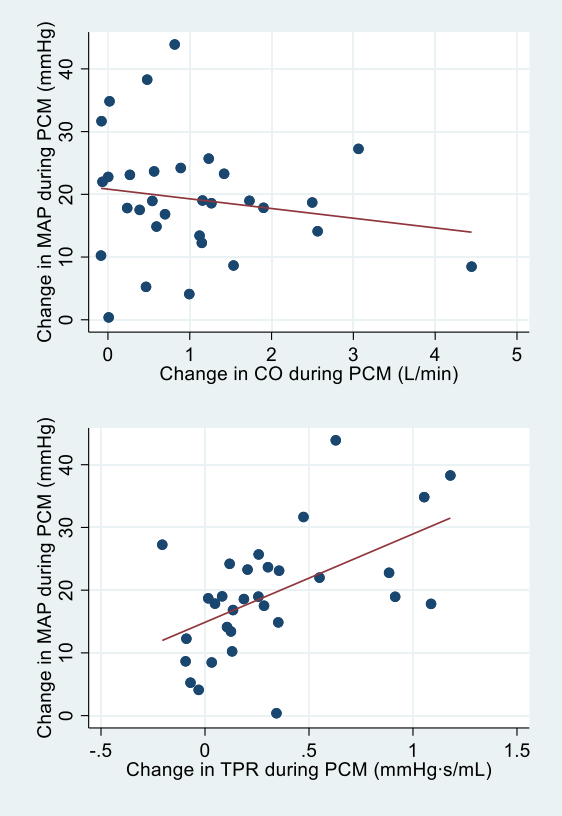

Figure 6-18: Scatterplots with fitted regression lines for: the change in MAP during PCM (mmHg) vs. change in CO during PCM (L/min); and change in TPR during PCM (mmHg·s/mL).

Table 6-16: Regression coefficients (β), standard error (S.E.), standardised regression coefficients (β Std), P-value, coefficient of determination (R2) and number of participants (N) from the linear regressions of the: change in MAP during PCM (mmHg) vs. change in CO during PCM (L/min); and change in TPR during PCM (mmHg·s/mL).

Change in MAP during PCM	**β**	**S.E.**	**β Std**	**P**	**R^2**	**N**
Change in CO during PCM	-1.54	1.71	-0.16	0.375	0.03	31
Change in TPR during PCM	14.09	4.06	0.54	0.002	0.29	31

Discussion

Overall, this study had five aims. First, to examine existing and emerging measures of muscle mass and function. Second, to investigate the relationship between these measures and early BP recovery after standing. Third, to examine the haemodynamics underlying this relationship and whether there was evidence for the role of the SMP, as determined by NIRS THb concentration and surface EMG activity. Fourth, to study the connection between muscle measures and PCM efficacy in terms of maximum MAP gain. Fifth, to examine the haemodynamic, NIRS and EMG signals to explore how PCMs are mediated.

Participants and Demographics

The recruited sample was a small convenience sample that was relatively healthy but still had some comorbidities. There were low rates of polypharmacy. Mean HGS was in the normal range for the Irish population [62]; however, the results were not stratified by sex. Median 5CST time (10.6 s, IQR 2.5) compared favourably with that in the Health, Aging and Body Composition Study in the US (mean 14.3 s, SD 4.0) [404]. Median ASMM 16.5 kg (IQR 6) was lower than that in a UK Biobank study mean 21.55 kg (SD 3.15) [405], but the mean age in UK biobank was 55.4 years. The data losses incurred illustrate the difficulties in acquiring continuous, high-resolution biological and bio-electrical signals in a real-world sample [406].

Muscle Mass and Strength

In terms of the comparison of new and existing measures of muscle mass and strength, there were a number of interesting findings. Maximum QMS was strongly correlated with HGS. This result agrees with previous studies that found close correlations between HGS and knee extensor peak torque [407] and lower limb extension power [408]. Measurement of QMS could be a useful alternative to HGS, especially in those unable to perform HGS or with osteoarthritis affecting their hands. QMS may be preferable to 5CST, which was not correlated with HGS in this sample and was shown in Study I to be a less powerful predictor of BP recovery after standing. RFMT and VLMT were moderately correlated with ASMM. The US measures directly visualise the muscle as opposed to BIA, which measures impedance and is then referenced to DXA via statistically derived equations [80]. Therefore, the two methods may be measuring different muscle aspects. As a reference standard, such as DXA, was not used in this study, I cannot comment on which method is superior. US, however, may give additional information on subcutaneous fat thickness and muscle architecture [409]. It may also be useful in those unable to perform BIA, those with

implanted electronic devices such as pacemakers, or those who are acutely unwell or bed-bound [410]. The current significant limitation with US is the lack of population reference values and cut-offs that limit its utility in clinical practice [411].

Visualisation

The visual trends observed across haemodynamics in Figure 6-3 were as expected with novel information provided by the addition of THb and EMG. The increased EMG activity during quiet standing fits with the previous findings of Masterson et al., who found increased EMG activity of the gastrocnemius muscle during quiet standing, with older participants having more EMG activity than their younger counterparts [304]. The increased THb observed visually during the standing phase also fits with previous findings by Bringard et al [412] and Truijen et al [413], who reported increased THb in the calf on standing and head-up tilt respectively.

Muscle Parameters and MAP in the First 30 s After Standing

No significant associations between muscle parameters and MAP were seen for the 0 – 10 s period. This fits with the findings of Studies I and II that the initial drop was not significantly affected by sarcopenia status. In contrast, higher HGS was found in those with initial OH compared to those without OH in the MELoR study [186]. Mol et al. [278] found that the rate but not magnitude of SBP drop in the first 15 s after standing was positively associated with 5CST time in a sample attending a Geriatric Medicine outpatients department. Differing methodologies in terms of continuous variable vs. a dichotomous definition may explain the results. Additionally, the physiology underlying the initial drop is incompletely elucidated [173] but is known to be influenced by the duration of supine rest, speed of standing [414] and muscular effort of standing [179].

The finding in the 10 – 20 s period that HGS, ASMM and RFMT were associated with MAP recovery is consistent with Studies I and II in terms of probable sarcopenia and sarcopenia. HGS was a consistent finding across all of my studies. RFMT had a stronger association in terms of coefficient of determination, but all were modest associations given the small sample with wide variability in the datapoints. Previously, de Bruine et al., [267] and Mol et al. [278] did not find HGS to be predictive of OH and BP recovery, respectively. Mol et al. reported slightly different findings, namely 5CST time to be associated with DBP recovery in the 30 – 60 s period. However, the sample in the Mol et al study was older, more comorbid and with slower BP recovery, whereas in the current study participants had already recovered by 30 s. De Bruin et al. used an OH classification

adapted from the consensus definition [178]. This points to the challenges in regard to the different measures in different studies. However, overall, there does appear to be a consistent relationship between BP recovery and muscle strength across studies.

This is reinforced by the 20 – 30 s findings in the current study, which demonstrate that those with higher muscle measures by HGS, QMS, ASMM and RFMT had less change in MAP during this period. As suggested in the BP visualisation, this may be because they have likely already recovered their MAP and therefore the magnitude of change in MAP is lower at this stage. These results are consistent with those of Study I, which found a small but significant positive association between HGS-defined probable sarcopenia and BP change at this time point, suggesting that the probable sarcopenia group were still recovering while the robust had already recovered. Similar to above, Mol et al. [278] found 5CST time to be associated with DBP recovery in a the 30 – 60 s time period after standing. Given that their sample was recruited from attendees to a Geriatric Medicine outpatients department, they were older and more comorbid with higher levels of polypharmacy. As a result, they likely had a slower recovery of BP after standing.

Haemodynamics Underlying the MAP Relationship

Examining the hemodynamic parameters underlying MAP, the 10 – 20 s changes appear to be related to the significant association of HGS with CO rather than TPR. Those with higher HGS recovered their CO more in the 10 – 20 s period. The CO-HGS findings appear driven by SV rather than HR. These findings are consistent with Study II-B, which found that the non-sarcopenic group had a quicker recovery from peak CO, mediated by SV rather than HR. This may be supportive of a SMP effect, in that those with increased HGS more efficiently return blood to the heart via the SMP leading to increased preload and therefore SV and CO. Wieling et al [378] found when comparing young subjects (10 – 15 years) to old subjects (>70 years) that the young group recovered to a significantly lower steady state SV than the older group, which may support these findings, although no measures of muscle were taken in that study.

In the 20 – 30 s period when MAP recovery had settled in many participants, those participants had little change in their CO and the only significant association seen was with maximum QMS, which again was mediated via SV rather than HR. TPR change in this period was significantly negatively associated with maximum HGS, ASMM and RFMT, as those with the highest values had stabilised their MAP and were now entering the steady-state phase, whereas the those with a MAP deficit were still recovering.

Muscle Blood Flow and Electrical Activity

In terms of haemoglobin concentration in the thigh, as measured by NIRS THb of the rectus femoris muscle, the change in THb in the 10 – 20 s period was associated with MAP in the same time interval. This suggests that those with higher concentrations of haemoglobin in the rectus femoris muscle, potentially signifying increased blood flow, had greater MAP recovery. This would be supportive of a SMP effect; however the MAP changes appear to be mediated by TPR rather than CO, which goes against the SMP hypothesis. Instead, it supports sympathetic-mediated increase in TPR with increasing THb. This is counterintuitive initially as one might expect vasodilation (reducing TPR) rather than vasoconstriction to lead to increased THb, however the contraction and relaxation of the blood vessels of the lower limbs is complex and contractions of the SMP may increase TPR while also increasing blood flow into and out of the muscles [415]. Furthermore, as discussed earlier, THb has been shown to increase during standing and head-up tilt [412,413] and so the association seen in this study may not be causative.

The EMG findings of lack of significant association between change in RMS EMG from baseline, and MAP change, across time intervals, also go against the SMP hypothesis that increased muscle activity may lead to increased venous return to the heart. In contrast, Shamsuzzaman et al [306] compared head-up tilt to head-up suspension (full relaxation of lower limb muscles, thereby likely inactivating the SMP completely). They found increased HR and BP with increased EMG and MSNA in head-up tilt compared to head-up suspension. This was accompanied by increased calf blood flow with lower SV and CO. The authors proposed that this was evidence of the lower limb muscles providing a SMP, acting via vasoconstriction rather than CO, in the head-up tilt, which was not possible in the head-up suspension.

It must be stated that the examination of the signals in the present study has been inter-participant, which is a significant limitation. Modeling the complex dynamic relationships between these signals remains a challenge. In this study, the intended approach was to present the raw data and use straightforward, transparent statistics to describe the relationships and built a hypothesis. This is in contrast to the complex statistical and signal modelling performed in other recent studies looking at the relationship between and EMG during standing which are difficult to externally validate [323,324]. Additionally, the relationships are of course associative, and any inference of causation is presumptive.

There are many feedback and feedforward loops in the control of BP and haemodynamics and no model will be able to capture this complexity with complete fidelity.

PCM

In terms of PCMs, surprisingly, the only muscle parameter associated with the maximum MAP gain during the standing PCM was 5CST time. Those with a faster 5CST time had a greater gain in MAP during the PCM. Perhaps there are similarities between the two tasks, lower limb tensing and squeezing, and lower limb muscle activation in a sit-to-stand test. The results may relate to the efficacy with which one can perform both manoeuvres rather than inherent muscle strength or mass *per se*. The relationship between muscle strength and mass and the effectiveness of PCMs has not been studied before, although in trials of PCM efficacy in syncope, higher syncope recurrence rates have been seen in older participants, with the authors hypothesising it may relate to reduced muscle mass and strength [402,403].

Further, also surprisingly, the change in MAP was not related to the change in THb, EMG or CO in the current study; instead, it was correlated with the change in TPR. This again goes against the SMP hypothesis of mechanical translocation of blood from the lower limbs and perhaps fits better with an exercise pressor type reflex leading to increased sympathetic activity and increased TPR and increasing MAP in that way. Again, the caveats of the previous paragraphs must hold, these are associative findings in a small sample. A recent semi-systematic review of PCM [256], which included 45 studies of various designs and settings, found that in most studies an increase in CO was seen during PCM, which does agree with the overall mean increase in CO in the current study. The semi-systematic review also found variability in the TPR findings of previous studies with some reporting increases and some decreases. Regarding the EMG findings, in a larger study of 90 participants with long COVID [416], I previously found a significant positive association between SBP rise and RMS EMG activity of the thigh during PCM, suggesting that the lack of association in the current study may be due to the small sample. However, the clinical characteristics of the two samples are very different.

Strengths of the Study

The results of the present study are strengthened by detailed signal acquisition of continuous beat-to-beat BP and haemodynamic measures, coupled with synchronous recording of NIRS and EMG, with robust signal preprocessing and processing following international best practice. This is complemented by measurement of multiple different

measures, both well-established and emerging, of muscle mass and function. Continuous variables were used rather dichotomous groupings and transparent statistics were presented along with raw data.

Limitations of the Study

There are however significant limitations to this study. It was a small sample with a female preponderance and there was wide variability in the data as evidenced on the scatter plots. The regressions had moderate associations at best as indicated by the coefficients of determination. The analyses were also unadjusted and bivariate in nature, more for exploratory purposes than confirmatory. As discussed earlier, the investigative approach was inter-participant rather than intra-participant and the full length time varying signals were not used but rather aggregated into time intervals. This may reduce the power to detect differences, however, it is statistically challenging to compare full length signals across multiple participants. Furthermore, there was data loss on some participants which meant it was not possible to look at all the collected signals.

Conclusion

In conclusion, consistent evidence was found for the association between muscle measures, especially HGS, and early MAP recovery after standing. This may be driven by SV increases, potentially suggesting SMP involvement, but conflicting evidence from the NIRS signals with an association between THb and TPR, and a lack of relationship between EMG and MAP changes, argue against this. PCM-related changes in MAP also appear sympathetically mediated via TPR. Measures of muscle strength such as QMS and muscle mass such as RFMT could be alternatives to HGS and BIA respectively especially where these are not available or feasible.

Chapter 7 – Discussion

Key Findings

Study I

- Probable sarcopenia was associated with an attenuated recovery, rather than maintenance, of BP during an active stand test.
- HGS-defined probable sarcopenia had a larger magnitude of effect on BP recovery than 5CST.
- HGS-defined probable sarcopenia was an independent predictor of OH30, but 5CST was not.
- Those with both HGS-defined probable sarcopenia and OH30 had a significantly higher odds of future recurrent falls.

Study II-A

- Probable sarcopenia and BIA-confirmed sarcopenia were associated with an attenuated recovery of SBP and DBP in the early 10–20 s after standing.
- This was independent of confounders and the effect of HR.
- There was a larger attenuation in BP recovery rate for the sarcopenia group compared to the probable sarcopenia group.

Study II-B

- Changes in MAP after standing appeared to be driven initially by a blunted peak in CO.
- This was followed by an attenuated recovery of CO from peak and TPR from nadir.
- CO findings appeared driven by SV rather than HR.

Study III

- In a healthy sample, muscle parameters, in particular HGS, were associated with MAP recovery, especially in the 10–20 s period.
- This relationship appeared to be driven by CO, and SV, rather than TPR or HR.
- MAP recovery was associated with change in THb of the thigh in the 10–20 s time period.
- However, this relationship appeared to be associated with TPR rather than CO.
- There was no evidence of an association between EMG and MAP in this sample.
- MAP change during PCM appeared driven by TPR rather than CO in this sample.

Sarcopenia and Orthostatic Haemodynamics

The key research question posed at the beginning of this thesis was:

What is the relationship between sarcopenia and BP recovery and maintenance after standing?

From the results of the three studies conducted, it has been shown that sarcopenia is related to an impairment in early BP recovery rather than later recovery or maintenance. The consequences of this may be an increased risk of falls, as demonstrated in the longitudinal follow-up. As discussed previously, these results differ from existing studies of sarcopenia and OH, which found a relationship at and after 1 minute, in sarcopenia and severe sarcopenia [200,263]. This is largely unsurprising, as previous studies were unable to assess BP recovery as they used intermittent measures of BP. The samples studied previously also differed from the samples in this doctoral investigation. Prior studies were set in Geriatric Medicine outpatients departments with a greater prevalence of sarcopenia and the inclusion of severe sarcopenia. Although I did not directly assess severe sarcopenia, it was unlikely to have been present given the relative health and functional independence of the samples in my studies. It is possible that the effect size seen in these relatively healthy samples did not translate into more severe impairment in BP maintenance.

My results extend beyond the pathological state of sarcopenia, into healthy ageing, where muscle measures appear to maintain their relationship with BP recovery. In particular, HGS continues its consistent association with the key 10–20 s period after standing, a time during which the majority of participants would be recovering from the nadir in BP. These results suggest that there is a continuum upon which muscle strength and mass are related to the recovery of BP. Whether this association is causative of course remains to be seen, however the relationship does appear to be mediated via CO and SV rather than TPR or HR and so may involve the SMP.

Another point of interest is the consistent superiority of HGS, an upper-limb measure, over 5CST, a lower-limb measure, across the three studies, in terms of association with BP recovery. As stated earlier, this may be more related to the specificity of HGS as a marker of muscle strength compared to 5CST, which incorporates elements of endurance and balance, than a pronouncement of the primacy of the upper limb *per se*. While QMS was not significantly associated with change in MAP 10–20 s in Study III, observing the scatter plot and the borderline P-value, this may be due to insufficient statistical power and the effect of outliers rather than the true absence of a relationship.

The Role of the Skeletal Muscle Pump

The further research questions of this doctoral investigation considered how the sarcopenia–BP recovery relationship was mediated and whether there was evidence for the role of the SMP. These questions, were explored in detail and answered to the best possible extent allowed by the research design. The proposed hypothesis was that sarcopenia might affect the SMP, leading to diminished venous return, reducing SV and hence CO, leading to an impairment in recovery of MAP.

This hypothesis was initially supported by the findings of Study II-A, that sarcopenia was associated with an attenuated early SBP and DBP recovery, independent of HR. The findings from Study II-B, that MAP changes were mediated, at least partially, by CO and SV rather than HR further support the hypothesis. However, the finding that TPR was strongly associated with MAP changes in the 10–20 s interval, confirm its likely predominance in BP recovery from nadir, but does not necessarily negate the supportive role of the SMP.

The hypothesis is further supported by Study III, in particular the findings of the HGS-MAP relationship in the 10–20 s period and that this appears to be driven by CO rather than TPR, and CO by SV rather than HR. While the hypothesis is further supported by the finding that THb is associated with MAP in the 10–20 s period, the finding that THb appears driven by changes in TPR rather than CO goes against the SMP hypothesis. However, this points to the logical conclusion that multiple factors, influencing a number of mechanisms, ultimately contribute to differences in BP recovery between participants.

Overall, it cannot be said that the sarcopenia-SMP hypothesis is proven. The limitations in methodology, as well as analyses, as will be discussed later, mean that at best support for its role can be demonstrated. Further analyses and investigations would be needed to prove the hypothesis as will be discussed later.

Challenges in Statistical Analysis of the BP Response to Standing

The BP response to standing is a complex signal that cannot easily be represented by an equation, nor expressed using analytical methods. Many differing techniques have been employed in the literature: absolute or relative change in BP at timepoints after standing [379], OH definitions [181], percentage recovery [363], recovery rates [282], clustering algorithms [274] and mixed-effects models with linear splines [272]. Each has inherent advantages and limitations. One of the key issues is the ability to statistically adjust for

potential confounders. This is the strength of using linear splines to model the complex shape of the BP response. Coupled with mixed-effects linear regression, which uses random effects to account for the repeated measurements in BP obtained for each participant, it becomes a powerful tool for these analyses. The choice of time-intervals for splines is important, in this thesis I continued the decision made by previous investigators from TILDA [342,414] to use five splines, with four splines modelling the first 40 s, the most dynamic phase, in 10 s intervals, with one further spline accounting for 40–180 s. There are limitations to this approach in terms of the fidelity with which the model captures the complex shape of the BP drop and recovery. Perhaps using seven splines to model the first 60 s at 10 s intervals may have more closely approximated the dynamic signal. However, this would be at the expense of model complexity, and on the basis of the principle of parsimony a less convoluted model is preferable.

Other approaches such as cubic splines may have captured the BP response more closely but would be more difficult to interpret and extrapolate. Principal component analysis, a statistical technique which reduces dimensionality in data analysis by identifying the key components of a signal, has been employed previously to analyse NIRS signals from the forehead during standing [417]. However, the output from this technique can be less tangible and its real-world meaning can be hard to interpret. Function-on-scalar regression is a novel technique that has recently been employed in TILDA to analyse the effect of diabetes on the BP and cerebral oxygenation response to standing [418]. It has the major advantage of estimating the independent effect of the variable of interest, while controlling for confounders, in a dynamic fashion over the whole active stand signal rather than at individual time-segments. With the appropriate statistical support it may prove an optimal method to encapsulate the dynamic nature of the orthostatic BP signal.

Challenges of Multimodal Signal Exploration

If statistical analysis of the BP response to standing was a significant challenge in Studies I and II of this doctoral investigation, in Study III, capturing, aligning, synchronising, and comparing signals from different modalities, captured on different devices, at different sampling rates, was an even greater challenge that necessitated much resource in terms of time. Visualisation proved an essential tool for validating the data and allowed qualitative analysis of temporal associations between signals. However, statistical inference regarding associations between multiple signals is more difficult.

In Study III, simple linear regression was used to compare values across participants. This has the advantages of interpretability and transparency, however, to understand the mechanisms further, an approach of comparing the signals both intra- and inter-participant might be necessary. Furthermore, the approach in Study III of aggregating change over 10 s intervals to produce single values for comparison, while commonly employed, discards the full temporal associations of these complex time-varying signals. However, the comparison of multiple high-resolution dynamic time-varying signals both intra- and inter-participant is a non-trivial task.

Approaches in the time domain such as linear correlation and cross-correlation, and frequency domain such as spectral analysis, between signals are often employed [406]. However, given the complexity of the signals in this study an advanced approach, such as wavelet transform coherence or convergent cross mapping may be needed. Wavelet transform coherence is an advanced signal processing technique that combines time-domain coherence methods with frequency domain wavelet analysis to allow combined time-frequency analysis of dynamic time-varying, non-stationary (i.e. varying mean and variance) signals [419]. Convergent cross mapping is another advanced statistical technique that aims to go beyond the associations between two signals and by using the temporal relationship between the signals, aims to infer a measure of causality [420]. It is an extension of Granger causality which allows measurement of causality in the linear relation between two time series. Convergent cross mapping develops non-linear connections between two time series by examining the association between lagged versions of one variable and the current values of the second variable [421]. As discussed in the introduction, these methodologies have been employed to good effect by a research group at Simon Fraser University to investigate the links between BP, postural sway and EMG of the lower limbs [322–324,422,423]. As such these techniques may be the way forward in future investigations involving multimodal signals.

Challenges in the Acquisition of Real-World Signals

Some of the challenges associated with signal acquisition from clinical and research participants were demonstrated in this project. In many physiological studies, young, healthy volunteers without co-morbidities are selected [424]. With older participants with co-morbidities, medications and physical frailty; signal variability and noise invariably increase [425]. The challenge of signal noise was especially encountered in the processing of beat-to-beat haemodynamic signals in Study II. In Study III, loss of data from poor

quality signals due to movement artefact and loss of electrode connection was encountered. Overall, measurement conditions, movement artefact, suboptimal digital artery perfusion all pose significant challenges to signal acquisition in clinical and research cohorts.

Filtering techniques such as moving average filtering can help to smooth out variation in the signals. Given that 10 s intervals were used in the statistical analysis, ±5 s moving averaging is unlikely to have a major impact on the outcomes of any models. Indeed, the relevance of short one or two beat changes in BP or HR is uncertain, Van der Velde et al. found that 5 s averages had the best association with falls in the previous year in 217 attendees to a Geriatric Medicine outpatients department [426]. However, to the best of my knowledge, the impact of short duration drops in BP on cerebral perfusion, symptoms and prospective falls is unknown. Given that with oscillometric measurement, usually three or four measurements in 3 minutes standing are taken, and used for the diagnosis of OH, the approach of averaging to 18 measurements over 3 minutes after standing taken in this doctoral investigation is a significant increase in temporal resolution and likely represents a pragmatic balance.

Standing time is another related issue. It is known that speed of standing affects the BP response as does the muscular effort involved in standing [427]. Older participants stand more slowly than younger and therefore may not have as pronounced an initial drop in BP [164]. Some investigators try to combat this by statistically adjusting for standing time [414]. In so doing they are effectively adjusting all participants in a study to a common mean time for transition from lying to standing. This is not something that I am in favour of for a number of reasons. Standing speed is a physiological variable, it is natural that the speed at which one can transition from lying to standing increases with age and is likely affected by many conditions including osteoarthritis and physical frailty, in the same way 5CST varies among participants. By statistically controlling, one is adjusting many participants to a speed of standing that they will, in reality, never attain. Given the relation between speed and effort of standing and initial drop in BP, it is with good reason that many older adults stand more slowly, to avoid initial OH and symptoms of cerebral hypoperfusion. Additionally, the active stand test is already an artificial procedure. Day-to-day most older adults are unlikely to jump up from the supine position on a regular basis and are more likely to make a supine-to-sitting and then sitting-to-standing transition gradually. While some provocation and stress can be useful to dynamically challenge haemodynamic regulation, adding to this with statistical adjustment of standing speed takes

it too far in my opinion. Additionally, the relationship between standing speed and initial BP drop could potentially be non-linear in which case the statistical treatments applied are inappropriate. What is more, in most protocols for assessment of physiological parameters the participant is encouraged to give their best effort, and this is taken as the true and valid measure, for example maximum HGS, forced vital capacity etc. It is not routine to measure a component of the procedure to allow for statistical adjustment of the effort committed to the measure of interest, as is proposed by some when analysing the active stand.

Limitations

This doctoral investigation had a number of limitations. As discussed previously, the samples studied were relatively healthy with no severe sarcopenia and this may have underestimated the effect size in terms of the relationship between sarcopenia and delayed BP recovery and OH. While Study I was well powered, it lacked measures of muscle mass and so couldn't determine confirmed sarcopenia. Study II, due to its smaller sample size had imprecise estimates as evidenced by the wide standard errors and so failed to demonstrate a prediction of delayed BP recovery, as defined by OH30, but rather a surrogate of this in the rate of recovery of BP in the 10–20 s period. The structural equation model also failed to predict falls as a cross-sectional outcome. Study III meanwhile was exploratory in nature rather than confirmatory but again a small sample, with female preponderance, and significant variability in signals limited the inferences that could be established.

The limitations of the statistical approach have been mentioned in the previous sections, but the methodological approach also had its limitations. The methodological approach was non-invasive, with derived parameters from the Finapres used for haemodynamic measures and NIRS and EMG used as approximation of SMP activity. The non-invasive derived haemodynamic variables have inherent limitations as they are derived from one another. Doppler echocardiography is an alternative non-invasive method to measure CO however Modelflow appears to agree well in with it in terms of relative changes [395]. TPR would be difficult to measure directly in any methodology and likely would have to be derived from CO in any event. NIRS and EMG gave a crude approximation of SMP activity and perhaps using more detailed measures such as doppler US to measure blood flow and plethysmography to measure the SMP ejection fraction may have been more precise. Furthermore, most previous investigations have measured calf muscle pump

activity, I chose to focus on the rectus femoris muscle for several reasons. The FRAILMatics research group and I had some previous experience with the TROPIC study in measuring NIRS and EMG of this muscle [428]. It is more straightforward to assess muscle mass with US at the thigh rather than calf. EMG of the calf was included in the assessment protocol but unfortunately there was significant data loss due to electrode disconnection during movement from supine to standing. Additionally, while the importance of splanchnic vasoconstriction and venoconstriction to BP recovery is well recognised [167], neither was measured in this project.

Overall, the limitations in this study mean that the role of the SMP is not proven as such but has been explored and suggestions made of its importance.

Clinical Importance of the Findings

As discussed previously the clinical significance of these findings stems from the fact that both sarcopenia and OH are major age-associated conditions associated with a host of adverse outcomes in older adults. The findings suggest a second pathway that may exist whereby sarcopenia, in addition to directly leading to falls via gait and balance impairment, could indirectly lead to falls via delayed recovery of BP on standing. This hypothesis is supported by the longitudinal findings from Study I which suggest that those with both probable sarcopenia and OH30 have a significantly increased odds of recurrent falls during follow-up. This adds strength to the recommendations in the World Guidelines for Falls to assess HGS as part of a multifactorial falls risk assessment [359]. However, sarcopenia assessment is not specifically advised in the guidelines. I feel that this is a missed opportunity to highlight a significant falls risk factor. Given the findings from Study II-A, that the sarcopenia group had a more pronounced impairment in recovery rate of BP compared to probable sarcopenia, it would be reasonable to consider including muscle mass assessment in order to make the diagnosis of sarcopenia. BIA is relatively inexpensive and straightforward. When measuring beat-to-beat BP with the Finapres, height and weight are needed for the calibrations and so the measurement protocol for these could easily be adapted to perform BIA, which will capture the weight concurrently during the process. Importantly sarcopenia is potentially reversible—the SPRINTT trial [123] and Travers et al. [124] both demonstrated straightforward interventions by which sarcopenia may be ameliorated. However, the impact these interventions have on falls is unclear, in the SPRINTT trial there was a higher rate of falls in the intervention group. The impact of these interventions on orthostatic BP recovery is also uncertain. Frith et al.

[247] did not find a significant difference in orthostatic BP drop with a lower limb muscle strengthening programme, but perhaps in a cohort with non-neurogenic OH, improvements in BP *recovery* might be apparent.

Future Directions

A number of potential future directions arise from this doctoral work. In terms of investigation, most immediately the investigation of the role of the SMP is ongoing. I am working with my collaborators in the FRAILMatics group to utilise more advanced statistical techniques to explore the role of the SMP. In particular, it is planned to use cross-correlation to investigate the effects of signal lags between EMG, NIRS and BP responses to the PCM in the sample from Study III. Linking this to the derived haemodynamic parameters using the advance statistical techniques of Granger Causality and Transfer Entropy may uncover further the mechanisms by which the SMP is employed to raise BP during PCM.

In addition to this investigative work, as mentioned in the previous section, an interventional study investigating the effect of sarcopenia interventions on BP recovery is warranted. For pragmatic reasons, perhaps nesting this within a study of the effects of sarcopenia intervention on falls would be useful. However, single interventions are notoriously difficult to link to improvements reductions in falls and so a robust methodology ensuring regular falls follow-up would be needed. A more practical approach would be incorporating sarcopenia interventions into multifactorial falls interventions and assessing the overall effect on falls, with BP recovery as a potential secondary outcome.

Finally, implementation studies are also due. While the generation of new knowledge and understanding is beneficial in its own right and the demonstration of the effects of an intervention provide an evidence base for health systems change, it is the application of research into clinical practice that is often the most difficult [429]. Studying the effects of routine clinical implementation of either existing knowledge around sarcopenia and falls interventions, or those arising from the two previous steps would be most illuminating and ultimately likely have the greatest impact on patient care.

Conclusion

Sarcopenia appears to be related to delayed recovery of BP after standing. This may increase the risk of adverse outcomes over and above those syndromes individually. The mechanisms underlying this are not fully elucidated but the effect of sarcopenia on the

SMP likely plays a role. Future research focusing on the benefits of sarcopenia interventions on BP recovery would be useful while the development of pathways to rapidly and continuously incorporate research findings into clinical practice in Falls and Syncope Units is essential in order to tackle the increasing challenges of an ageing population.

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Appendices

List of Appendices

Appendix A: Study I – Full Mixed Effects Regression Outputs

Change in SBP and 5CST-defined Probable Sarcopenia

```
mixed delta_sys c.(t1-t5)##(i.CST15) c.age i.sex  c.height c.weight  i.CVDhbp i.CVDdiabetes
i.CVDheartfail i.MDcardiovascular i.MDpsychotropic  i.FOFactivitylimit || tilda_serial:,
residuals(ar1, t(samp_no))
Note: time gaps exist in the estimation data

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -195879.93
Iteration 1:   log likelihood =  -188580.4  (not concave)
Iteration 2:   log likelihood = -187000.39
Iteration 3:   log likelihood = -186776.97
Iteration 4:   log likelihood = -186582.11
Iteration 5:   log likelihood = -186557.18
Iteration 6:   log likelihood = -186557.08
Iteration 7:   log likelihood = -186557.08

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =     54,078
Group variable: tilda_serial                    Number of groups  =      2,858

                                                Obs per group:
                                                              min =         12
                                                              avg =       18.9
                                                              max =         19

                                                Wald chi2(21)     =   53437.86
Log likelihood = -186557.08                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
         delta_sys |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
                t1 |  -2.941039   .0169918  -173.09   0.000    -2.974342   -2.907735
                t2 |   2.208043   .0169414   130.33   0.000     2.174839    2.241248
                t3 |   .2056394   .0168126    12.23   0.000     .1726874    .2385914
                t4 |    -.03121   .0164927    -1.89   0.058     -.063535    .0011151
                t5 |   .0371082   .0018553    20.00   0.000     .0334718    .0407447
           1.CST15 |  -.1599362   .6304583    -0.25   0.800    -1.395612    1.075739
                   |
        CST15#c.t1 |
                1  |   .0705008   .0337948     2.09   0.037     .0042641    .1367374
                   |
        CST15#c.t2 |
                1  |  -.2481254   .0336799    -7.37   0.000    -.3141367   -.1821141
                   |
        CST15#c.t3 |
                1  |   .0829571   .0334277     2.48   0.013     .0174401    .1484742
                   |
        CST15#c.t4 |
                1  |   .0492422    .032793     1.50   0.133    -.0150308    .1135153
                   |
        CST15#c.t5 |
                1  |   .0110012   .0036981     2.97   0.003      .003753    .0182494
                   |
               age |  -.0017494    .031904    -0.05   0.956    -.0642801    .0607812
                   |
               sex |
            Female |   .7093118   .6817654     1.04   0.298    -.6269239    2.045548
            height |  -.1959006   .0388588    -5.04   0.000    -.2720624   -.1197387
            weight |    .136956   .0190086     7.20   0.000     .0996999    .1742121
                   |
            CVDhbp |
               Yes |   .9418509   .7180112     1.31   0.190    -.4654252    2.349127
                   |
       CVDdiabetes |
               Yes |  -1.510809   .9716073    -1.55   0.120    -3.415124    .3935067
                   |
```

```
      CVDheartfail |
               Yes |  -2.662156   3.200275    -0.83   0.405     -8.93458    3.610267
1.MDcardiovascular |  -1.701912   .7205518    -2.36   0.018    -3.114168   -.2896567
  1.MDpsychotropic |  -.6613335   .6959098    -0.95   0.342    -2.025292    .7026245
1.FOFactivitylimit |   .7401937   1.022285     0.72   0.469    -1.263448    2.743836
             _cons |   26.63867   7.036104     3.79   0.000     12.84816    40.42918
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
tilda_serial: Identity       |
                  var(_cons) |    123.569   3.767279      116.4015    131.1778
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho |   .6330362   .0045684      .6239974    .6419056
                     var(e) |     84.299   1.024718      82.31433    86.33153
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 71590.57              Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Change in DBP and 5CST-defined Probable Sarcopenia

```
mixed delta_dia c.(t1-t5)##(i.CST15) c.age i.sex  c.height c.weight  i.CVDhbp i.CVDdiabetes
i.CVDheartfail i.MDcardiovascular i.MDpsychotropic  i.FOFactivitylimit || tilda_serial:,
residuals(ar1, t(samp_no))
Note: time gaps exist in the estimation data

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -158767.82
Iteration 1:   log likelihood =  -154923.6  (not concave)
Iteration 2:   log likelihood = -154345.74
Iteration 3:   log likelihood = -154177.59
Iteration 4:   log likelihood = -153643.56
Iteration 5:   log likelihood = -153640.76
Iteration 6:   log likelihood = -153640.76

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =     53,995
Group variable: tilda_serial                    Number of groups  =      2,854

                                                Obs per group:
                                                              min =          8
                                                              avg =       18.9
                                                              max =         19

                                                Wald chi2(21)     =   62024.01
Log likelihood = -153640.76                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
         delta_dia |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
                t1 |  -1.846351   .0097074  -190.20   0.000    -1.865378   -1.827325
                t2 |   1.309127   .0096803   135.24   0.000     1.290154      1.3281
                t3 |   .2721416   .0095715    28.43   0.000     .2533819    .2909013
                t4 |   .0866411   .0090978     9.52   0.000     .0688097    .1044724
                t5 |   .0041543   .0008168     5.09   0.000     .0025535    .0057551
           1.CST15 |   .5916009   .3180847     1.86   0.063    -.0318336    1.215035
                   |
       CST15#c.t1  |
                1  |   .0342209   .0192796     1.77   0.076    -.0035664    .0720082
                   |
       CST15#c.t2  |
                1  |  -.1394776   .0192289    -7.25   0.000    -.1771656   -.1017895
                   |
       CST15#c.t3  |
                1  |   .0311418   .0190214     1.64   0.102    -.0061395    .0684231
                   |
```

```
        CST15#c.t4 |
                1  |   .0083411   .0180828     0.46   0.645    -.0271005    .0437827
                   |
        CST15#c.t5 |
                1  |   .0049955   .0016272     3.07   0.002     .0018062    .0081848
                   |
               age |  -.0721272   .0161578    -4.46   0.000    -.1037958   -.0404586
                   |
               sex |
            Female |   1.522606   .3452614     4.41   0.000     .8459063    2.199306
            height |   -.038156   .0196751    -1.94   0.052    -.0767185    .0004064
            weight |   .0400935   .0096293     4.16   0.000     .0212204    .0589667
                   |
             CVDhbp |
               Yes |   .4731429   .3641136     1.30   0.194    -.2405066    1.186792
                   |
          CVDdiabetes |
               Yes |  -2.029404   .4918239    -4.13   0.000    -2.993361   -1.065447
                   |
        CVDheartfail |
               Yes |  -.0991254       1.62    -0.06   0.951    -3.274268    3.076017
1.MDcardiovascular |  -.7654438      .3653    -2.10   0.036    -1.481419   -.0494689
  1.MDpsychotropic |  -.4319322   .3522942    -1.23   0.220    -1.122416    .2585517
1.FOFactivitylimit |   .0451196   .5174681     0.09   0.931    -.9690991    1.059338
             _cons |   10.41218   3.562969     2.92   0.003     3.428892    17.39547
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
tilda_serial: Identity       |
                  var(_cons) |   33.26378   .9555804      31.44263    35.19041
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho  |    .483945   .0047578       .474565    .4932151
                     var(e)  |   19.46738   .1778926      19.12182    19.81918
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 61509.04              Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Change in SBP and HGS-defined Probable Sarcopenia

```
mixed delta_sys c.(t1-t5)##(i.GRP16_27) c.age i.sex  c.height c.weight  i.CVDhbp i.CVDdiabetes
i.CVDheartfail i.MDcardiovascular i.MDpsychotropic  i.FOFactivitylimit || tilda_serial:,
residuals(ar1, t(samp_no))
Note: time gaps exist in the estimation data

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -195879.52
Iteration 1:   log likelihood = -191580.83  (not concave)
Iteration 2:   log likelihood = -187356.84  (not concave)
Iteration 3:   log likelihood = -186678.59
Iteration 4:   log likelihood = -186564.17
Iteration 5:   log likelihood = -186546.16
Iteration 6:   log likelihood = -186546.15

Computing standard errors:

Mixed-effects ML regression                    Number of obs     =     54,078
Group variable: tilda_serial                   Number of groups  =      2,858

                                               Obs per group:
                                                             min =         12
                                                             avg =       18.9
                                                             max =         19

                                               Wald chi2(21)     =   53492.47
Log likelihood = -186546.15                    Prob > chi2       =     0.0000
```

```
------------------------------------------------------------------------------
         delta_sys |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
                t1 |  -2.930826   .0151894  -192.95   0.000    -2.960597   -2.901055
                t2 |   2.180286    .015142   143.99   0.000     2.150608    2.209964
                t3 |   .2179659   .0150276    14.50   0.000     .1885124    .2474194
                t4 |  -.0276573   .0147427    -1.88   0.061    -.0565526    .0012379
                t5 |   .0390728   .0016611    23.52   0.000     .0358171    .0423285
       1.GRP16_27 |  -.8234009   1.113788    -0.74   0.460    -3.006386    1.359584
                  |
     GRP16_27#c.t1 |
                1 |   .1164818   .0593665     1.96   0.050     .0001255     .232838
                  |
     GRP16_27#c.t2 |
                1 |  -.5350662   .0591897    -9.04   0.000    -.6510759   -.4190564
                  |
     GRP16_27#c.t3 |
                1 |   .1324412   .0587479     2.25   0.024     .0172976    .2475849
                  |
     GRP16_27#c.t4 |
                1 |   .1360594   .0576329     2.36   0.018     .0231011    .2490178
                  |
     GRP16_27#c.t5 |
                1 |    .012228    .006482     1.89   0.059    -.0004765    .0249324
                  |
               age |   .0076469   .0318065     0.24   0.810    -.0546927    .0699865
                  |
               sex |
            Female |   .5829041   .6846934     0.85   0.395    -.7590704    1.924879
            height |  -.2026648   .0390283    -5.19   0.000    -.2791589   -.1261707
            weight |   .1366799   .0189807     7.20   0.000     .0994785    .1738813
                  |
             CVDhbp |
               Yes |   .9266174   .7176594     1.29   0.197    -.4799691    2.333204
                  |
       CVDdiabetes |
               Yes |  -1.488982   .9705876    -1.53   0.125    -3.391299    .4133346
                  |
      CVDheartfail |
               Yes |  -2.701263   3.198484    -0.84   0.398    -8.970176     3.56765
1.MDcardiovascular |  -1.697508   .7201429    -2.36   0.018    -3.108962   -.2860541
  1.MDpsychotropic |  -.6110978   .6956428    -0.88   0.380    -1.974533    .7523371
1.FOFactivitylimit |   .7944933   1.020168     0.78   0.436       -1.205    2.793986
             _cons |   27.25866   7.017676     3.88   0.000     13.50427    41.01305
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
tilda_serial: Identity       |
                  var(_cons) |   123.3849   3.763338      116.2251    130.9859
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho |   .6334104   .0045687       .624371    .6422801
                     var(e) |   84.33974   1.026258      82.35211    86.37534
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 71579.48              Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Change in DBP and HGS-defined Probable Sarcopenia

```
mixed delta_dia c.(t1-t5)##(i.GRP16_27) c.age i.sex  c.height c.weight  i.CVDhbp i.CVDdiabetes
i.CVDheartfail i.MDcardiovascular i.MDpsychotropic  i.FOFactivitylimit || tilda_serial:,
residuals(ar1, t(samp_no))
Note: time gaps exist in the estimation data

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -158734.91
Iteration 1:   log likelihood = -154012.29
```

```
Iteration 2:   log likelihood = -153769.45
Iteration 3:   log likelihood = -153616.17
Iteration 4:   log likelihood =  -153603.6
Iteration 5:   log likelihood = -153603.57
Iteration 6:   log likelihood = -153603.57

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =     53,995
Group variable: tilda_serial                    Number of groups  =      2,854

                                                Obs per group:
                                                              min =          8
                                                              avg =       18.9
                                                              max =         19

                                                Wald chi2(21)     =   62189.92
Log likelihood = -153603.57                     Prob > chi2       =     0.0000
```

delta_dia	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
t1	-1.838796	.00867	-212.09	0.000	-1.855789	-1.821803
t2	1.298312	.0086462	150.16	0.000	1.281366	1.315258
t3	.2753452	.0085503	32.20	0.000	.2585869	.2921034
t4	.084387	.0081278	10.38	0.000	.0684568	.1003172
t5	.0050964	.0007304	6.98	0.000	.0036648	.006528
1.GRP16_27	.8903633	.5619149	1.58	0.113	-.2109697	1.991696
GRP16_27#c.t1						
1	.017128	.0338579	0.51	0.613	-.0492323	.0834883
GRP16_27#c.t2						
1	-.3742253	.0337703	-11.08	0.000	-.4404138	-.3080368
GRP16_27#c.t3						
1	.0716893	.0333952	2.15	0.032	.006236	.1371426
GRP16_27#c.t4						
1	.0668682	.0317443	2.11	0.035	.0046505	.1290858
GRP16_27#c.t5						
1	.0048197	.0028483	1.69	0.091	-.000763	.0104023
age	-.0639089	.0161127	-3.97	0.000	-.0954893	-.0323286
sex						
Female	1.477801	.3468533	4.26	0.000	.7979807	2.157621
height	-.0408162	.0197664	-2.06	0.039	-.0795577	-.0020747
weight	.0403795	.009618	4.20	0.000	.0215286	.0592305
CVDhbp						
Yes	.4639661	.36403	1.27	0.202	-.2495195	1.177452
CVDdiabetes						
Yes	-2.000553	.4914379	-4.07	0.000	-2.963754	-1.037353
CVDheartfail						
Yes	-.108258	1.619519	-0.07	0.947	-3.282457	3.065941
1.MDcardiovascular	-.7624023	.3651888	-2.09	0.037	-1.478159	-.0466454
1.MDpsychotropic	-.391235	.3522525	-1.11	0.267	-1.081637	.2991672
1.FOFactivitylimit	.1081533	.5165344	0.21	0.834	-.9042355	1.120542
_cons	10.41409	3.55471	2.93	0.003	3.446987	17.38119

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
tilda_serial: Identity				
var(_cons)	33.2447	.9549957	31.42466	35.17015
Residual: AR(1)				
rho	.4840464	.0047567	.4746687	.4933143
var(e)	19.44248	.1776711	19.09735	19.79385

```
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 61539.21              Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Appendix B: Study II-A – Full Mixed Effects Regression Outputs

Change in SBP and Sarcopenia Status

```
mixed delta_sys c.(t1-t5)##(i.Sarc_status c.delta_hr) c.age i.sex i.cvddiabetes i.cvdhtn
i.mdcardiovascular i.mdpsychotropic || id:, residuals(ar1, t(samp_no)) cformat(%9.2f)

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -8137.9206
Iteration 1:   log likelihood = -8022.6752  (not concave)
Iteration 2:   log likelihood = -7789.5033  (not concave)
Iteration 3:   log likelihood = -7598.6424  (not concave)
Iteration 4:   log likelihood = -7531.0888
Iteration 5:   log likelihood =  -7524.644  (not concave)
Iteration 6:   log likelihood = -7519.9705
Iteration 7:   log likelihood = -7514.9543
Iteration 8:   log likelihood = -7514.6148
Iteration 9:   log likelihood =   -7514.61
Iteration 10:  log likelihood =   -7514.61

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =      2,071
Group variable: id                              Number of groups  =        109

                                                Obs per group:
                                                              min =         19
                                                              avg =       19.0
                                                              max =         19

                                                Wald chi2(29)     =    1428.63
Log likelihood =   -7514.61                     Prob > chi2       =     0.0000
```

delta_sys	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
t1	-2.36	0.16	-14.78	0.000	-2.67	-2.04
t2	0.66	0.17	3.83	0.000	0.32	0.99
t3	1.01	0.15	6.60	0.000	0.71	1.31
t4	0.32	0.14	2.31	0.021	0.05	0.60
t5	0.06	0.02	2.66	0.008	0.01	0.10
Sarc_status						
Probable Sarcopenia	-0.52	4.40	-0.12	0.906	-9.14	8.10
Sarcopenia	2.97	5.61	0.53	0.597	-8.02	13.96
delta_hr	-0.26	0.15	-1.74	0.082	-0.56	0.03
Sarc_status#c.t1						
Probable Sarcopenia	0.10	0.20	0.51	0.610	-0.28	0.48
Sarcopenia	0.32	0.26	1.26	0.206	-0.18	0.83
c.t1#c.delta_hr	-0.03	0.01	-2.35	0.019	-0.06	-0.01
Sarc_status#c.t2						
Probable Sarcopenia	-0.59	0.20	-3.02	0.003	-0.97	-0.21
Sarcopenia	-0.85	0.26	-3.28	0.001	-1.35	-0.34
c.t2#c.delta_hr	0.06	0.01	5.30	0.000	0.03	0.08
Sarc_status#c.t3						
Probable Sarcopenia	0.20	0.19	1.01	0.313	-0.18	0.58
Sarcopenia	-0.07	0.26	-0.26	0.794	-0.57	0.44
c.t3#c.delta_hr	-0.00	0.01	-0.22	0.829	-0.02	0.02
Sarc_status#c.t4						
Probable Sarcopenia	0.13	0.19	0.70	0.486	-0.24	0.51
Sarcopenia	-0.15	0.25	-0.57	0.569	-0.64	0.35

```
     c.t4#c.delta_hr |       0.01       0.01     0.86   0.392        -0.01        0.03
                     |
    Sarc_status#c.t5 |
Probable Sarcopenia  |       0.03       0.03     0.92   0.359        -0.03        0.08
         Sarcopenia  |       0.05       0.04     1.34   0.181        -0.02        0.13
                     |
     c.t5#c.delta_hr |       0.00       0.00     0.16   0.876        -0.00        0.00
                     |
                 age |      -0.22       0.16    -1.34   0.181        -0.53        0.10
                     |
                 sex |
              Male   |      -3.87       3.04    -1.27   0.203        -9.82        2.09
       1.cvddiabetes |       1.18       4.28     0.27   0.783        -7.21        9.56
            1.cvdhtn |      -0.13       3.66    -0.03   0.972        -7.29        7.04
  1.mdcardiovascular |       1.32       3.69     0.36   0.721        -5.92        8.56
    1.mdpsychotropic |      -4.34       3.36    -1.29   0.197       -10.93        2.25
               _cons |      21.36      10.76     1.99   0.047         0.27       42.44
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                  var(_cons) |     166.97      34.58        111.26      250.57
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho |       0.79       0.02          0.75        0.83
                     var(e) |     197.26      20.15        161.46      240.99
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 3173.10               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Change in DBP and Sarcopenia Status

```
mixed delta_dia c.(t1-t5)##(i.Sarc_status c.delta_hr) c.age i.sex i.cvddiabetes i.cvdhtn
i.mdcardiovascular i.mdpsychotropic || id:, residuals(ar1, t(samp_no)) cformat(%9.2f)

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -6929.9792
Iteration 1:   log likelihood =   -6728.28  (not concave)
Iteration 2:   log likelihood =  -6442.967  (not concave)
Iteration 3:   log likelihood = -6401.1858
Iteration 4:   log likelihood = -6392.5549
Iteration 5:   log likelihood = -6392.3933
Iteration 6:   log likelihood = -6392.3931

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =      2,071
Group variable: id                              Number of groups  =        109

                                                Obs per group:
                                                              min =         19
                                                              avg =       19.0
                                                              max =         19

                                                Wald chi2(29)     =    1399.39
Log likelihood = -6392.3931                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
           delta_dia |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------------+--------------------------------------------------------------
                  t1 |      -1.46       0.09   -15.71   0.000        -1.65       -1.28
                  t2 |       0.05       0.10     0.47   0.636        -0.15        0.24
                  t3 |       0.82       0.09     9.14   0.000         0.64        0.99
                  t4 |       0.26       0.08     3.15   0.002         0.10        0.42
                  t5 |       0.02       0.01     1.62   0.105        -0.00        0.04
                     |
```

```
         Sarc_status |
Probable Sarcopenia  |      -0.57       2.47    -0.23   0.819        -5.41        4.27
         Sarcopenia  |       1.79       3.15     0.57   0.570        -4.39        7.97
                     |
            delta_hr |       0.07       0.09     0.76   0.450        -0.11        0.24
                     |
    Sarc_status#c.t1 |
Probable Sarcopenia  |       0.48       0.11     4.23   0.000         0.26        0.71
         Sarcopenia  |       0.49       0.15     3.26   0.001         0.20        0.78
                     |
     c.t1#c.delta_hr |      -0.03       0.01    -3.79   0.000        -0.05       -0.01
                     |
    Sarc_status#c.t2 |
Probable Sarcopenia  |      -0.45       0.11    -3.99   0.000        -0.68       -0.23
         Sarcopenia  |      -0.65       0.15    -4.35   0.000        -0.95       -0.36
                     |
     c.t2#c.delta_hr |       0.05       0.01     9.04   0.000         0.04        0.07
                     |
    Sarc_status#c.t3 |
Probable Sarcopenia  |      -0.15       0.11    -1.32   0.185        -0.37        0.07
         Sarcopenia  |      -0.16       0.15    -1.04   0.300        -0.45        0.14
                     |
     c.t3#c.delta_hr |      -0.00       0.01    -0.26   0.795        -0.01        0.01
                     |
    Sarc_status#c.t4 |
Probable Sarcopenia  |      -0.04       0.11    -0.35   0.727        -0.26        0.18
         Sarcopenia  |      -0.10       0.15    -0.69   0.491        -0.39        0.19
                     |
     c.t4#c.delta_hr |       0.01       0.01     0.86   0.390        -0.01        0.02
                     |
    Sarc_status#c.t5 |
Probable Sarcopenia  |       0.01       0.02     0.59   0.554        -0.02        0.04
         Sarcopenia  |       0.04       0.02     1.83   0.067        -0.00        0.08
                     |
     c.t5#c.delta_hr |       0.00       0.00     1.04   0.296        -0.00        0.00
                     |
                 age |      -0.24       0.09    -2.68   0.007        -0.41       -0.06
                     |
                 sex |
              Male   |      -3.40       1.69    -2.02   0.043        -6.71       -0.10
       1.cvddiabetes |      -1.07       2.37    -0.45   0.651        -5.72        3.58
            1.cvdhtn |       1.28       2.03     0.63   0.527        -2.69        5.26
  1.mdcardiovascular |       2.40       2.05     1.17   0.241        -1.61        6.41
    1.mdpsychotropic |      -1.10       1.86    -0.59   0.554        -4.76        2.55
               _cons |      22.13       5.97     3.70   0.000        10.42       33.83
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                  var(_cons) |      50.60      10.79         33.32       76.84
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho  |       0.78       0.02          0.73        0.83
                     var(e)  |      64.78       6.89         52.59       79.80
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 2953.60               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Appendix C: Study II-B — Full Mixed Effects Regression Outputs

Change in MAP and Sarcopenia

```
mixed delta_MAP c.(t1-t5)##(i.Sarc) c.age i.sex i.cvddiabetes i.cvdhtn i.mdcardiovascular
i.mdpsychotropic || id:, residuals(ar1, t(samp_no)) cformat(%9.2f)

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -7275.4792
Iteration 1:   log likelihood = -7031.6787  (not concave)
Iteration 2:   log likelihood = -6872.8684
Iteration 3:   log likelihood = -6769.4256
Iteration 4:   log likelihood = -6767.8971
Iteration 5:   log likelihood = -6767.8382
Iteration 6:   log likelihood = -6767.8381

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =      2,033
Group variable: id                              Number of groups  =        107

                                                Obs per group:
                                                              min =         19
                                                              avg =       19.0
                                                              max =         19

                                                Wald chi2(17)     =    1709.82
Log likelihood = -6767.8381                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
         delta_MAP |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
                t1 |      -2.52       0.07   -35.50   0.000        -2.66       -2.38
                t2 |       1.06       0.07    14.93   0.000         0.92        1.20
                t3 |       0.68       0.07     9.59   0.000         0.54        0.82
                t4 |       0.37       0.07     5.29   0.000         0.23        0.51
                t5 |       0.05       0.01     4.62   0.000         0.03        0.07
                   |
              Sarc |
       Sarcopenia  |       4.69       3.68     1.27   0.203        -2.53       11.90
                   |
         Sarc#c.t1 |
       Sarcopenia  |       0.23       0.18     1.23   0.217        -0.13        0.59
                   |
         Sarc#c.t2 |
       Sarcopenia  |      -0.67       0.18    -3.65   0.000        -1.03       -0.31
                   |
         Sarc#c.t3 |
       Sarcopenia  |      -0.05       0.18    -0.26   0.792        -0.41        0.31
                   |
         Sarc#c.t4 |
       Sarcopenia  |      -0.10       0.18    -0.52   0.601        -0.45        0.26
                   |
         Sarc#c.t5 |
       Sarcopenia  |       0.03       0.03     1.17   0.241        -0.02        0.08
                   |
               age |      -0.29       0.11    -2.75   0.006        -0.50       -0.08
                   |
               sex |
              Male |      -3.38       2.08    -1.63   0.104        -7.44        0.69
     1.cvddiabetes |      -0.70       2.92    -0.24   0.810        -6.42        5.01
          1.cvdhtn |       1.76       2.54     0.69   0.490        -3.23        6.74
1.mdcardiovascular |       0.28       2.55     0.11   0.911        -4.72        5.28
  1.mdpsychotropic |      -2.62       2.27    -1.15   0.249        -7.06        1.83
             _cons |      26.88       7.25     3.71   0.000        12.68       41.09
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
```

```
id: Identity                 |
                  var(_cons) |      79.99      16.24         53.73      119.08
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho |       0.76       0.02          0.71        0.81
                     var(e) |      96.91       9.46         80.04      117.33
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 2873.76              Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Change in CO and Sarcopenia

```
mixed delta_CO c.(t1-t5)##(i.Sarc) c.age i.sex i.cvddiabetes i.cvdhtn i.mdcardiovascular
i.mdpsychotropic || id:, residuals(ar1, t(samp_no)) cformat(%9.2f)

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1735.0582
Iteration 1:   log likelihood = -1536.1827  (not concave)
Iteration 2:   log likelihood =  -1479.225  (not concave)
Iteration 3:   log likelihood = -1450.8081
Iteration 4:   log likelihood =  -1443.677
Iteration 5:   log likelihood = -1440.4948
Iteration 6:   log likelihood = -1440.4677
Iteration 7:   log likelihood = -1440.4677

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =      2,033
Group variable: id                              Number of groups  =        107

                                                Obs per group:
                                                              min =         19
                                                              avg =       19.0
                                                              max =         19

                                                Wald chi2(17)     =     910.50
Log likelihood = -1440.4677                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
          delta_CO |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
                t1 |       0.12       0.01    21.99   0.000         0.11        0.13
                t2 |      -0.09       0.01   -17.50   0.000        -0.11       -0.08
                t3 |      -0.05       0.01   -10.04   0.000        -0.06       -0.04
                t4 |      -0.01       0.01    -2.28   0.023        -0.02       -0.00
                t5 |       0.00       0.00     1.65   0.099        -0.00        0.00
                   |
              Sarc |
       Sarcopenia  |      -0.09       0.24    -0.38   0.701        -0.56        0.37
                   |
         Sarc#c.t1 |
       Sarcopenia  |      -0.05       0.01    -3.78   0.000        -0.08       -0.03
                   |
         Sarc#c.t2 |
       Sarcopenia  |       0.06       0.01     4.46   0.000         0.03        0.09
                   |
         Sarc#c.t3 |
       Sarcopenia  |       0.01       0.01     0.62   0.538        -0.02        0.04
                   |
         Sarc#c.t4 |
       Sarcopenia  |       0.01       0.01     0.67   0.501        -0.02        0.04
                   |
         Sarc#c.t5 |
       Sarcopenia  |      -0.00       0.00    -1.38   0.167        -0.00        0.00
                   |
                age |       0.02       0.01     2.40   0.016         0.00        0.03
                   |
                sex |
```

```
            Male  |       0.34       0.14     2.53   0.011         0.08        0.61
     1.cvddiabetes |       0.19       0.19     1.01   0.312        -0.18        0.57
         1.cvdhtn  |      -0.16       0.17    -0.97   0.333        -0.49        0.17
1.mdcardiovascular |      -0.15       0.17    -0.92   0.356        -0.48        0.17
  1.mdpsychotropic |      -0.11       0.15    -0.72   0.470        -0.40        0.18
             _cons |      -1.15       0.47    -2.42   0.015        -2.08       -0.22
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                  var(_cons) |       0.41       0.06          0.30        0.56
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho  |       0.58       0.02          0.53        0.62
                     var(e)  |       0.32       0.02          0.29        0.35
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 2249.09               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Change in TPR and Sarcopenia

```
mixed delta_TPR c.(t1-t5)##(i.Sarc) c.age i.sex i.cvddiabetes i.cvdhtn i.mdcardiovascular
i.mdpsychotropic || id:, residuals(ar1, t(samp_no)) cformat(%9.2f)

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -112.03684
Iteration 1:   log likelihood =  409.89423
Iteration 2:   log likelihood =  417.05887  (not concave)
Iteration 3:   log likelihood =  438.14565
Iteration 4:   log likelihood =  441.54366
Iteration 5:   log likelihood =  443.01928
Iteration 6:   log likelihood =  443.02319
Iteration 7:   log likelihood =  443.02319

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =      2,033
Group variable: id                              Number of groups  =        107

                                                Obs per group:
                                                              min =         19
                                                              avg =       19.0
                                                              max =         19

                                                Wald chi2(17)     =     762.10
Log likelihood =  443.02319                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
         delta_TPR |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------------+----------------------------------------------------------------
                t1 |      -0.04       0.00   -20.06   0.000        -0.05       -0.04
                t2 |       0.02       0.00     8.18   0.000         0.01        0.02
                t3 |       0.03       0.00    12.14   0.000         0.02        0.03
                t4 |       0.01       0.00     4.59   0.000         0.01        0.01
                t5 |       0.00       0.00     1.99   0.046         0.00        0.00
                   |
              Sarc |
       Sarcopenia  |       0.13       0.09     1.44   0.150        -0.05        0.32
                   |
         Sarc#c.t1 |
       Sarcopenia  |       0.00       0.01     0.14   0.889        -0.01        0.01
                   |
         Sarc#c.t2 |
       Sarcopenia  |      -0.02       0.01    -4.26   0.000        -0.03       -0.01
                   |
         Sarc#c.t3 |
       Sarcopenia  |       0.01       0.01     1.54   0.122        -0.00        0.02
```

```
                  |
        Sarc#c.t4 |
       Sarcopenia |      -0.01       0.01    -1.02   0.306        -0.02        0.00
                  |
        Sarc#c.t5 |
       Sarcopenia |       0.00       0.00     1.37   0.171        -0.00        0.00
                  |
              age |      -0.01       0.00    -3.33   0.001        -0.01       -0.00
                  |
              sex |
             Male |      -0.18       0.05    -3.82   0.000        -0.28       -0.09
     1.cvddiabetes |      -0.02       0.07    -0.36   0.720        -0.16        0.11
         1.cvdhtn |       0.08       0.06     1.30   0.195        -0.04        0.19
1.mdcardiovascular |      -0.01       0.06    -0.25   0.799        -0.13        0.10
  1.mdpsychotropic |      -0.02       0.05    -0.31   0.757        -0.12        0.09
             _cons |       0.68       0.17     4.04   0.000         0.35        1.01
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                  var(_cons) |       0.03       0.01          0.02        0.06
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho |       0.76       0.02          0.71        0.80
                     var(e) |       0.08       0.01          0.07        0.10
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 2350.37               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Change in SV and Sarcopenia

```
mixed delta_SV c.(t1-t5)##(i.Sarc) c.age i.sex i.cvddiabetes i.cvdhtn i.mdcardiovascular
i.mdpsychotropic || id:, residuals(ar1, t(samp_no)) cformat(%9.2f)

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -7032.8247
Iteration 1:   log likelihood = -6770.2142  (not concave)
Iteration 2:   log likelihood = -6716.7119  (not concave)
Iteration 3:   log likelihood = -6670.9436
Iteration 4:   log likelihood = -6663.2361
Iteration 5:   log likelihood = -6662.2939
Iteration 6:   log likelihood =  -6662.291
Iteration 7:   log likelihood =  -6662.291

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =      2,033
Group variable: id                              Number of groups  =        107

                                                Obs per group:
                                                              min =         19
                                                              avg =       19.0
                                                              max =         19

                                                Wald chi2(17)     =     380.97
Log likelihood =  -6662.291                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
     delta_SV |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
           t1 |       0.74       0.07    10.72   0.000         0.60        0.87
           t2 |      -0.85       0.07   -12.48   0.000        -0.99       -0.72
           t3 |      -0.47       0.07    -6.94   0.000        -0.61       -0.34
           t4 |      -0.17       0.07    -2.55   0.011        -0.30       -0.04
           t5 |       0.01       0.01     1.31   0.190        -0.01        0.03
              |
         Sarc |
```

```
       Sarcopenia  |      -0.58       3.44    -0.17   0.866        -7.33        6.17
                   |
        Sarc#c.t1  |
       Sarcopenia  |      -0.37       0.18    -2.10   0.036        -0.72       -0.02
                   |
        Sarc#c.t2  |
       Sarcopenia  |       0.54       0.18     3.03   0.002         0.19        0.88
                   |
        Sarc#c.t3  |
       Sarcopenia  |       0.18       0.18     1.00   0.317        -0.17        0.52
                   |
        Sarc#c.t4  |
       Sarcopenia  |       0.09       0.17     0.49   0.621        -0.25        0.43
                   |
        Sarc#c.t5  |
       Sarcopenia  |      -0.02       0.02    -1.20   0.231        -0.06        0.02
                   |
               age |       0.41       0.10     3.96   0.000         0.21        0.61
                   |
               sex |
              Male |       3.23       2.02     1.60   0.110        -0.73        7.19
     1.cvddiabetes |       5.20       2.84     1.83   0.067        -0.37       10.76
         1.cvdhtn  |      -2.73       2.48    -1.10   0.271        -7.58        2.13
1.mdcardiovascular |      -1.68       2.48    -0.68   0.499        -6.55        3.19
  1.mdpsychotropic |      -2.31       2.21    -1.05   0.296        -6.64        2.02
             _cons |     -31.41       7.05    -4.46   0.000       -45.23      -17.60
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                  var(_cons) |      88.76      14.19         64.89      121.41
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                        rho  |       0.67       0.02          0.62        0.71
                     var(e)  |      64.34       4.41         56.26       73.59
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 2664.00               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Change in HR and Sarcopenia

```
mixed delta_HR c.(t1-t5)##(i.Sarc) c.age i.sex i.cvddiabetes i.cvdhtn i.mdcardiovascular
i.mdpsychotropic || id:, residuals(ar1, t(samp_no)) cformat(%9.2f)

Obtaining starting values by EM:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -6155.0276
Iteration 1:   log likelihood = -5923.8503  (not concave)
Iteration 2:   log likelihood = -5880.9649  (not concave)
Iteration 3:   log likelihood = -5866.1179
Iteration 4:   log likelihood = -5863.3636
Iteration 5:   log likelihood =   -5861.94
Iteration 6:   log likelihood = -5861.9384
Iteration 7:   log likelihood = -5861.9384

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =      2,033
Group variable: id                              Number of groups  =        107

                                                Obs per group:
                                                              min =         19
                                                              avg =       19.0
                                                              max =         19

                                                Wald chi2(17)     =     479.27
Log likelihood = -5861.9384                     Prob > chi2       =     0.0000
```

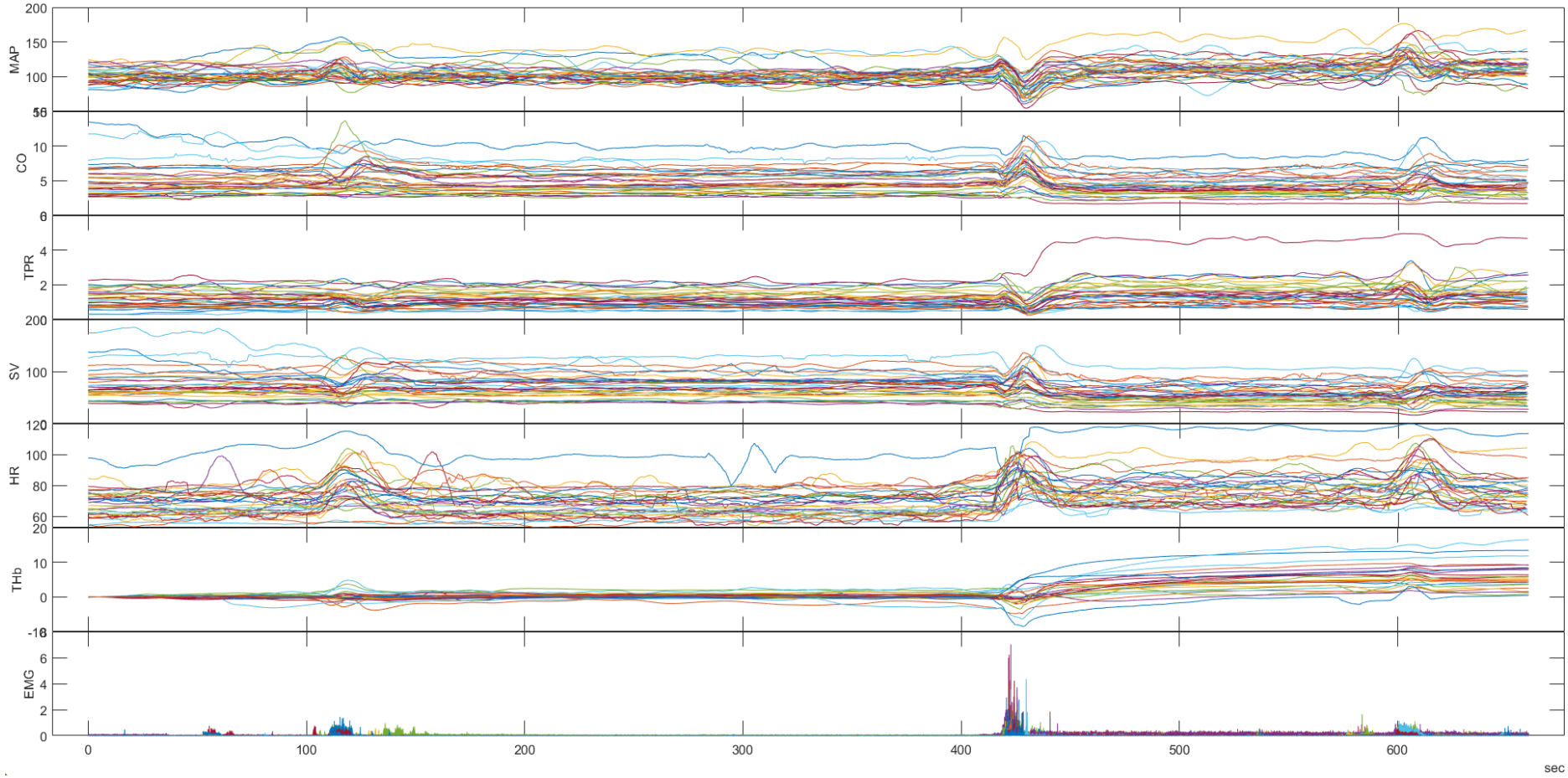
delta_HR	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
t1	0.93	0.05	19.73	0.000	0.84	1.02
t2	-0.17	0.05	-3.59	0.000	-0.26	-0.08
t3	-0.26	0.05	-5.62	0.000	-0.35	-0.17
t4	0.00	0.05	0.05	0.958	-0.09	0.09
t5	0.00	0.01	0.60	0.551	-0.01	0.01
Sarc						
Sarcopenia	2.80	2.03	1.38	0.168	-1.18	6.78
Sarc#c.t1						
Sarcopenia	-0.16	0.12	-1.33	0.182	-0.40	0.08
Sarc#c.t2						
Sarcopenia	-0.15	0.12	-1.26	0.208	-0.39	0.09
Sarc#c.t3						
Sarcopenia	0.03	0.12	0.21	0.832	-0.21	0.26
Sarc#c.t4						
Sarcopenia	0.02	0.12	0.13	0.897	-0.22	0.25
Sarc#c.t5						
Sarcopenia	-0.01	0.01	-0.84	0.401	-0.04	0.01
age	-0.23	0.06	-4.09	0.000	-0.34	-0.12
sex						
Male	-0.66	1.12	-0.59	0.554	-2.85	1.53
1.cvddiabetes	-0.96	1.57	-0.61	0.540	-4.04	2.11
1.cvdhtn	0.17	1.37	0.12	0.903	-2.51	2.85
1.mdcardiovascular	-0.82	1.37	-0.60	0.549	-3.51	1.87
1.mdpsychotropic	0.05	1.22	0.04	0.964	-2.34	2.45
_cons	19.75	3.90	5.06	0.000	12.10	27.40

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
id: Identity				
var(_cons)	25.80	4.42	18.45	36.09
Residual: AR(1)				
rho	0.63	0.03	0.58	0.68
var(e)	27.81	1.91	24.31	31.81

LR test vs. linear model: chi2(2) = 2193.74 Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference

Appendix D: Study III – Individual Haemodynamic, NIRS and EMG Signals



Appendix E: Previously Published Papers

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
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OXFORD

Research Article

Differential Associations Between Two Markers of Probable Sarcopenia and Continuous Orthostatic Hemodynamics in The Irish Longitudinal Study on Ageing

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Abstract

Background: Sarcopenia and orthostatic hypotension are growing age-related health burdens associated with adverse outcomes, including falls. Despite a possible pathophysiological link, the association between the 2 disorders is not well elucidated. We sought to investigate this relationship in The Irish Longitudinal Study on Ageing (TILDA).

Methods: Data from 2 858 participants at wave 3 of TILDA were analyzed. Probable sarcopenia was defined as per the European Working Group on Sarcopenia in Older People revised definition cutoffs (hand grip strength [HGS] <27 kg in men, <16 kg in women, and/or 5-chair stand test [5CST] time >15 seconds). Participants underwent an active stand orthostatic test with continuous blood pressure (BP) monitoring. Multilevel mixed-effects models, controlling for possible confounders, were used to assess the effect of probable sarcopenia by HGS and 5CST criteria on the change in BP after standing.

Results: HGS- and 5CST-defined probable sarcopenia were independently associated with an attenuated BP recovery at 10–20 seconds poststand (systolic BP: β −0.54, $p < .001$; β −0.25, $p < .001$). On average, those meeting HGS probable sarcopenia criteria had a significantly lower BP at 20, 30, and 40 seconds (differences in systolic BP: −5.01 mmHg, −3.68 mmHg, −2.32 mmHg, $p < .05$ for all). Those meeting 5CST probable sarcopenia criteria had a significant difference in systolic BP at 20 seconds (−1.94 mmHg, $p = .002$) but not at 30 or 40 seconds.

Conclusion: Probable sarcopenia had a significant association with delayed orthostatic BP recovery, with HGS-defined probable sarcopenia having a stronger association than 5CST-defined probable sarcopenia. Results support a modest but significant pathophysiological link between probable sarcopenia and orthostatic hypotension.

Keywords: 5-Chair stands test, Grip strength, Orthostatic hypotension, Sarcopenia

Sarcopenia, a condition characterized by accelerated loss of muscle mass and function, is increasingly recognized as a cause of falls, adverse health outcomes, and mortality (1). Some have labeled it the biological substrate of physical frailty and propose that it is the pathway through which the consequences of physical frailty develop (2,3).

Orthostatic hypotension (OH), classically defined as a sustained drop of 20 mmHg systolic blood pressure (SBP) and/or 10 mmHg diastolic blood pressure (DBP) within 3 minutes of standing (4), is a common condition in older people, is increasing in prevalence (5) and is a well-recognized cause of falls (6), with risk of resultant hospitalization and institutionalization (7).

The association between OH and frailty has been well established (8,9). However, the relationship between sarcopenia and OH is less well characterized (10). This is somewhat surprising as one might hypothesize a direct link between the 2, namely via the skeletal

muscle pump, which aids venous return from the lower limbs via rhythmic muscle activity during standing (11). The reduced muscle mass of sarcopenia might be expected to attenuate the effects of the skeletal muscle pump, potentially increasing the risk of OH.

One previous study found that severe sarcopenia, as classified by the European Working Group on Sarcopenia in Older People (EWGSOP) revised definition (12), was a significant predictor of OH at 1 minute and systolic OH at 5 minutes, when compared to the robust, probable sarcopenia and sarcopenia groups (13). They, however used the head-up tilt test, which gives a different hemodynamic pattern to the active stand (14) and may reduce the contribution of the skeletal muscle pump. Another smaller study found that EWGSOP-defined sarcopenia, was an independent predictor of classical OH (15). They utilized the active stand test but adjusted for only a small number of confounders. Both studies used oscillometric blood pressure (BP) and so were unable to study the early phase of BP recovery (ie, the first minute post active stand).

With the limitations of these previous studies, we sought to further investigate the relationship between sarcopenia and OH using a large, well-characterized sample with continuous noninvasive beat-to-beat BP measurements from The Irish Longitudinal Study on Ageing (TILDA).

Method

Study Population

TILDA is an ongoing, nationally representative longitudinal cohort study of adults aged 50 years and older (16,17). This study utilized baseline data from wave 3 of TILDA (March 2014–December 2015), with follow up of participants at wave 5 (2018). For wave 3, participants underwent a computer aided personal interview (CAPI) with a trained interviewer, which addressed questions on socioeconomic, physical, cognitive, and mental health factors. Participants were also invited to attend a dedicated health center for a research nurse-led comprehensive health assessment. At wave 5 only the CAPI was undertaken. Ethical approval for each wave was provided by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin. All participants provided written informed consent, and the study adhered to the Declaration of Helsinki. Participants with complete data for the active stand test, probable sarcopenia measurements and covariates, and without a self-reported diagnosis of idiopathic Parkinson's disease were included in the analysis.

Assessment of Probable Sarcopenia

Probable sarcopenia was defined as per the EWGSOP revised definition (12) with cutoffs for hand grip strength (HGS) of less than 27 kg in men and 16 kg in women and/or time taken on the 5-chair stand test (5CST) of greater than 15 seconds. HGS was measured with a Baseline® Hydraulic Hand Dynamometer (Fabrication Enterprises Inc., White Plains, NY) while standing. The maximum value of 2 attempts on each hand was taken. For the 5CST, the time was measured to the nearest centi-second for a participant to stand up from a sitting position and sit back down again 5 times from a standard chair (approximate seat height of 46 cm), as fast as possible, without the use of arms.

Assessment of Orthostatic Hypotension

Participants underwent an active stand orthostatic test with noninvasive beat-to-beat BP monitoring using digital photoplethysmography (Finometer® MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands). Participants rested supine for 10 minutes in a quiet room at ambient temperature before being asked to stand quickly, unaided. They remained standing quietly while BP and heart rate continued to be measured for 3 minutes. The beat-to-beat BP data were preprocessed to remove artifacts, perform 10-second moving average filtering and feature extraction as described previously (18). Baseline supine SBP and DBP values were derived from the average of values occurring 30–60 seconds prior to standing. OH at 30 seconds (OH30), an important marker of impaired BP recovery (19,20) was defined as a drop of SBP ≥ 20 mmHg and/or DBP ≥ 10 mmHg from baseline values. Consensus OH (cOH) was defined as a sustained (10 seconds) drop in SBP of ≥ 20 mmHg and/or DBP ≥ 10 mmHg occurring between 60 and 180 seconds. If there was baseline hypertension (≥140/90 mmHg) then a drop of ≥30/15 mmHg was necessary (4).

Covariates

Potential covariates were explored with a directed acyclic graph, and variables that may confound the relationship between sarcopenia and orthostatic BP were identified and included as covariates in the model. These included: age; sex; height; weight; the presence or absence of self-reported hypertension, diabetes, and heart failure; self-reported cardiovascular medications: World Health Organization Anatomical Therapeutic Chemical (ATC) Classification codes C01—antiarrhythmics, C02—antihypertensives, C03—diuretics, C04—vasodilators, C07—beta-blocking agents, C08—calcium-channel blockers, C09—agents acting on renin–angiotensin system; self-reported psychotropic medications: ATC codes N03A—antiepileptics, N05—antipsychotics, anxiolytics, hypnotics and sedatives, N06A antidepressants; and presence or absence of fear of falling with activity limitation. Variables that mediated the relationship between sarcopenia and OH but lay on the causal pathway were not included as covariates in the model.

Longitudinal Follow-Up

To examine the impact of probable sarcopenia defined by both 5CST and HGS, longitudinal outcomes were assessed at wave 5. The outcomes included were: self-reported recurrent falls (2 or more falls in the last year), fear of falling with activity limitation, self-reported hospital admission (1 or more hospital admissions in the last year), and mortality (from linkage with official death registration data (21)).

Statistical Analysis

Statistical analysis was performed in Stata version 15.1 (Stata Corp LLC, College Station, TX). Descriptive statistics were presented as the mean and standard deviation of continuous variables and count and percentage of categorical variables. Differences in means and frequencies between the non-sarcopenia and probable sarcopenia groups were evaluated with the *t* test and chi-squared test, respectively.

To assess the effect of probable sarcopenia on the change in SBP and DBP from baseline after standing, multilevel mixed-effects models were used, with fixed and random effects accounting for the repeated measurements within participants. Piecewise linear splines modeling time points 0–10, 10–20, 20–30, 30–40, and 40–180 seconds after standing were used as previously described (22,23). Residual variance was modeled with a first order autoregressive process to account for the strong correlation between adjacent timepoints. The spline parameters were

included as independent parameters in the mixed-effects model along with the interaction term of probable sarcopenia, 5CST criteria or HGS criteria (0—no, 1—yes), at each time segment. The potential confounders listed previously were entered as covariates in the model. Where there was a significant change in terms of the interaction of the probable sarcopenia parameters on the BP response over specific time intervals, contrast analysis was used to assess differences in the mean change from baseline in BP at the relevant time points. Marginal effect plots (holding covariates at their means) were produced for the predicted mean change from baseline in SBP and DBP for those with and without probable sarcopenia by 5CST and HGS criteria.

Multivariable logistic regression models were used to investigate the prediction of OH30 by probable sarcopenia by 5CST and HGS criteria, while controlling for confounders. Finally, differences in follow-up outcomes for the HGS- and 5CST-defined probable sarcopenia groups compared with the non-sarcopenic group were examined with the chi-squared test.

Results

Complete data were available for 2 858 participants (Figure 1). The demographics and characteristics of the sample, grouped by probable sarcopenia criteria are detailed in Table 1. Compared to the non-sarcopenic group, those meeting the HGS criteria for probable sarcopenia were older, with a higher proportion of women, shorter stature, lower weight, a higher prevalence of diabetes, were more likely to be on cardiovascular and psychotropic medications and had a higher prevalence of cOH.

Figure 2 shows the mean change in SBP and DBP from baseline, predicted from the mixed-effects models, stratified by those meeting 5CST and HGS probable sarcopenia criteria. Both 5CST- and HGS-defined probable sarcopenia were independently associated with an attenuated SBP and DBP recovery in the 10–20 second period. This agrees with the model output (Table 2), with the negative coefficient indicating a decrease in the rate of recovery. Notably, the effect size of HGS was twice that of 5CST. Those meeting the HGS criteria had a significantly lower SBP and DBP at 20, 30, and 40 seconds compared to those who did not: differences in SBP: –5.01 mmHg, –3.68 mmHg, –2.32 mmHg, $p < .05$ for all; differences in DBP: –2.68 mmHg, –1.96 mmHg, –1.30 mmHg, $p < .05$ for all. Those meeting the 5CST criteria had a significant difference in SBP at 20 seconds (–1.94 mmHg, $p = .002$) but not at 30 or 40 seconds.

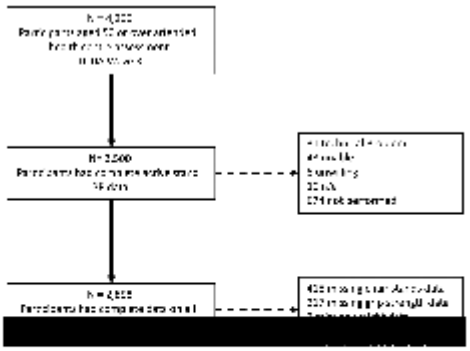

Figure 1. Flowchart of participants. BP = blood pressure; TILDA = The Irish Longitudinal Study on Ageing.

In the initial phase (0–10 seconds), probable sarcopenia by 5CST criteria had a weak effect on SBP but not DBP drop, while in the steady state (40–180 seconds), both 5CST and HGS had very little effect on SBP and DBP (Table 2).

HGS-defined probable sarcopenia was an independent predictor of OH30 in a multivariable logistic regression model (Table 3), whereas 5CST was not (odds ratio 0.93, $p = .538$).

At follow-up in wave 5, those with probable sarcopenia by the HGS criteria in wave 3 had higher proportions of recurrent falls (10.5% vs 5.7%, $p = .014$), fear of falling with activity limitation (12.4% vs 6.9%, $p = .011$), hospital admission (24.2% vs 12.5%, $p < .001$), and death (4.8% vs 1.9%, $p = .006$) when compared to the non-sarcopenic group. Those with probable sarcopenia by 5CST criteria had a higher proportion of recurrent falls (8.0% vs 5.3%, $p = .012$), fear of falling with activity limitation (11.1% vs 5.9%, $p < .001$) but not hospital admission (15.3% vs 12.5%, $p = .07$) or death (2.8% vs 1.8%, $p = .126$), when compared with the non-sarcopenic group.

Discussion

In this study, probable sarcopenia was associated with a significantly attenuated BP recovery from nadir after standing. The effect of HGS-defined probable sarcopenia was twice as strong as that of 5CST-defined probable sarcopenia. Those with HGS-defined probable sarcopenia had significantly lower SBP and DBP at 20, 30, and 40 seconds after standing, and HGS-defined probable sarcopenia was an independent predictor of OH30. The follow-up results at wave 5 show that 4 years later, there was a higher occurrence of falls, hospital admissions and mortality in the group categorized as probable sarcopenia by HGS criteria. This is the first study to examine the association between probable sarcopenia and orthostatic hemodynamics measured with continuous beat-to-beat digital photoplethysmography allowing precise characterization of BP phenotype. The results are further strengthened by a large and well-characterized sample allowing adjustment for potential confounders, and longitudinal follow-up 4 years after the initial assessment.

These results point to possible subtle differences in the underlying pathophysiology of the effects of probable sarcopenia on BP recovery after standing and are interesting in that the upper limb measures of probable sarcopenia seemed to predict orthostatic hemodynamics better than lower limb measures. This is somewhat surprising as a priori one might expect the lower limb to have a greater effect on BP, via the skeletal muscle pump, than the upper limb. There are 2 main possibilities for this result. The upper limbs may be more important in terms of the skeletal muscle pump than the lower limbs, or 5CST time may not be as good a measure of lower limb muscle strength. Indeed, others have raised the fact that 5CST tests not only strength but balance, proprioception, mobility, and endurance (24). To the best of our knowledge, there is no literature examining the relative contributions of the upper and lower limbs to the skeletal muscle pump in orthostatic BP recovery. Given that HGS correlates better with muscle mass than 5CST time (25,26), it may be a better proxy for lower limb strength and correlate better with orthostatic BP recovery.

Probable sarcopenia, as defined by 5CST criteria, had a weak but positive association with SBP in the initial 10 second period. However, as SBP was dropping at this time, this positive association means that those meeting the 5CST criteria had a less steep fall in

Table 1. Characteristics of the Study Population Grouped by Probable Sarcopenia Cutoffs Versus Non-Sarcopenic: 5-Chair Stands Test (5CST) Time > 15 Seconds; Hand Grip Strength (HGS) < 16 kg (Women)/27 kg (Men)

Demographics and Characteristics	5CST Criteria No		5CST Criteria Yes		HGS Criteria No		HGS Criteria Yes	
N	2 135	74.7%	723	25.3%	2 671	93.5%	187	6.5%
Age (years; mean/*SD*)	63.1	7.3	66.5	8.1***	63.5	7.3	70.2	9.0***
Female (*n*/%)	1 138	53.3%	387	53.5%	1 443	54.0%	82	43.9%**
Tertiary education (*n*/%)	962	45.1%	24	40.7%	1 194	44.7%	62	33.2%***
Height (cm; mean/*SD*)	166.2	9.1	166.4	9.3	166.4	9.1	163.7	9.2***
Weight (kg; mean/*SD*)	77.7	14.9	79.1	15.4*	78.2	15.1	75.9	15.0*
Hypertension (*n*/%)	626	29.3%	249	34.4%*	808	30.3%	67	35.8%
Diabetes (*n*/%)	112	5.3%	59	8.2%**	153	5.7%	18	9.6%*
Heart failure (*n*/%)	9	0.4%	5	0.7%	13	0.5%	1	0.5%
Cardiovascular medications (*n*/%)	737	34.5%	308	42.6%***	955	35.8%	90	48.1%**
Psychotropic medications (*n*/%)	231	10.8%	105	14.5%**	302	11.3%	34	18.2%**
Fear of falling with activity limitation (*n*/%)	86	4.0%	60	8.3%***	129	4.8%	17	9.1%*
Consensus OH (*n*/%)	154	7.2%	58	8%	191	7.2%	21	11.2%*

Notes: *T* test/Chi-squared test of probable sarcopenia versus non-sarcopenia for each criterion. OH = orthostatic hypotension; *SD* = standard deviation.
*$p < .05$; **$p < .01$; ***$p < .001$.

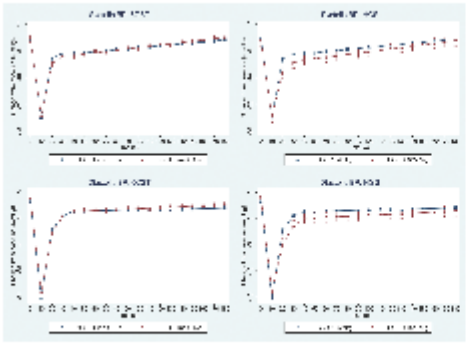

Figure 2. Predicted means and 95% confidence intervals, from mixed effect models, for systolic and diastolic blood pressure change (mmHg) after standing, stratified by probable sarcopenia status for both 5-chair stands test (5CST) and hand grip strength (HGS) criteria (5CST > 15 seconds, HGS < 16 kg women/27 kg men). Model adjusted for age, sex, height, weight, hypertension, diabetes, heart failure, cardiovascular and psychotropic medications, and fear of falling with activity limitation. BP = blood pressure.

their SBP after standing. This differs from the findings from Mol et al. (27), who found that the rate of SBP decline but not the magnitude was associated with 5CST time in seconds. However, there were significant differences in methodology: Mol et al. used 5-second averaging of BP and examined the first 15 second period, whereas we used 10-second averaging and looked at the first 10 second period, which may account for the differences. Furthermore, the mechanisms behind the initial drop in BP are not fully elucidated (28) and recent evidence has found better outcomes in those with initial OH (29,30), suggesting that a larger initial drop is physiological rather than pathological.

What is clearer, however, is the importance of BP recovery from nadir (31,32). The strongest and most consistent associations in our study were found in this BP recovery phase. Both 5CST- and HGS-defined probable sarcopenia were negatively associated with SBP and DBP recovery in the 10–20 second phase, with a high degree of statistical significance. This means that those with probable sarcopenia had a slower rate of BP recovery. The strength of the effect for HGS was more than twice that of 5CST. Furthermore, those with HGS-defined probable sarcopenia had significantly lower SBP and DBP as 20, 30, and 40 seconds. Lower SBP recovery at 30 seconds has been found previously to be associated with a greater proportion of orthostatic intolerance symptoms (19). The reduced BP recovery in those with HGS-defined probable sarcopenia could hence increase the risk of falls with resultant risk of fracture (33) and subsequent morbidity and mortality (34). The results also fit with a conceptual model of the skeletal muscle pump, which aids BP recovery and maintenance (11).

The majority of existing studies that investigated HGS and OH (8,13,15,35,36) used oscillometric BP, and therefore they were unable to consider the BP recovery phase. Romero-Ortuno et al. (9) assessed the relationship between frailty and OH with continuous BP and did not find a difference in HGS in those with delayed BP recovery; however, they used a morphological clustering approach rather than a strict OH definition and had a smaller sample ($n = 442$). In terms of 5CST and BP recovery, Mol et al. (37) found, using continuous BP measurement, that slower DBP recovery in the 15–30 and 30–60 second periods poststand, but not SBP recovery, was associated with longer 5CST time in older adults after adjustment for relevant confounders.

In the 20–30 and 30–40 second phases, those with HGS-defined probable sarcopenia had a small but significant positive association with SBP and DBP, suggesting faster BP recovery during these phases. However, given that those participants had, on average, entered those time periods with a lower BP, it is physiologically plausible that their rate of recovery would be greater during these phases.

In the steady state period, postrecovery (40–180 seconds), probable sarcopenia had little (5CST) or no (HGS) association with SBP or DBP. Studies looking at classically measured (oscillometric) OH at 3 minutes have found it to be associated with weak HGS (35,36) and confirmed sarcopenia (15), they however, adjusted for limited confounders, and recruited in outpatient (15,36) or hospital inpatient (35) setting, where the demographics and prevalence of OH, sarcopenia and severe sarcopenia may be different. Soysal et al. (13)

Table 2. Coefficients and 95% Confidence Intervals for Probable Sarcopenia Criteria (5-Chair Stands Test (5CST) Time > 15 Seconds, Hand Grip Strength (HGS) < 16 kg Women/27 kg Men) From Mixed-Effects Models for Change in Systolic and Diastolic Blood Pressure (mmHg) From Baseline After Standing at Time Intervals 0–10 Seconds, 10–20 Seconds, 20–30 Seconds, 30–40 Seconds, and 40–180 Seconds

	0–10 Seconds β (95% CI)	10–20 Seconds β (95% CI)	20–30 Seconds β (95% CI)	30–40 Seconds β (95% CI)	40–180 Seconds β (95% CI)
Systolic BP (mmHg)					
5CST-defined probable sarcopenia	0.07 (<0.01, 0.14)*	−0.25 (−0.31, −0.18)***	0.08 (0.02, 0.15)*	0.05 (−0.02, 0.11)	0.01 (<0.01, 0.02)**
HGS-defined probable sarcopenia	0.12 (<0.01, 0.23)	−0.54 (−0.65, −0.42)***	0.13 (0.02, 0.25)*	0.14 (0.02, 0.25)*	0.01 (<0.01, 0.02)
Diastolic BP (mmHg)					
5CST-defined probable sarcopenia	0.03 (<0.01, 0.07)	−0.14 (−0.18, −0.10)***	0.03 (−0.01, 0.07)	0.01 (−0.03, 0.04)	<0.01 (<0.01, 0.01)**
HGS-defined probable sarcopenia	0.02 (−0.05, 0.08)	−0.37 (−0.44, −0.31)***	0.07 (0.01, 0.14)*	0.07 (<0.01, 0.13)*	<0.01 (<0.01, 0.01)

Notes: Model adjusted for age, sex, height, weight, hypertension, diabetes, heart failure, cardiovascular and psychotropic medications, and fear of falling with activity limitation. BP = blood pressure; CI = confidence interval.
*$p < .05$; **$p < .01$; ***$p < .001$.

Table 3. Multivariable Logistic Regression for Orthostatic Hypotension at 30 Seconds (OH30), for Probable Sarcopenia Defined by Hand Grip Strength (HGS) Criteria (<16 kg Women/27 kg Men)

OH30	Odds Ratio	*p*	95% Confidence Interval	
HGS-defined probable sarcopenia	1.64	.012	1.11	2.42
Age	1.05	.000	1.03	1.06
Female	1.23	.247	0.87	1.74
Height	1.03	.003	1.01	1.05
Weight	0.98	.001	0.97	0.99
Hypertension	1.34	.092	0.95	1.88
Diabetes	1.49	.063	0.98	2.27
Heart failure	1.88	.304	0.56	6.29
Cardiovascular medications	1.22	.272	0.86	1.72
Psychotropic medications	1.28	.140	0.92	1.78
Fear of falling with activity limitation	0.63	.106	0.36	1.10

did not find a significant relationship between OH at 3 minutes and either probable or confirmed sarcopenia. As regards those studies using beat-to-beat BP, Mol et al. (37) did not find an independent association between 5CST time and SBP or DBP from 60 to 180 seconds. Meanwhile, de Bruïne et al. (38) found that participants with the worst performance on the 5CST had significantly higher odds of OH between 15 and 180 seconds compared to those with the best or intermediate performance. The discrepant findings in the published literature may have much to do with the heterogeneity in the methods used and the definitions employed.

The follow up at wave 5 highlights the negative outcomes of probable sarcopenia. Increased rates of recurrent falls were shown in both the HGS- and 5CST-defined probable sarcopenia groups. Some of those falls may be mediated via the OH pathway; others may be directly associated with probable sarcopenia. Both groups also had higher rates of fear of falling with activity limitation, a significant burden on the quality of life in older people (39). HGS- but not 5CST-defined probable sarcopenia had higher rates of hospital admission and mortality, suggesting that HGS might more precisely identify a cohort at risk of adverse outcomes.

Our results are important as they highlight that probable sarcopenia is a potentially modifiable risk factor for OH. They add to the importance of assessing probable sarcopenia; in addition to its well-known direct risk of falls and adverse outcomes (40), a second pathway is emerging, namely the effects of sarcopenia on the skeletal muscle pump with attendant risk of delayed BP recovery from standing and overt OH, adding further to falls risk. The recently published World Falls Guidelines (41) advise consideration of muscle strength assessment with 5CST or HGS as part of a multifactorial falls assessment but do not include it as a graded recommendation in their guidelines from the working groups, nor do they recommend the diagnosis or treatment of probable sarcopenia as routine in their falls work-up. Our results suggest that given its direct risk of falls and the OH-mediated falls pathway, research is needed on the role of identifying probable sarcopenia and sarcopenia in falls risk assessment clinics, and subsequently on the efficacy of interventions to ameliorate sarcopenia.

It must be stated, however, that the size of the effects reported have been modest. This is in keeping with the relatively small contribution of the skeletal muscle pump (vis-à-vis the main cardiac pump) to BP regulation on standing. Although to the best of our knowledge, there exist no published quantitative data on the exact numerical contribution of the skeletal muscle pump to orthostatic BP, a study looking at muscle pumping maneuvers (tip-toeing), in

healthy participants, found an average increase of 17 ± 9 mmHg SBP (42). It is likely that the BP rise from quiet standing is significantly less than this and closer to the nonsignificant 4 ± 7 mmHg found with leg crossing in the study. Indeed, baroreflex-mediated heart rate increases and splanchnic vasoconstriction likely contribute to the bulk of BP recovery and maintenance during quiet standing (11).

There are a number of limitations to this study that must be considered. Most significantly, as no measurement of muscle mass was obtained in the TILDA study, we cannot differentiate between participants with probable and confirmed sarcopenia. Therefore, there is the possibility that weak HGS reflected pathological processes other than sarcopenia, such as rheumatological or neurological causes. However, this is tempered by the fact that in clinical practice, HGS assessment is significantly easier to implement than direct measurement of muscle mass with dual-energy x-ray absorptiometry or bioimpedance analysis, perhaps, therefore, making the results more generalizable. This was also an observational study, and unmeasured confounding remains a possibility, although every effort was taken to minimize this. Diseases and medications were self-reported and, therefore, subject to recall bias. In addition, while beat-to-beat BP measurement is the state of the art in terms of assessment of orthostatic BP response, there do exist limitations and challenges with its employment. Previous research has shown low to moderate intraperson reliability of absolute measures, however not on relative measures of changes from baseline (43) as were used in our study. Furthermore, patterns of hemodynamic response to standing have been found to vary over time (44). Factors such as hydration status, meal timing, and caffeine intake can affect results (45), none of which we were able to control for. Comorbidities and medications can also influence BP response and were controlled for in our study, although not the timing of medications in relation to testing.

In summary, probable sarcopenia had a significant association with delayed BP recovery, with HGS-defined probable sarcopenia having a greater effect than 5CST-defined probable sarcopenia. HGS-defined probable sarcopenia was also an independent predictor of OH30. Future studies should investigate if this relationship is maintained for confirmed sarcopenia with direct measurement of muscle mass.

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Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

Conceptualization—E.D. and R.R.-O.; Formal analysis—E.D., C.H.M., J.R.C.D., S.P.K., A.M.O., and R.R.-O.; Funding acquisition—R.A.K. and R.R.-O.; Methodology—R.A.K.; Project administration—R.A.K., R.R.-O., and A.M.O.; Supervision—R.R.-O.; Writing—original draft—E.D.; Writing—review and editing—E.D., C.H.M., J.R.C.D., S.P.K., A.M.O., R.A.K., and R.R.-O. All authors have read and agreed to the published version of the manuscript.

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RESEARCH PAPER

Relationship between sarcopenia and orthostatic blood pressure recovery in older falls clinic attendees

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Key Summary Points

Aim To determine the association between sarcopenia and orthostatic blood pressure (BP) recovery in falls clinic attendees aged 50 years or older.

Findings Sarcopenia had a significantly slower rate of BP recovery (both systolic and diastolic) during the 10–20 s period after standing, independent of confounders.

Message Sarcopenia had a modest but significant attenuating effect on early orthostatic haemodynamics.

Abstract

Purpose Sarcopenia and delayed orthostatic blood pressure (BP) recovery are two disorders increasingly associated with adverse clinical outcomes in older adults. There may exist a pathophysiological link between the two via the skeletal muscle pump of the lower limbs. Previously in a large population-based study, we found an association between probable sarcopenia and orthostatic BP recovery. Here, we sought to determine the association between confirmed sarcopenia and orthostatic BP recovery in falls clinic attendees aged 50 years or over.

Methods One hundred and nine recruited patients (mean age 70 years, 58% women) underwent an active stand with non-invasive beat-to-beat haemodynamic monitoring. Hand grip strength and five-chair stands time were measured, and bio-electrical impedance analysis was performed. They were then classified as robust, probable sarcopenic or sarcopenic as per the European Working Group on Sarcopenia in Older People guidelines. Mixed effects models with linear splines were used to model the effect of sarcopenia status on orthostatic BP recovery, whilst controlling for potential confounders.

Results Probable sarcopenia was identified in 32% of the sample and sarcopenia in 15%. Both probable and confirmed sarcopenia were independently associated with an attenuated rate of recovery of both systolic and diastolic BP in the 10–20 s period after standing. Attenuation was larger for confirmed than probable sarcopenia (systolic BP $\beta -0.85$ and -0.59, respectively, $P<0.01$; diastolic BP $\beta -0.65, -0.45$, $P<0.001$).

Conclusion Sarcopenia was independently associated with slower BP recovery during the early post-stand period. The potentially modifiable effect of the skeletal muscle pump in orthostatic haemodynamics requires further study.

Keywords Sarcopenia · Blood pressure recovery · Orthostatic hypotension · Skeletal muscle pump · Orthostasis · Older people

Introduction

Sarcopenia is emerging as one of the major age-associated health challenges of the twenty-first century [1]. Accumulating evidence suggests that sarcopenia is one of the central pathological processes driving physical frailty [2] and it is implicated in a wide range of adverse health outcomes in older adults [3, 4]. Additionally, sarcopenia is associated with cardiovascular diseases including coronary artery disease, atrial fibrillation, and heart failure [5, 6].

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Delayed blood pressure (BP) recovery on standing, previously under-recognised in comparison to the classic syndrome of orthostatic hypotension (OH), is also emerging as a key driver of falls and adverse clinical outcomes in older adults [7, 8, 9]. Whereas previously OH was defined in terms of a sustained drop in BP (≥ 20 mmHg systolic and/or≥ 10 mmHg diastolic) at 3 min after standing, the prevalence of delayed BP recovery has been identified through the use of beat-to-beat orthostatic BP measurement in a number of population cohort studies [10, 11].

There is reason to suspect a pathophysiological link between sarcopenia and both delayed BP recovery and OH, given the role of the skeletal muscle pump in BP recovery and maintenance. The skeletal muscle pump is thought to aid venous return to the heart during exercise and standing, via rhythmic activity of the muscles of the lower limbs [12]. Loss of muscle strength and mass in sarcopenia could affect skeletal muscle pump function, leading to slower BP recovery and OH. This could then lead to falls, fractures, increased morbidity and even subsequent mortality. The clinical importance here is that unlike many other causes of OH, sarcopenia is potentially preventable and/or reversible through physical exercise and nutrition interventions [13].

Two previous studies found significant association between sarcopenia and OH measured with intermittent oscillometric devices [14, 15]; however, the relationship between sarcopenia and beat-to-beat orthostatic BP recovery is less well known. Our previous research in a large population-based cohort found an association between probable sarcopenia and orthostatic BP recovery and OH at 30 s [16]; however, we were limited to measures of probable sarcopenia in that cohort. The present study sought to determine the association between bioelectrical impedance analysis-confirmed sarcopenia and continuous non-invasive orthostatic BP recovery in falls clinic attendees aged 50 years or over.

Methods

Attendees to the Falls and Syncope Unit (FASU) at St. James's Hospital, Dublin, Ireland were recruited prospectively between November 2021 and November 2022. The FASU setting has been described elsewhere [17]. Inclusion criteria for the study were: age 50 years or older, able to provide written informed consent, able to mobilise independently (with or without aid) and able to transfer with minimal assistance of one person from lying to standing. Exclusion criteria were: history of confirmed or presumed neurogenic OH, or contraindication to bioelectrical impedance analysis (e.g. presence of an indwelling electronic device such as a cardiac pacemaker). Ethics approval for the study was granted from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (Project ID: 0221; approval date: 4 May 2021). Approval was also granted by St James's Hospital Research & Innovation Office (Reference: 6567, approval date: 26 July 2021). All included patients provided written informed consent to partake in the study. The study adhered to the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects.

Participants' disease status and medication use were obtained from a combination of self-report, medical chart review and correspondence from the participants' General Practitioner where available. Multimorbidity was defined as two or more chronic conditions and polypharmacy as five or more regular medications excluding supplements. Physical frailty status was determined using the SHARE Frailty Instrument for Primary Care (SHARE-FI) [18]. Cardiovascular medication use was coded as 'Yes' if the participant was taking one or more of the following medications (coded using the Anatomical Therapeutic Chemical Classification (ATC)): anti-arrhythmics (ATC C01), anti-hypertensives (ATC C02), diuretics (ATC C03), vasodilators (ATC C04), beta-blocking agents (ATC C07), calcium channel blockers (ATC C08), or agents acting on the renin–angiotensin system (ATC C09). Psychotropic medication use was coded as 'Yes' if the participant was taking one or more of the following: anti-epileptics (ATC N03A), anti-psychotics, anxiolytics, hypnotics or sedatives (ATC N05), or anti-depressants (ATC N06A).

Hand grip strength (HGS) was assessed using a Jamar Hydraulic Hand Dynamometer (Performance Health, Wisconsin, USA). The maximum value of two consecutive measurements taken on the left and right hands, whilst seated, was used. Values were rounded to the nearest 2 kg, as per the precision of the device. The time taken on the five-chair stands test (5CST) was measured as the time to the nearest centi-second taken for a participant to stand up and sit back down again, as fast as possible, five times from a standard chair (approximate seat height 43 cm). Height was measured to the nearest 0.01 m (Seca 222 Stadiometer, Seca Ltd, Birmingham, UK). Bioelectrical impedance analysis was performed with the TANITA® DC-430 MAP Body Composition Analyser (Tanita Europe, Amsterdam, The Netherlands). Participants stood barefoot on the scale, which also provided weight measurement to the nearest 0.01 kg. Participants were asked to remove their outerwear and empty their pockets, and 0.5 kg was entered as a standard tare value for clothing. Appendicular skeletal muscle mass was calculated using the Sergi equation [19]. The European Working Group on Sarcopenia in Older People (EWGSOP) revised cutoffs for probable sarcopenia (HGS of less than 27 kg in men and 16 kg in women and/or 5CST greater than 15 s) and sarcopenia (muscle mass less than 20 kg in men and 15 kg in women) were used [20].

Participants underwent a continuously monitored active stand test as per recommended guidelines [21], with a signal calibration and resting phase of 5–10 min, followed by standing as quickly as possible (with assistance if necessary) and remaining standing quietly for 3 min. Continuous non-invasive beat-to-beat BP was measured with a Finapres® Nova (Finapres Medical Systems, Amsterdam, The Netherlands). The signals were calibrated using brachial artery measurements and Physiocal™, with the height correction unit correcting for hydrostatic pressure differences.

Beat-to-beat signals were exported from the Finapres® Nova software and analysed using custom written software in MATLAB® version 9.11 (The MathWorks, Inc., Natick, MA, USA). Signals were inspected for poor quality and those with excess noise or artefacts were excluded. If there was a suspicion of delay between the marker for standing and actual standing, the height correction unit signal was examined and the stand time corrected. The baseline signal was taken as the mean from 60 to 30 s before standing. Ten-second averages were taken from 0 to 180 s after standing and used in the analysis. OH at 30 s (OH30) was defined as a drop of SBP ≥ 20 mmHg and/or DBP ≥ 10 mmHg from baseline values.

Statistical analysis was performed with Stata® version 15.1 (StataCorp LLC, College Station, TX, USA). The distributions of continuous variables were examined visually with histograms and distributional diagnostic plots and tested using the skewness kurtosis test for normality [22]. For the demographics of the sample, continuous normally distributed variables were summarised by the mean and standard deviation (SD), and non-normal continuous variables by the median and interquartile range (IQR). Proportions were given as count and percentage. Given that sarcopenia status was a three-level ordinal variable (i.e. robust, probable sarcopenia and sarcopenia), trends in continuous variables across those three levels were examined with Kendall's rank correlation coefficient [23, 24], whilst trends in dichotomous variables were examined using Chi-square for trend. Additionally, the effect of sarcopenia status on systolic and diastolic BP after standing was represented graphically, from standing to 180 s, with the mean change in BP and standard error of the mean, by sarcopenia group.

Given that multiple repeated measures of BP were taken for each participant, a statistical method that accounted for this and allowed adjustment for potentially confounding factors was needed. As per previous work by our group and others, we implemented mixed-effects models with piecewise linear splines to model time points 0–10, 10–20, 20–30, 30–40 and 40–180 s after standing [16, 25, 26]. Residual variance was modelled with a first order autoregressive process to account for the strong correlation between adjacent time points. The linear splines were entered into the model as independent parameters along with interaction terms with sarcopenia status (robust—0; probable sarcopenia—1; sarcopenia—2) and potential confounders as covariates. The potential confounders considered were: age, sex, diabetes, hypertension, cardiovascular medications and psychotropic medications. In addition, in an attempt to isolate the effect of the skeletal muscle pump's contribution to BP response from that of the main cardiac pump, we also controlled for heart rate (HR), as an interaction term with each linear spline. Variables that theoretically lay on the causative pathway to sarcopenia, for example multimorbidity [27], were considered mediators rather than confounders and as such not controlled for in the models. Fully adjusted beta (β) coefficients with 95% confidence intervals (CI) for the five time periods were obtained from the mixed-effects models outputs. The level of statistical significance was defined as $P < 0.05$ throughout.

Results

Over the recruitment period, 123 patients consented to participate in the study. Of these, 5 had a contraindication to or declined BIA, 7 had probable or confirmed neurogenic OH, and in 2 there was no active stand test or the active stand signal was of poor quality. Thus, the included sample size was 109. Overall, the mean age of the included sample was 70 years (SD 10.5, range 5093), and 58% were women.

The descriptives of the included sample grouped by sarcopenia status are presented in Table 1. Statistically significant trends with sarcopenia status were identified for increasing age and presence of multimorbidity, physical frailty, polypharmacy, psychotropic medications, and increasing 5CST. Weight, height, HGS and appendicular skeletal muscle mass significantly decreased as sarcopenia status increased. The difference in the prevalence of OH30 across sarcopenia status did not meet statistical significance.

The raw data-based mean changes in systolic BP, diastolic BP and HR after standing, grouped by sarcopenia status, are displayed in Fig. 1. Visually, the probable sarcopenia and sarcopenia groups appeared to have slower recoveries from the BP nadir, and there seemed to be a less pronounced HR response especially in the sarcopenia group.

The β coefficients and CI for the five time points in the mixed-effects models for systolic and diastolic BP, by sarcopenia status, controlling for confounders, are presented in Table 2. To aid interpretation, the predicted marginal means for change from baseline in systolic and diastolic BP, grouped by sarcopenia status, are shown in Fig. 2. There was significantly attenuated recovery of both systolic and diastolic BP during the 10–20 s period post-standing for both the probable sarcopenia and sarcopenia groups when compared to the robust group, as evidenced by the negative coefficients during a period where the overall BP trend was positive.

Table 1 Characteristics of the sample grouped by sarcopenia status

	Robust (58/53.2%)	Probable sarcopenia (35/32.1%)	Sarcopenia (16/14.7%)	*P*
Age (years) (mean/SD)	66.1 (9.8)	73.8 (8.8)	76.0 (11.2)	<0.001
Female (n/%)	30 (51.7)	24 (68.6)	9 (56.3)	0.383
Weight (kg) (median/IQR)	75.4 (18.7)	73.8 (19.4)	57.7 (16.8)	0.034
Height (cm) (mean/SD)	169.3 (9.5)	165.3 (7.7)	162.9 (9.1)	0.007
BMI (kg/m^2) (median/IQR)	25.5 (4.8)	27.8 (4.3)	23.0 (5.8)	0.502
5CST (s) (median/IQR)	12.0 (2.8)	19.7 (6.2)	18.7 (11.1)	<0.001
HGS (kg) (median/IQR)	29.0 (14.0)	20.0 (11.0)	16.5 (9.0)	<0.001
ASMM (kg) (median/IQR)	19.2 (6.9)	18.6 (6.5)	14.5 (6.3)	0.034
Frail (n/%)	1 (1.7)	10 (28.6)	6 (37.5)	<0.001
Multimorbidity (n/%)	41 (70.7)	31 (88.6)	15 (93.8)	0.014
Polypharmacy (n/%)	21 (36.2)	21 (60.0)	11 (68.8)	0.006
Hypertension (n/%)	26 (44.8)	18 (51.4)	9 (56.3)	0.368
Diabetes (n/%)	8 (13.8)	7 (20.0)	1 (6.3)	0.756
Cardiovascular Meds (n/%)	29 (50.0)	16 (45.7)	10 (62.5)	0.564
Psychotropic Meds (n/%)	11 (19.0)	18 (51.4)	7 (43.8)	0.006
OH30 (n/%)	14 (24.1)	13 (37.1)	7 (43.8)	0.083

BMI, body mass index; 5CST, five-chair stands test; HGS, hand grip strength; ASMM, appendicular skeletal muscle mass; OH30, orthostatic hypotension at 30 s after standing; Meds, medications; SD, standard deviation; n, number; IQR, interquartile range

However, for both systolic and diastolic BP, the sarcopenia group had a more attenuated recovery than the probable sarcopenia group. The probable sarcopenia and sarcopenia groups also had an attenuation in the initial drop in BP on standing as evidenced by the significant positive β coefficients at a time when the overall BP trend was negative.

Discussion

In this study, we determined the association between sarcopenia (probable and bioimpedance-confirmed) and continuous orthostatic BP recovery in 109 falls clinic attendees aged 50 years or older. We observed that both probable sarcopenia and sarcopenia were associated with an attenuated rate of recovery of both systolic and diastolic BP in the 10–20 s period after standing, with a larger attenuation for the sarcopenia group compared to the probable sarcopenia group. These effects were independent of age, sex, diabetes, hypertension, cardiovascular and psychotropic medications, and heart rate response, supporting the hypothesis that they could reflect the effect of sarcopenia on the skeletal muscle pump of the lower limbs in supporting early post-standing haemodynamic stabilisation. The results are strengthened by the comprehensive characterisation of the sample, allowing robust adjustment for potential confounders, the continuous non-invasive beat-to-beat BP measurements, and the use of the consensus EWGSOP revised definitions for the diagnosis of sarcopenia.

These results extend our previous population-based work on probable sarcopenia [16] and, to the best of our knowledge, show for the first time an association between confirmed sarcopenia and delayed BP recovery using continuous non-invasive orthostatic haemodynamic measurements. Findings are clinically important as even in the absence of OH at 30 s, delayed BP recovery in the early post-standing phase can contribute to reduced cerebral perfusion and increase the risk of falls and syncope [8, 28, 29], which in turn can lead to fractures, hospital admissions, loss of functional independence, and risk of institutionalisation [9, 30]. Although sarcopenia can directly lead to falls [31], our results suggest the existence of an indirect mechanism whereby sarcopenia could also contribute to falls by impairing early post-standing BP recovery. The clinical importance of this is that unlike many other causes of OH, sarcopenia is a potentially reversible risk factor. Recent evidence from the SPRINTT trial found that a multicomponent intervention could reduce sarcopenia and mobility disability in older adults [32]. If similar interventions were implemented in those at risk of OH via the sarcopenia-mediated impaired orthostatic BP recovery pathway, lower limb strengthening and nutrition could potentially reduce the risk of subsequent falls by optimising the skeletal muscle pump and BP recovery.

This study adds to the importance of identifying and treating sarcopenia. The recent World Guidelines for Falls Prevention and Management for Older Adults [33] advise muscle strength measurement as part of a multifactorial falls assessment but they do not give any specific

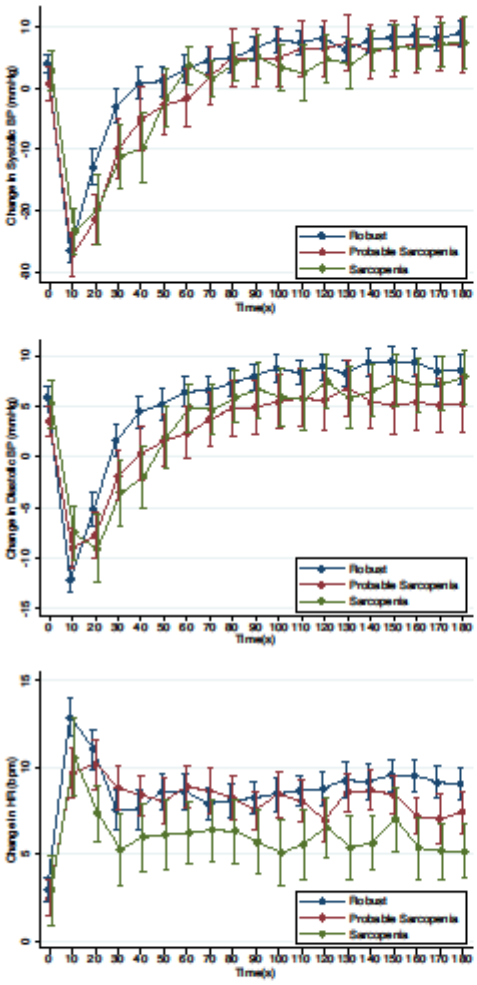

Fig. 1 Mean change in systolic blood pressure, diastolic blood pressure (mmHg) and heart rate (beats per minute—bpm) after standing grouped by sarcopenia status. Unadjusted. Error bars: standard error of the mean

recommendations regarding sarcopenia diagnosis or treatment. Given the potential existence of a second OH-mediated pathway by which sarcopenia could lead to falls, further research may be warranted as to the role of sarcopenia identification in falls risk assessment clinics.

The proposed mechanism by which sarcopenia is linked to OH is via the skeletal muscle pump. Based on our results, we hypothesise that sarcopenia may lead to reduced activity of the skeletal muscle pump during early orthostasis, and hence reduced venous return from the lower limbs resulting in a slower or incomplete recovery of BP. However, despite the theory of its existence being nearly 100 years old [34], the skeletal muscle pump remains understudied and its precise contribution to orthostatic haemodynamics in older adults is uncertain [35]. Some studies have examined the role of the skeletal muscle pump in specific populations. Stewart and colleagues [36] investigated muscle pump function in patients with postural orthostatic tachycardia syndrome finding that the amount of blood ejected by the skeletal muscle pump is related to calf circumference and calf blood flow whilst supine. Kondo et al. [37] showed that in patients with heart failure with reduced ejection fraction, the skeletal muscle pump indirectly assists cardiac output by increasing venous return.

To the best of our knowledge, no studies had assessed the function of the skeletal muscle pump in sarcopenia, although a number have examined the relationship between sarcopenia and OH. A higher prevalence of oscillometric-determined OH in older participants with sarcopenia has been found when measured lying and standing [14, 38], and using a head-up tilt test [15]. Other studies have indirectly looked at muscle strength or mass separately. For instance, diastolic BP recovery, as measured with beat-to-beat BP, in the 15–30 s and 30–60 s periods post-standing was associated with worse 5CST performance [28]. De Bruine et al. [39] found that participants with the worst performance on 5CST, compared to intermediate and best groups, had significantly higher odds of OH measured with beat-to-beat BP. Chen et al. [40] found significantly increased odds of OH with auscultatory BP measurements for those with weak grip strength, whilst Roca et al. [41] reported similar results with oscillometric measurement of BP. Looking at muscle mass alone, Benton et al. [42] found greater drops in BP measured oscillometrically on standing, in a low muscle mass group compared to a normal muscle mass group, both before and after overnight fast.

Thus, the results of these previous studies suggest first a relationship between sarcopenia and OH, and second the existence of a relationship between skeletal muscle pump function and BP. By demonstrating that sarcopenia is related to the continuous BP recovery after standing, independent of heart rate, our study supports these previous findings and gets closer to investigating the mechanism at play. It is clear, however, that further research is needed to characterise the skeletal muscle pump.

Additionally, in our study, we found an attenuated fall in diastolic BP in the initial 10 s after standing for the probable sarcopenia and sarcopenia groups compared to the robust group, as demonstrated by the significant positive β coefficients during a time when the overall BP was falling. It has been argued that the initial drop in BP on active standing,

Table 2 Beta-coefficients and 95% confidence intervals for the effect of sarcopenia status on the change in systolic and diastolic blood pressure (mmHg) from baseline at time intervals 0–10 s, 10–20 s, 20–30 s, 30–40 s and 40–180 s after standing

	0–10 s β (95% CI)	10–20 s β (95% CI)	20–30 s β (95% CI)	30–40 s β (95% CI)	40–180 s β (95% CI)
Systolic BP					
Probable sarcopenia	0.10 (− 0.28, 0.48)	− 0.59 (− 0.97, − 0.21)**	0.20 (− 0.18, 0.58)	0.13 (− 0.24, 0.51)	0.03 (− 0.03, 0.08)
Sarcopenia	0.32 (− 0.18, 0.83)	− 0.85 (− 1.35, − 0.34)**	− 0.07 (− 0.57, 0.44)	− 0.15 (− 0.64, 0.35)	0.05 (− 0.02, 0.13)
Diastolic BP					
Probable sarcopenia	0.48 (0.26, 0.71)***	− 0.45 (− 0.68, − 0.23)***	− 0.15 (− 0.37, 0.07)	− 0.04 (− 0.26, 0.18)	0.01 (− 0.02, 0.04)
Sarcopenia	0.49 (0.20, 0.78)**	− 0.65 (− 0.95, − 0.36)***	− 0.16 (− 0.45, 0.14)	− 0.10 (− 0.39, 0.19)	0.04 (< − 0.01, 0.08)

Models were adjusted for age, sex, diabetes, hypertension, cardiovascular and psychotropic medications and heart rate. *$P<0.05$, **$P<0.01$, ***$P<0.001$

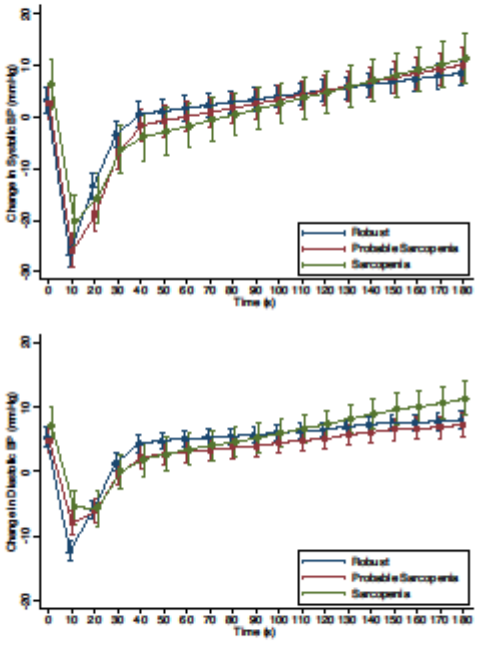

Fig. 2 Predicted means and standard error of the mean from mixed-effects models for change in systolic and diastolic blood pressure (mmHg) after standing, grouped by sarcopenia status. Models were adjusted for age, sex, diabetes, hypertension, cardiovascular and psychotropic medications and heart rate

which is not seen in passive changes in posture, i.e. the head-up tilt [43], may be more physiological than pathological and mostly related to the effort and speed of standing [44, 45]. As applied to our results, this is plausible as those with sarcopenia would be expected to have a lower standing speed with a slower initial fall in BP and a less pronounced nadir.

The present study did not replicate a finding of our previous population-based study, namely the statistical significance of the association between probable sarcopenia and OH30 [16]. This may have been due to the imprecision of the estimates, given the small sample size in the present study and the higher variability in the data as evidenced by the wider standard errors shown in the data visualisations. This suggests that the magnitude of the muscle pump effect is at best modest, and this is in keeping with known physiology. Indeed, the predominant mechanisms known to be involved in BP recovery after standing are the baroreflex-mediated splanchnic and peripheral vasoconstriction and the increased cardiac output via vagal withdrawal causing an increase in heart rate [46]. Yet, even if the muscle pump contribution is modest, it is one that is potentially more modifiable, via physical training to improve muscle mass and strength, than other autonomic nervous system mechanisms.

As well as the relatively small sample size, limitations of the present study include the known limitations of bioimpedance analysis for determination of muscle mass; for example, measurements can be influenced by hydration status and the measurements themselves are an estimate referenced to a dual-energy X-ray absorptiometry standard, and do not represent the gold standard [47]. Patients were not required to fast for the minimum required time of 4–6 h before measurements. Furthermore, although we collected medication records, no information was available in relation to timing of medication ingestion in relation to the active stand test routinely performed in the clinic. Different medications will have different half-lives, and therefore their effect on the BP response after standing may vary depending on the time of ingestion in relation to the active stand test.

In conclusion, in this study, we found that older falls clinic patients with sarcopenia had a slower rate of recovery of BP early after standing, as measured by continuous non-invasive haemodynamics. This may put them at risk of OH, falls and fractures. This has important implications for the role of sarcopenia identification in falls risk assessment. The more detailed quantification and potentially modifiable

effect of the skeletal muscle pump in orthostatic haemodynamics requires further study.

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Data Availability The data that support the findings of this study are not openly available due to the conditions of ethics approval for the study and current data protection legislation. Dependent on compliance with data protection legislation and ethical approval they may be available from the corresponding author upon reasonable request.

Declarations

Ethics approval Ethics approval for the study was granted from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (Project ID: 0221; approval date: 4 May 2021). Approval was also granted by St James's Hospital Research & Innovation Office (Reference: 6567, approval date: 26 July 2021). All study participants provided written informed consent to partake in the study. The study adhered to the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects.

Consent to participate All patients provided written, explicit, informed consent.

Conflict of interest The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Haemodynamic Parameters Underlying the Relationship between Sarcopenia and Blood Pressure Recovery on Standing

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Abstract: Background: Sarcopenia, delayed blood pressure (BP) recovery following standing, and orthostatic hypotension (OH) pose significant clinical challenges associated with ageing. While prior studies have established a link between sarcopenia and impaired BP recovery and OH, the underlying haemodynamic mechanisms remain unclear. Methods: We enrolled 107 participants aged 50 and above from a falls and syncope clinic, conducting an active stand test with continuous non-invasive haemodynamic measurements. Hand grip strength and five-chair stand time were evaluated, and muscle mass was estimated using bioelectrical impedance analysis. Participants were categorised as non-sarcopenic or sarcopenic. Employing mixed-effects linear regression, we modelled the effect of sarcopenia on mean arterial pressure and heart rate after standing, as well as Modelflow®-derived parameters such as cardiac output, total peripheral resistance, and stroke volume, while adjusting for potential confounders. Results: Sarcopenia was associated with diminished recovery of mean arterial pressure during the 10–20 s period post-standing (β −0.67, $p < 0.001$). It also resulted in a reduced ascent to peak (0–10 s) and recovery from peak (10–20 s) of cardiac output (β −0.05, $p < 0.001$; β 0.06, $p < 0.001$). Furthermore, sarcopenia was associated with attenuated recovery (10–20 s) of total peripheral resistance from nadir (β −0.02, $p < 0.001$) and diminished recovery from peak (10–20 s) of stroke volume (β 0.54, $p < 0.001$). Notably, heart rate did not exhibit a significant association with sarcopenia status at any time interval post-standing. Conclusion: The compromised BP recovery observed in sarcopenia appears to be driven by an initial reduction in the peak of cardiac output, followed by attenuated recovery of cardiac output from its peak and total peripheral resistance from its nadir. This cardiac output finding seems to be influenced by stroke volume rather than heart rate. Possible mechanisms for these findings include cardio-sarcopenia, the impact of sarcopenia on the autonomic nervous system, and/or the skeletal muscle pump.

Keywords: sarcopenia; delayed blood pressure recovery; orthostatic hypotension; orthostatic haemodynamics; orthostasis

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1. Introduction

Humans stand on average 60 times per day [1]. One of the key challenges associated with orthostasis is the maintenance of blood pressure (BP) in the upright position. Gravity leads to a pooling of blood in the lower limbs and below the level of the heart and therefore to a reduction in intrathoracic blood volume [2]. As a consequence, this leads to a decrease in central venous pressure and therefore stroke volume (SV), resulting in a decline in cardiac output (CO) [3]. Without counter-regulatory measures, a precipitous fall in mean arterial pressure (MAP) would occur [4].

A number of mechanisms are involved in the recovery of BP on standing. Carotid and cardiopulmonary baroreceptors detect a fall in BP triggering a reduction in cardiac vagal activity and an increase in sympathetic activity leading to an increase in heart rate (HR), which limits the fall in CO (caused by the drop in SV) [5]. Total peripheral resistance

(TPR) increases via sympathetic mediated vasoconstriction in splanchnic and peripheral blood vessels [6]. Finally, the rhythmic activity of the skeletal muscle pump of the lower limbs may also improve venous return and subsequent SV and CO, thus helping maintain MAP [7].

Impairment of these mechanisms with ageing or disease may result in a delayed recovery of BP or a failure of BP to recover—orthostatic hypotension (OH) [8]. In general, a 'classic' non-recovery OH pattern observed at three minutes post-standing, especially when accompanied by a reduced or absent HR increase, is more likely to be 'neurogenic' or largely caused by either primary or secondary autonomic failure [9]. However, the importance of causes such as heart failure, medications, and hypovolaemia are increasingly recognised in non-neurogenic presentations [10].

A potential contributor to OH is sarcopenia, a clinical condition of low muscle mass and function [11] that is prevalent in older people [12] and has been associated with many adverse outcomes [13]. Previous research has demonstrated an association between classic OH, assessed with intermittent BP measurement, and sarcopenia [14,15]. We previously found an association between beat-to-beat orthostatic BP recovery and both probable sarcopenia in a population study [16] and sarcopenia in a clinical setting [17].

However, the potential mechanisms underlying these associations have not been investigated and remain unclear. Departing from the well-established physiology equations: $MAP = CO \times TPR$ and $CO = SV \times HR$ [18], the aim of this study was to explore how the relationship between orthostatic BP recovery and sarcopenia may be mediated in haemodynamic terms.

2. Materials and Methods

Participants were recruited from the Falls and Syncope Unit at Mercer's Institute for Successful Ageing in St James's Hospital, Dublin, Ireland [19]. Typically, participants had been referred to the unit by their general practitioner due to a recent history of falls, syncope, pre-syncope, light-headedness, or dizziness. Criteria for inclusion in this study were as follows: age 50 years or older, able to provide written informed consent, able to mobilise independently (with or without aid), and able to transfer independently or with minimal assistance of one person from lying to standing. Exclusion criteria were as follows: history of confirmed or presumed neurogenic OH or contraindication to bioelectrical impedance analysis (BIA) (e.g., presence of an indwelling electronic device such as a cardiac pacemaker). Ethical approval for this study was granted from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (Project ID: 0221; approval date: 4 May 2021), and approval was also granted by St James's Hospital Research & Innovation Office (Reference: 6567, approval date: 26 July 2021). All participants in this study provided explicit, written informed consent. This study adhered to the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects.

Participants' medical history and use of medications were obtained from sources including self-report, electronic health record review, and general practitioner correspondence. Cardiovascular medication use was defined as regular use of one or more of the following medications (coded using the Anatomical Therapeutic Chemical Classification (ATC)): anti-arrhythmics (ATC C01), anti-hypertensives (ATC C02), diuretics (ATC C03), vasodilators (ATC C04), beta-blocking agents (ATC C07), calcium channel blockers (ATC C08), or agents acting on the renin–angiotensin system (ATC C09). Psychotropic medication use was defined as taking one or more of the following: anti-epileptics (ATC N03A), anti-psychotics, anxiolytics, hypnotics or sedatives (ATC N05), or anti-depressants (ATC N06A).

Hand grip strength (HGS) was assessed using a Jamar hydraulic hand dynamometer (Performance Health, Cedarburg, WI, USA). The maximum value of two seated, consecutive measurements taken on the left and right hands was used. Values were rounded to the nearest 2 kg as per the precision of the device. The five-chair stand test time (5CST) was measured as the time to the nearest centi-second taken for a participant to stand up and

sit back down five times from a standard chair (approximate height 43 cm), as fast as possible. Height was measured to the nearest 0.01 m with a Seca 222 Stadiometer (Seca Ltd., Birmingham, UK). BIA was performed with a TANITA® DC-430 MAP Body Composition Analyser (Tanita Europe, Amsterdam, The Netherlands). Participants stood barefoot on the scale, which also provided weight measurement to the nearest 0.01 kg. Participants were asked to remove their outerwear and empty their pockets, and 0.5 kg was entered as a standard tare value for clothing. Appendicular skeletal muscle mass was estimated using the Sergi equation [20]. The European Working Group on Sarcopenia in Older People (EWGSOP) revised criteria for sarcopenia (HGS of less than 27 kg in men and 16 kg in women and/or 5CST greater than 15 s, with muscle mass less than 20 kg in men and 15 kg in women) were used [21].

Participants underwent an active stand test with continuous non-invasive beat-to-beat BP measurement with Finapres® Nova (Finapres Medical Systems, Amsterdam, The Netherlands). The active stand test consisted of a supine signal calibration and resting phase of 5–10 min, followed by standing as quickly as possible and remaining standing quietly for 3 min [22]. Signal calibration was performed using oscillometric brachial calibration and the Physiocal function on Finapres® Nova with the height correction unit adjusting for differences in hydrostatic pressure. Finapres® Nova automatically measures HR and calculates MAP per beat as the integral of the arterial pressure waveform.

Beat-to-beat signals for the haemodynamic parameters CO, TPR, and SV are derived by Finapres® Nova using the built-in Modelflow® algorithm. The Modelflow® algorithm calculates the aortic flow waveform by simulating a non-linear three-element model of aortic input impedance [23]. This is integrated to compute SV, and from this, CO is calculated by multiplying by HR [24]. TPR is then derived from MAP divided by CO.

Values were exported from Finapres® Nova software and analysed using custom-written software in MATLAB® version 9.14 (The MathWorks, Inc., Natick, MA, USA) in accordance with previously published recommendations [25]. The baseline signal was taken as the mean of 60 to 30 s before standing. For the period from 0 to 180 s after standing, a ±5 s moving average filter was applied to the signals. The relative change in haemodynamic parameters, at 10 s time intervals from 0 to 180 s, was then calculated by subtracting the baseline from the absolute values.

Statistical analysis was performed with Stata® version 15.1 (StataCorp LLC, College Station, TX, USA). To assess the relationship between sarcopenia and each of the haemodynamic parameters, we used multi-level mixed-effects models, as previously employed by our group and others [16,17,26,27]. The fixed and random effects accounted for the repeated measures within participants. Piecewise linear splines were used to model five time intervals: 0–10, 10–20, 20–30, 30–40, and 40–180 s after standing. Residual variance was modelled with a first-order autoregressive process to account for the strong correlation between adjacent timepoints. The linear splines were entered into the model as independent parameters along with the interaction of sarcopenia status (no sarcopenia = 0; sarcopenia = 1) and potential confounders as covariates. The potential confounders considered were age, sex, diabetes, hypertension, cardiovascular medications, and psychotropic medications.

3. Results

Of the 123 participants recruited to this study, 5 had a contraindication to or declined BIA, 7 had probable or confirmed neurogenic OH, 1 had no active stand test, and in 3, the beat-to-beat haemodynamic signals were of poor quality. This left a final analytical sample size of 107 with a mean age of 69.7 years (standard deviation of 10.4 years), with 61 (57%) being women. Further characteristics of this sample, grouped by sarcopenia status, are presented in Table 1.

Table 1. Characteristics of the sample grouped by sarcopenia status. Meds—medications; * Pearson's chi-squared test. † Fisher's exact test.

	No Sarcopenia (91/85%)	Sarcopenia (16/15%)	*p*-Value
Age Group (*n*/%)			0.143 †
50–64 years	30 (90.9)	3 (9.1)	
65–74 years	34 (89.5)	4 (10.5)	
75+ years	27 (75.0)	9 (25.0)	
Women (*n*/%)	52 (57.1)	9 (56.3)	0.947 *
Hypertension (*n*/%)	42 (46.2)	9 (56.3)	0.456 *
Diabetes (*n*/%)	15 (16.5)	1 (6.3)	0.457 †
Cardiovascular Meds (*n*/%)	44 (48.4)	10 (62.5)	0.297 *
Psychotropic Meds (*n*/%)	27 (29.7)	7 (43.8)	0.265 *

The beta coefficients with confidence intervals and *p*-values, at each of the five time segments, from the adjusted mixed-effects models for the relationship between sarcopenia status and each of the haemodynamic parameters are shown in Table 2. Plots of the marginal effects of the means for the two groups are shown in Figure 1 for each of the haemodynamic parameters.

Table 2. Beta coefficients (β) and 95% confidence intervals (CIs) for the effect of sarcopenia status on the change in mean arterial pressure (MAP; mmHg), cardiac output (CO; L/min), total peripheral resistance (TPR; mmHg·s/mL), stroke volume (SV; mL), and heart rate (HR; beats per minute) from baseline at time intervals 0–10 s, 10–20 s, 20–30 s, 30–40 s, and 40–180 s after standing. Models were adjusted for age, sex, diabetes, hypertension, cardiovascular, and psychotropic medications. *** $p < 0.001$.

	0–10 s β (95% CI)	10–20 s β (95% CI)	20–30 s β (95% CI)	30–40 s β (95% CI)	40–180 s β (95% CI)
MAP	0.23 (−0.13, 0.59)	−0.67 (−1.03, −0.31) ***	−0.05 (−0.41, 0.31)	−0.10 (−0.45, 0.31)	0.03 (−0.02, 0.08)
CO	−0.05 (−0.08, −0.03) ***	0.06 (0.03, 0.09) ***	0.01 (−0.02, 0.04)	0.01 (−0.02, 0.04)	<−0.01 (<−0.01, <0.01)
TPR	<0.01 (−0.01, 0.01)	−0.02 (−0.03, −0.01) ***	0.01 (<−0.01, 0.02)	−0.01 (−0.02, <0.01)	<0.01 (<−0.01, <0.01)
SV	−0.37 (−0.72, −0.02)	0.54 (0.19, 0.88) ***	0.18 (−0.17, 0.52)	0.09 (−0.25, 0.43)	−0.02 (−0.06, 0.02)
HR	−0.16 (−0.40, 0.08)	−0.15 (−0.39, 0.09)	0.03 (−0.21, 0.26)	0.02 (−0.22, 0.25)	−0.01 (−0.04, 0.01)

The recovery in MAP in the 10–20 s post-stand period was significantly attenuated in the sarcopenia group compared with the no sarcopenia group as evidenced by the highly statistically significant negative beta coefficient, at a time when the overall MAP trend was upwards.

CO for the sarcopenia group had an attenuated initial rise to peak in the 0–10 s period, shown by the significant negative coefficients when overall CO was rising. This was followed by an attenuated recovery of CO from peak, for the sarcopenia group, in the 10–20 s period, demonstrated by the significant positive beta coefficient at a time when CO was returning to baseline.

TPR showed a significantly attenuated recovery in the 10–20 s period after standing for the sarcopenia group compared with no sarcopenia, again as indicated by a significant negative coefficient at a time when overall TPR was recovering.

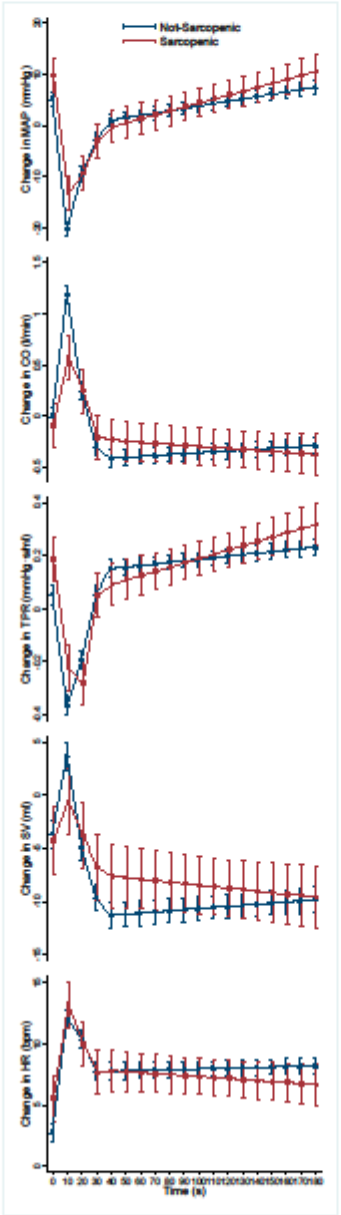

Figure 1. Predicted means and standard error of the mean from mixed-effects models for change in mean arterial pressure (MAP; mmHg), cardiac output (CO; L/min), total peripheral resistance (TPR; mmHg·s/mL), stroke volume (SV; mL), and heart rate (HR; beats per minute) from baseline after standing grouped by sarcopenia status. Models were adjusted for age, sex, diabetes, hypertension, cardiovascular, and psychotropic medications.

For SV, the sarcopenia group had an attenuated recovery in the 10–20 s period, demonstrated by a significant positive coefficient. For HR, no significant differences were seen between the two groups at any of the time intervals.

4. Discussion

In this study, we explored the relationship between sarcopenia status (present vs. absent) and the haemodynamic response to standing. We found that sarcopenia was associated with an attenuated recovery of MAP during the 10–20 s period after standing, in keeping with our previous findings regarding systolic and diastolic BP [17]. We expanded upon our previous findings by examining the components of MAP, namely CO and TPR, demonstrating early post-standing changes in both factors that may drive the alterations observed in MAP. Furthermore, CO is determined by SV and HR, and we observed significant changes in SV in the 10–20 s period after standing but no significant difference in HR between sarcopenia and non-sarcopenia groups. These results are important as they provide insights into the possible underlying pathophysiology of delayed BP recovery in older adults with sarcopenia, and this may have implications for the clinical management of this condition. Our findings are strengthened by a well-characterised participant cohort, enabling adjustments for potential confounders. Additionally, the use of continuous beat-to-beat haemodynamic measurements allows for a non-invasive and precise characterisation of the haemodynamic response to orthostasis.

The finding of an attenuated rate of recovery of MAP in the 10 to 20 s period after standing is in keeping with our previous study, which also found an attenuated rate of systolic and diastolic BP recovery in both probable and confirmed cases of sarcopenia during the same timeframe [17]. To the best of our knowledge, apart from our previous study, no previous studies had examined the relationship between sarcopenia and the early BP response to standing. However, one study [28] found an association between 5CST (a component of the EWGSOP criteria for probable sarcopenia) and diastolic BP recovery, 30 to 60 s after standing, with a longer 5CST being associated with worse diastolic BP recovery. Another study [29] found that those in the slowest category for 5CST had significantly higher odds of initial orthostatic hypotension in the first 15 s after standing. Together with our study, they add weight to the hypothesis that muscle function and mass may be linked to BP recovery early after standing.

CO showed a significantly attenuated initial increase in the sarcopenic group when compared with the non-sarcopenic. The sarcopenic group also showed an attenuated recovery from peak CO in the 10 to 20 s period. Thus, we can surmise that the changes in MAP were related to the attenuated CO response in the initial 10 s contributing to subsequent slower MAP recovery in the 10 to 20 s period. The initial increase in CO on standing followed by prompt recovery seen in the non-sarcopenic group has been previously established in healthy participants [30,31]. While no previous data had been reported in subjects with sarcopenia, Wieling et al. [32] found that older participants had a less pronounced rise in CO to peak after standing when compared with younger participants, similar to our finding in CO in the same period. The effects of ageing on skeletal muscle may have played a role in these findings. On the other hand, Van Wijnen and colleagues [33] found that in a group with delayed BP recovery, there was no significant difference on average in CO compared with a normal BP recovery group, but there was a large interparticipant variation in the delayed BP recovery group; yet, muscle mass or strength was not assessed in this study, and since the participants were 18 years and older, the likelihood of sarcopenia within this cohort is low.

Examining the TPR response, it is known that in healthy adults, TPR falls initially due to a number of mechanisms related to the muscular effort of standing, before recovering from nadir [34]. The attenuated recovery of TPR in the sarcopenia group in the 10–20 s period is similar to that of MAP, suggesting that the attenuated MAP recovery is driven at least partially by TPR [6]. Indeed, Van Wijnen et al. [33] found that TPR recovery was impaired in those with delayed BP recovery compared with normal BP recovery, while

changes in CO were not different, suggesting that TPR was the primary driver of delayed BP recovery in that group. Decreased TPR leading to OH has been previously reported in diabetics [35], and Pérez-Denia et al. [36] found impaired TPR recovery in those with multimorbidity and suggested that this might drive impairments in BP recovery. Again, in these two studies, muscle parameters were not examined, but we know that both multimorbidity [37] and diabetes [38] are related to sarcopenia, and so it may be one of the factors involved.

When breaking down CO into its constituents, SV and HR, we observed that SV showed an attenuated recovery in the 10–20 s period, while there were no significant differences in HR. This suggests that CO changes were driven by SV rather than HR. This finding is somewhat unexpected, as one might anticipate an increase in HR in individuals with sarcopenia to compensate for the potential reduction in venous return due to impaired skeletal muscle pump function, which can result in decreased SV. The association between sarcopenia and SV/HR after standing has not been previously investigated, but the response of SV to standing has been previously shown to differ between younger and older subjects. Wieling et al. [32] demonstrated stable SV with a large increase in HR in the initial 7 s after standing in the younger group, while in the older group, there was less of an HR increase with the initial fall in SV followed by transient recovery and subsequent further fall. As before, although muscle factors were not included, it is possible that they played a role in the differential response seen in older people.

There are several potential mechanisms underlying our findings. Specifically, in this sample, the effects on CO seemed primarily driven by SV rather than HR. It is established that SV is determined by preload, contractility, and afterload [39]. Afterload is largely determined by MAP itself, thereby acting as a negative feedback mechanism [40]. Contractility is determined in part through preload via the Frank–Starling mechanism, as well as intrinsic factors [41]. It is here that the influences of sarcopenia on the heart muscle might act. Cardio-sarcopenia is a relatively novel concept [42], especially as traditionally hypertrophy rather than wasting of the heart is seen with ageing. However, a small number of studies have shown reductions in the left ventricular mass in sarcopenia [43,44]. If correct, one might hypothesise that cardio-sarcopenia can lead to decreased contractility, leading to decreased SV, in turn impacting CO and subsequently leading to delayed recovery of MAP as seen in our study. When examining preload, it is influenced by the end-diastolic volume, which is influenced by venous return [40]. It is in this aspect that the skeletal muscle pump may play a role [7], potentially contributing to the effects of sarcopenia. This impairment in preload might subsequently affect SV, consequently leading to impaired MAP recovery as described in the pathway above. With regard TPR, this may be an effect of sarcopenia on the autonomic nervous system. It has been shown that general muscle sympathetic nerve activity (MSNA) is proportional to the muscle mass involved [45]. Therefore, those with sarcopenia might have reduced MSNA leading to impaired recovery of TPR and resultant delayed recovery of MAP.

Of course, there may be other mechanisms at play. Other syndromes such as frailty may be involved, although the underlying pathophysiology between sarcopenia and physical frailty is increasingly recognised as likely being common [46]. Impairment of the exercise pressor reflex [47] may be involved, although this is less likely as no significant differences in HR were found in our study. In a cross-sectional analysis, we cannot assert causality. However, it is more plausible that the pathway from sarcopenia to impaired BP recovery is the causal direction rather than the reverse pathway from impaired BP recovery to sarcopenia. There is the possibility of a positive feedback loop in that those with impaired BP recovery leading to falls may restrict activity due to fear of falling, which could lead to sarcopenia. We were unable to adjust for this pathway in our analysis and so acknowledge it as a limitation.

The relatively small sample size in this study is another limitation. We conducted a post hoc power analysis for the difference in predicted mean change in CO at 10 s for the non-sarcopenic group vs. the sarcopenic and found that the power was 0.72 for an

alpha of 0.05 (means 1.19 L/min and 0.57 L/min and standard deviations 0.85 L/min and 0.87 L/min, respectively). It appears, however, that the repeated-measures nature of the mixed-effects models is sufficiently sensitive to change to allow us to discern subtle differences in slopes of recovery of the haemodynamic parameters after standing.

Other limitations of this study include the inherent limitations of BIA in the estimation of muscle mass [48] and the lack of information on timing of medications with respect to the active stand test. Furthermore, the use of Modelflow® derived haemodynamics has inherent limitations [49]. While the gold standard would be invasive measurement [50], conducting this procedures would be neither practical nor ethical in this population. Doppler echocardiography can be used; however, Modelflow® has been shown to be an acceptable alternative [51] especially when relative haemodynamic changes are required rather than absolute [52], as in our design. Finally, as participants were recruited from patients referred to a falls and syncope unit, they may not be representative of the general population, thus limiting the generalizability of our results.

Our results are important for a number of reasons. Firstly, from a pure pathophysiological and scientific point of view, they are novel. To the best of our knowledge, no previous study has utilised our methodology to address the question as to how sarcopenia can contribute to delayed BP recovery in older individuals. Secondly, results are of clinical importance. Through the use of beat-to-beat BP monitoring, impaired BP recovery has become increasingly recognised [53,54] and has been shown to independently predict falls, fractures, and mortality [55–57]. Our results link sarcopenia with impaired BP recovery, and this, in turn, can potentially be implicated in subsequent falls and fractures. Importantly, sarcopenia is potentially reversible, and multicomponent interventions that improve sarcopenia [58] could also be used to ameliorate delayed BP recovery. This, of course, underlines the importance of identifying sarcopenia in the falls and syncope unit in the first place [59]. Pressor agents such as fludrocortisone and midodrine are routinely prescribed for OH and delayed BP recovery [60] despite their off-label use and potential side effects [61]. Perhaps increasing use of multicomponent intervention as well as training in physical counterpressure manoeuvres [62] would lessen the use of these medications and also benefit cases of combined supine hypertension and OH [63], where physical interventions can help both.

5. Conclusions

We observed sarcopenia to be associated with an attenuated rate of recovery of MAP early after standing. This appeared to be driven by initial blunted peak of CO followed by attenuated recovery of CO from peak and TPR from nadir. The CO finding appeared to be driven by SV rather than HR. There are a number of potential mechanisms implicated, including cardio-sarcopenia, the effects of sarcopenia on the autonomic nervous system, and the skeletal muscle pump, and further research is needed to clarify the mechanisms involved and their relative contributions.

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Informed Consent Statement: Written, explicit, informed consent was obtained from all subjects involved in this study.

Data Availability Statement: Contingent on compliance with data protection legislation and ethical approval, data may be available from the corresponding author upon reasonable request.

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Differential Associations Between Two Markers of Probable Sarcopenia and Continuous Orthostatic Hemodynamics in The Irish Longitudinal Study on Ageing

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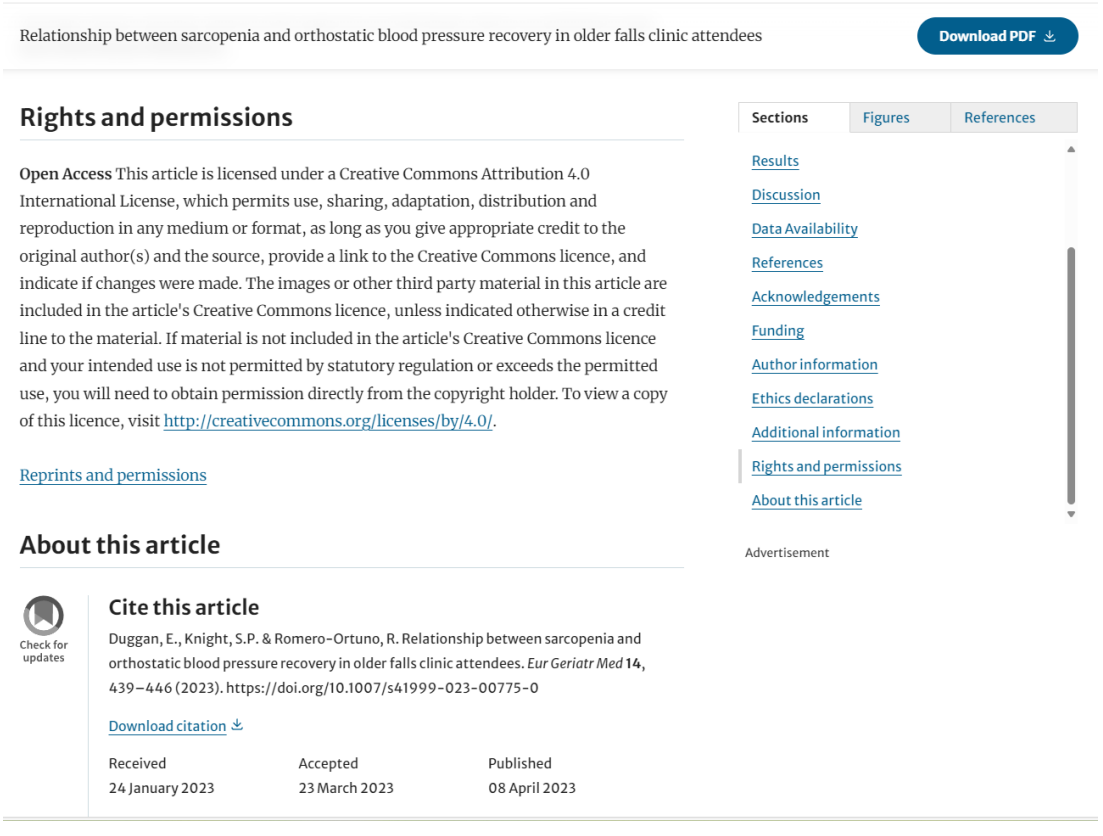

Relationship between sarcopenia and orthostatic blood pressure recovery in older falls clinic attendees

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