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Orthostatic Hypotension as a marker of Frailty in Older People

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Declaration

I declare that this Ph.D. thesis:

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Roman Romero-Ortuno

Summary

This doctoral investigation endeavoured to explore the association between orthostatic hypotension (OH) and frailty in community-dwelling older people, in order to assess the validity of to-date untested, clinically grounded claims that OH could be a marker of frailty in older people. Both OH and frailty are complex, heterogeneous clinical entities without universally agreed definitions. The operationalisations and clinical significance of both entities are reviewed in the first part of the investigation.

The investigation is based on *comprehensive geriatric assessment* data collected by a multidisciplinary team (including the candidate) at the Technology Research for Independent Living (TRIL) Clinic at St James's Hospital Dublin between August 2007 and May 2009. A *convenience* sample of 442 community-dwelling subjects aged ≥ 60 years (without dementia or risk factors for autonomic neuropathy) was cross-sectionally studied. The orthostatic hemodynamic assessments were conducted via active stand tests with Fimometer®, a validated non-invasive beat-to-beat blood pressure monitor.

Based on Fimometer® data, the sample was classified according to five OH definitions: *consensus* OH (COH), Fedorowski *et al*.'s modification of COH (i.e. FOH), *initial* OH (IOH), a novel 3-group *morphological* classification based on decreasing systolic blood pressure (SBP) recoverability after standing (MOH), and a clinical definition based on symptoms of orthostatic intolerance (OI). Individual orthostatic hemodynamic variables were also used in the analyses. The comprehensive geriatric assessment data were used to construct two ordinal frailty classifications (i.e. *non-frail*, *pre-frail* and *frail*), one based on a modification of Fried's *phenotypes* and another one on Rockwood's *frailty index* approach (TRIL-FI).

Appropriate bivariate statistics were used to correlate frailty and the OH definitions, and multivariable *structural equation models* (SEM) were used to assess the extent to which *postulated* causal relationships between variables were supported by the data.

Amongst the OH definitions considered, *OI was the only significant marker of frailty*. IOH was also associated with frailty, but this may have been due to the inclusion of OI in its definition. *Impaired SBP recoverability* was found as the *hemodynamic hallmark of OI*. The degree of SBP drop (i.e. delta) was the main predictor of SBP recoverability, but delta SBP itself had no independent correlation with OI or falls. SEM supported OI as a *mediator* between orthostatic hemodynamic changes and previous falls, but did not find orthostatic hemodynamic variables in independent association with falls. In the face of frailty (which had a significant correlation with previous falls), OI had only a modest ($P < 0.05$) independent association with previous falls.

Considered as a screening tool for the presence of pre-frailty or frailty, the *presence of OI after standing* and *at least one fall in the last six months* had, in the sample, a positive predictive value of 88.9% (modified Fried's classification) and 96.3% (TRIL-FI). If externally validated, such a screening tool could be useful in primary care.

The findings of this cross-sectional exploratory study represent an original contribution to the understanding of the clinical relevance of beat-to-beat orthostatic hemodynamics in older people, and a methodological advancement in the area. Given the limitations of the research setting, findings warrant confirmation in a longitudinal context such as The Irish Longitudinal Study on Ageing (TILDA).

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Publications

During the course of this investigation, the candidate has produced a number of papers that are related to the work presented in this thesis. They are listed here for reference:

Peer-reviewed papers

- Romero-Ortuno R, Cogan L, O'Shea D, Lawlor BA, Kenny RA. Orthostatic hemodynamics are impaired in frailty. *Age and Ageing* (under review).
- Romero-Ortuno R, Cogan L, Foran T, Kenny RA, Fan CW. Finometer®-measured orthostatic blood pressure responses and their relationship with orthostatic intolerance, falls and frailty in older people. *Journal of the American Geriatrics Society* (accepted on November 14th, 2010, in press).
- Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A Frailty Instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). *BMC Geriatrics*. 2010 Aug 24;10(1):57.
- Romero-Ortuno R, Cogan L, Fan CW, Kenny RA. Intolerance to initial orthostasis relates to systolic BP changes in elders. *Clinical Autonomic Research*. 2010 Feb;20(1):39-45.
- Romero-Ortuno R, Cogan L, Foran T, Fan CW, Kenny RA. Using the Finometer to examine sex differences in hemodynamic responses to orthostasis in older people. *Blood Pressure Monitoring*. 2010 Feb;15(1):8-17.
- Kenny RA, Romero-Ortuno R, Cogan L. Falls. *Medicine*. 2009;37(2):84-7.

Non-peer-reviewed

- Romero-Ortuno R. Frailty: the great confounder, the great forgotten. *Heart*. 2010 Apr;96(7):550. [Letter].
- Romero-Ortuno R, Kenny RA. Is it cardiac? Assessment of syncope with a scoring system. *Heart*. 2008 Dec;94(12):1528-9. [Editorial].

Abstract publications

- Romero-Ortuno R, Cogan L, Fan CW, Kenny RA. Polypharmacy and falls: is orthostatic hypotension a mediator? *Journal of Nutrition, Health and Aging*. 2009 13(Supplement 1):S257.
- Romero-Ortuno R, Fan CW, Cogan L, Healy M, Crowley VEF, Walsh JB, et al. Is Vitamin D an independent predictor of systolic blood pressure drop during active stand with Finometer®? A case for a cardiovascular mechanism underlying the action of Vitamin-D in falls prevention. *Irish Journal of Medical Science*. 2008 177(Supplement 9):S308.

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General Introduction

This doctoral thesis, submitted in candidature for the degree of Ph.D., presents the work carried out by the candidate over three years of full-time study (2007 – 2010). The main area of study, namely *frailty in older adults*, is a core concept in Geriatric Medicine and Medical Gerontology with crucial *clinical* and *epidemiological* implications. Frailty is a *syndrome* characterised by dysregulation of multiple biological systems, accumulation of deficits, vulnerability to stressors and adverse outcomes. Frailty more closely relates to the *biological* than to the *chronological* age of individuals (1).

Although clinicians have long been familiar with frailty, clear *operationalisations* of the concept have not been proposed until recently. For instance, according to Fried *et al*., the key *markers* of the frailty *phenotype* include *exhaustion*, *weakness*, *weight loss*, *slowness*, and *low physical activity* (2). Alternatively, Rockwood *et al*. operationalise frailty in terms of an *index* of *deficits* (i.e. symptoms, signs, diseases and disabilities) that accumulate with age (3).

From a clinical perspective, *falls* in older people have been defined as a manifestation of complex system failure (4); indeed, a great degree of overlap exists between the risk factors for falls and the multisystem dysregulations that define frailty, to the extent that falls are considered as a *hallmark of frailty* (5, 6). Dysregulations of the cardiovascular (7, 8) and autonomic nervous (9, 10) systems have been described as constituents of the frailty syndrome, and dysregulations in those same systems have been associated with increased risk of falls in older people (11, 12).

Orthostatic hypotension (OH) is a type of neurocardiovascular instability that clinicians often implicate in the aetiology of falls in older people; however, a systematic review found that OH does not predict falls after controlling for other factors (13). One of the challenges to the understanding of the relationship between OH and falls relates to how to optimally define and measure OH in older people; for instance, OH can be defined in *hemodynamic* terms (i.e. based on blood pressure changes with or without consideration of heart rate changes), *clinical* terms (i.e. based on symptoms of *orthostatic intolerance* [OI]) or *mixed* terms. In addition, orthostatic blood pressure changes may be measured by different methods. Routinely, clinicians use the auscultatory or oscillometric method with sphygmomanometer, but the introduction of new non-invasive beat-to-beat finger arterial blood pressure monitors led to concerns that the *consensus* definition of OH, which was originally intended for sphygmomanometer (14), may lack clinical relevance when applied to beat-to-beat data (15, 16).

This investigation focuses on the assessment of orthostatic hemodynamic responses in older people using the Finometer®, a non-invasive beat-to-beat monitor, and addresses various knowledge gaps. Firstly, it explores the clinical correlates of various definitions of OH to establish which is the most clinically meaningful when applied to beat-to-beat data. Secondly, it explores the relationship of the OH definitions with frailty in order to answer the questions whether OH is a marker of frailty in older people and whether OH is independently associated with falls in the face of frailty. A clinical implication is that if *hemodynamic OH* and/or *symptomatic OI* were, respectively, a *sign* and a *symptom* of frailty in older people, then they could be useful as frailty screening tools to identify those at risk who may benefit from further geriatric assessment and/or interventions.

Chapter 1

Orthostatic Hypotension: literature review

This chapter reviews the epidemiology of orthostatic hypotension (OH) and presents five approaches to its definition: classical (or *consensus*) (COH), an adjustment to COH by Fedorowski *et al*. (FOH), *initial* (IOH), *morphological* (MOH) and *orthostatic intolerance* (OI). The clinical significance of OH is reviewed in terms of its associations with cardiovascular disease, cerebrovascular disease and stroke, cognition, falls, psychosocial health and mortality.

Epidemiology of orthostatic hypotension

Orthostatic hypotension (OH) is the most common disorder of blood pressure regulation after essential hypertension and in normal community-dwelling older subjects the prevalence is reported between 5% and 34%, increasing with age (17-19). In a primary care setting, the prevalence of OH in older hypertensive subjects was found to be 14.6% (20). The prevalence is higher (i.e. over 50%) in patients attending geriatric clinics (21), admitted to acute hospitals (22) and residing in nursing homes (23, 24). In the US, the estimated annual rate of OH-related hospitalisations is 36 per 100,000 adults, increasing to 233 per 100,000 in people aged 75 years and over (25).

As well as depending on the population studied, the prevalence of OH depends on the definition of OH used (26). The most recent (2009) European Society of Cardiology *Guidelines for the Diagnosis and Management of Syncope* summarised the definition and characteristics of three main OH syndromes in older people: *classical*, *initial* and *delayed* (or *progressive*) OH (27).

Classical (or consensus) OH (COH)

In 1996, a *consensus* committee of the American Autonomic Society and the American Academy of Neurology defined OH as a drop of at least 20 mmHg in systolic (SBP) and/or 10 mmHg in diastolic blood pressure (DBP) within the first three minutes of orthostasis (14). This definition was primarily intended for clinical situations where orthostatic blood pressure changes are measured with sphygmomanometer or automatic oscillometric blood pressure monitors (28, 29).

Initial OH

Initial OH (IOH) can only be measured with continuous non-invasive monitoring (30), and is defined as a *transient* blood pressure decrease, within 15 seconds after standing, of more than 40 mmHg in SBP and/or more than 20 mmHg in DBP, *with symptoms* of cerebral hypoperfusion (31).

Delayed (or progressive) OH

Delayed OH is characterised by a slow progressive decrease in SBP *beyond three minutes* of assuming erect posture (32-34).

An adjustment to the consensus definition

Fedorowski *et al*. argued that whilst the COH cut-offs are reasonable in normotensive and mildly hypertensive individuals, higher limits should be considered in moderate and severe hypertension. In an attempt to increase the clinical accuracy of the COH definition, they proposed to apply a 30 mmHg cut-off in SBP drop in subjects with baseline supine SBP $\geq$ 160 mmHg, and a cut-off of 15 mmHg in subjects with SBP $<$ 120 mmHg (with the DBP criterion remaining as in the original COH definition) (35). The potential merit of this adjustment by Fedorowski *et al*. (FOH) was subsequently voiced (15, 16). As in COH, FOH was also primarily intended for sphygmomanometer.

Morphological classification

In contrast with the conventional sphygmomanometer or oscillometric measurement methods, the assessment of orthostatic hemodynamic responses with continuous non-invasive measurement of finger arterial blood pressure has the advantage of offering

clinicians and scientists a continuous pattern of response that can be visualised and analysed, not only for blood pressure but also for derived hemodynamic parameters. As a result, three different orthostatic response patterns have been recognised and studied in adults and older people, based on the *morphology* of the blood pressure recovery after standing (30, 36, 37): *quick recovery* pattern or normal physiological response; *slow recovery* pattern, which is known to occur in pathological conditions such as carotid sinus denervation (38) or carotid sinus hypersensitivity (39-41); and *failure to recover* pattern, which is classically observed in patients with autonomic failure (42). The latter is believed to be the most pathological; however, slow and non-recovery patterns are also seen in older people with no history of (nor risk factors for) autonomic neuropathy, and in those cases their clinical significance and prognosis are not clear.

Orthostatic intolerance

OH may cause symptoms of orthostatic intolerance (OI) such as dizziness, light-headedness, visual disturbances and/or loss or near-loss of consciousness (43, 44). These symptoms are generally attributed to retinal and cerebral hypoperfusion (45). OI symptoms may correlate with the nadir blood pressure on orthostasis, with the magnitude of blood pressure drop, and also with the rate of blood pressure change (46).

OI *per se* may have diagnostic value in OH; for example, the American *Joint National Committee* (JNC) *on Prevention, Detection, Evaluation and Treatment of High Blood Pressure* proposed in its Seventh Report that symptoms induced during a decrease in blood pressure, not fully meeting the strict definition for COH, should still be considered expressions of *possible* OH (47). There is evidence that in non-demented

community-dwelling older people, early OI during active orthostasis is related to SBP changes (48), and especially to the rate of SBP recovery during the first 30-60 seconds following active stand (49).

It has been postulated that lower cerebral blood flow (CBF) during orthostasis may account for the reporting of OI (50-54). Some studies have suggested that ageing *per se* may lead to *cerebral autoregulation* failing to compensate completely for postural changes in systemic blood pressure and may predispose older subjects to ischaemic cerebral symptoms during orthostasis (55, 56). However, Franke *et al*. showed that while severe orthostatic stress can compromise CBF velocity in all age groups, *healthy* older adults appear to autoregulate CBF as well as most younger subjects do (57).

Importantly, patients with dementia may not report OI despite marked blood pressure changes (58); however, that can also be the case in some cognitively intact patients (20, 59-64). Furthermore, clinical complaints of OI may be caused by conditions other than OH, such as vestibular (65, 66) or psychosomatic (67) disorders. Despite the clinical heterogeneity of the OI syndrome (62), this investigation takes into account the views of the Seventh Report of the JNC (47) and considers OI as a potential marker of OH.

The clinical significance of orthostatic hypotension

Clinical reviews and updates on OH have been regularly appearing in international biomedical literature since the 1980s (43, 46, 68-98). OH has been associated with cardiovascular and cerebrovascular disease, syncope, falls and excess mortality.

OH: associations with cardiovascular disease

The combination of arterial *hypertension* and OH has long been recognised (35, 99-104), including the *syndrome of supine hypertension–orthostatic hypotension* (SH-OH), the treatment of which continues to be a challenge for clinicians (105-108).

In 24-hour ambulatory blood pressure monitoring, OH has been found in association with an abnormal blood pressure profile of reversal of circadian pattern (i.e. nocturnal hypertension, non-dipping), postprandial hypotension, and non-compensatory heart rate variability (109-113). In addition, various studies have suggested a pathophysiological association between OH and increased *arterial stiffness* (114-118).

OH has also been associated with congestive heart failure (119, 120), including increased left ventricular wall thickness, decreased left ventricular preload, and alterations of left ventricular diastolic filling (121, 122). One study found that the presence of OH among middle-aged adults predicts long-term incidence of heart failure hospitalisations independently of conventional risk factors (123).

In the *Atherosclerosis Risk in Communities* (ARIC) study, subjects with OH had an increased risk of coronary heart disease (124). Luukinen *et al*. showed that a DBP drop immediately after standing up identifies older subjects at a high risk of subsequent myocardial infarction (125). In the most recent literature, OH has been described as a marker of *decreased cardiovascular reserve* (126) and *increased cardiovascular risk* (127-133).

OH: associations with cerebrovascular disease and stroke

In 1981, Riley and Friedman published a seminal case report of OH-triggered focal seizures in a 75-year-old post-stroke patient, showing that previously compromised cerebral tissue or vessels may be vulnerable to changes in blood pressure (134). In 1983, Stark and Wodak described patients with the 'poorly documented syndrome of *primary orthostatic cerebral ischaemia*' (135), and in 1984, Somerville published the first review on *orthostatic transient ischemic attacks* (TIAs) (136). In 1989, Dobkin suggested that focal cerebral hypoperfusion from the combination of occlusive vascular disease and OH may be an underreported, treatable cause of TIA and stroke (137). The ARIC study (1987–1996) confirmed OH as an independent risk factor for ischaemic stroke (138).

In particular, older hypertensives with OH may have an elevated risk of developing cerebrovascular disease (139). Hypertensive patients with greater postural blood pressure changes seem to have increased risk of advanced silent brain lesions (140), which could be aggravated by the associated multivessel atherosclerotic lesions of the carotid arteries and other large cervical and intracranial vessels, which also compromise cerebral circulation (141, 142).

Conversely, there is evidence that established cerebral ischaemic lesions may contribute to the development of OH (142, 143). For example, the bilateral perfusion of the anterior cingulate gyrus in Parkinson's disease patients with OH was significantly decreased compared to that of patients without OH, suggesting that the disorder of anterior cingulate gyrus may precipitate the autonomic failure in Parkinson's disease

(144). In post-stroke patients, the appearance of OH symptoms has been linked with decreased cerebral blood velocity in the affected brain side (145), which may be related to a stroke-induced impairment of the cerebral autoregulation (146, 147).

OH: associations with cognition

In a Finnish community-based study, OH was not found to be associated with cognitive deterioration (as measured by changes in the Mini-Mental State Examination score), nor did it predict cognitive decline during a 2-year follow-up (148). The ARIC study showed that although OH was associated with less favourable cognitive function (as assessed by tests of delayed word recall, digit symbol substitution, and word fluency), the association was largely attributable to demographic and cardiovascular risk factors (149). However, suggestion remains in literature that individuals with less effective blood pressure regulation in response to orthostasis may be at higher risk of cognitive impairment (150, 151), as measured by reaction times and serial list learning (152) or concentration and verbal memory (153). In patients with pure autonomic failure, cognitive impairment is not always associated with cerebral white matter abnormalities, which supports that the cognitive impairment may represent a consequence of systemic hypotension with cerebral under-perfusion (154).

In a large Chinese community-based study, OH was, in general, not associated with cognitive impairment. However, among the hypotensive subgroup, OH increased the odds of cognitive impairment, suggesting that *hypotension with OH* may be an early comorbid marker of primary incipient dementia (155); indeed, this phenotype is frequent in established dementia (156, 157).

OH is often found in patients with Alzheimer's disease (158), and in these patients OH can contribute to frontal brain changes, which may in turn aggravate the blood pressure dysregulation (159).

In Parkinson's disease, OH has been proposed as a marker for disease progression and cognitive decline (160), and this is supported by evidence of association between the severity of Parkinson's disease-related neuropathology in the insular cortex and OH (161). OH is also frequent in established Parkinson's disease dementia (162) and dementia with Lewy bodies (163, 164).

OH: association with falls

There is some evidence that OH is a risk factor for falls in older people (165, 166), although the association is not universal (13, 167). Syncope causes falls, and OH is common in patients with syncope (168). The prevalence of OH in syncope patients attending an emergency department was reported at 24% (169); the *Evaluation of Guidelines in Syncope* study found a prevalence of *OH syncope* of 12.4% in patients aged 65 and over (170). In patients with syncope and falls, OH often co-exists with carotid sinus hypersensitivity and vasovagal syndrome (39). OH could also be a cause of non-syncopal falls; for example, in Parkinson's disease, a posture and gait instability motor phenotype has been associated with greater severity of autonomic symptoms (171).

OH: psychosocial associations

Individuals with less effective blood pressure regulation (even if subsyndromal) in response to an orthostatic challenge may be at increased risk of affective problems such as hopelessness (153). In a recent study, OH and orthostatic intolerance (OI) were more frequent in subjects with depression compared to those who were not depressed, suggesting that OH may be an important factor in explaining the absence of an excess of clinically determined vascular risk factors in late-life depression (172). The ARIC investigators showed that subjects with lower education were more likely to have exaggerated increases or decreases in systolic blood pressure (SBP) on standing (173).

OH: association with mortality

In 1998, Masaki *et al*. reported OH as a significant independent predictor of 4-year all-cause mortality in the cohort of older ambulatory men of the *Honolulu Heart Program*'s fourth examination (1991–1993); they showed a significant linear association between orthostatic change in SBP and 4-year mortality rates (174, 175). In 1999, Luukinen *et al*. showed that the presence of diastolic OH at 1 minute and systolic OH at 3 minutes after orthostasis predict vascular death in older persons (176). Consistently, the ARIC study (177) and the *Malmö Preventive Project* confirmed OH as an independent risk factor for all-cause mortality (178). In clinical populations, OH has also been identified as a risk factor for death. Patients older than 75 years with OH attending the emergency department had significantly increased mortality (179). OH at the introductory phase of haemodialysis is now being considered as a novel independent predictor of all-cause mortality among haemodialysis patients (180). Older diabetes mellitus patients with OH have a higher risk of vascular death than those without OH (181).

Chapter 2

Frailty: literature review

This chapter introduces the biopsychosocial concept of *frailty* in older people and reviews its epidemiology and measurement tools, with special attention to Fried *et al*.'s *phenotypic* approach and Rockwood *et al*.'s *frailty index* approach. The clinical significance of frailty is reviewed in terms of its associated molecular dysregulations, burden of comorbidities, falls, psychosocial and socioeconomic aspects, utilisation of health and social care services, and mortality risk.

The concept of frailty in older adults

Frailty in older adults is an entity recognised by clinicians, with multiple manifestations and with no single symptom being sufficient or essential in its presentation. In part due to its syndromic nature, and despite a number of reviews and calls for consensus in the last decade (3, 182-218), an operational definition of frailty that meets international consensus is still regarded as the 'holy grail' of Geriatric Medicine (219).

Common elements in the various existing definitions are that frailty is a *bio-psycho-social* syndrome *associated with* (but different from) chronological ageing (220), characterised by *multiple physiological systems dysregulation*, *deficit accumulation* and increased *vulnerability to stressors*. There is recognition that frailty among older people may be a dynamic process, characterised by frequent transitions between frailty states over time (221, 222). A recently proposed *integral* conceptual definition of frailty is '*a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes*' (223). Interestingly, orthostatic hypotension (OH) shares many aspects of this definition.

Epidemiology of frailty

Frailty is an *emerging geriatric syndrome* (224) and, similarly to OH, its prevalence increases with age and has multiple adverse associations including falls, morbidity, disability, excess utilisation of health and social care services (e.g. hospitalisations, institutionalisations), and increased risk of mortality (4, 225-227). Frailty confers loss of independence and vulnerability, and impairs the quality of life and psychological

well-being of many older people; it also poses an enormous challenge and creates strain on families, carers and other structures of social care and social support. In the face of the rapid population ageing occurring in Western societies, frailty is set to reach epidemic proportions over the next few decades (228).

As in OH, the prevalence of frailty depends on the population studied and the definition used. Using Fried's criteria (2), the French *Three-City Study* found a prevalence of frailty of 7% in community-dwelling adults aged 65 or more (229). In the Hertfordshire Cohort Study (UK), the prevalence of frailty was 8.5% among women and 4.1% among men (230). In a Spanish urban older population, the estimated prevalence of frailty was 10.3% (231). The *Survey of Health and Living Status of the Elderly* in Taiwan found a prevalence of non-frailty, pre-frailty and frailty of 55.1%, 40.0% and 4.9%, respectively (232). Santos-Eggimann *et al*., using the *Survey of Health, Ageing and Retirement in Europe*, established that the prevalence of frailty in community-dwelling Europeans aged 65 years and older varies between 5.8% and 27.3%; in addition, between 34.6% and 50.9% were classified as pre-frail (233).

Using a *frailty index* approach, the *National Population Health Survey of Canada* found a prevalence of frailty of 22.7% in community-dwelling adults aged 65 or more (234); previously, the *Canadian Study of Health and Aging* showed that 4.4% of those aged 85 years and older were *very* frail (235). In both studies, the prevalence of frailty increased with age and at any age lessened survival.

Frailty measurement tools

Numerous frailty measurement tools have been developed in clinical practice and research, and this has been the focus of many reviews and comparative studies (193, 225, 236-253). Table 2.1 summarises a selection of existing frailty measurement tools.

Table 2.1. A selection of frailty measurement tools from the literature.

Year	Author	Measure name	Measure components	Validation sample	Validation design	Validation endpoints
1991	Winograd *et al*. (254)	*Rapid screening tool*	Clinical geriatric assessment	Male inpatients aged ≥ 65	Prospective	Length of stay Nursing home utilisation Mortality
1992	Weiner *et al*. (255)	*Functional reach test*	Maximal safe standing forward reach (yardstick method)	Community-dwelling aged ≥ 65	Cross-sectional	IADL Mobility Balance Walking speed
1994	Owens *et al*. (256)	*Short screening questionnaire*	Cognition Mobility Nutrition Medications Hospitalisation	Older inpatients	Prospective	Hospitalisation cost Nursing home utilisation Mortality
1996	Rockwood *et al*. (257)	*Multifactorial definition of frailty*	Gender Marital status Absence of a caregiver Cognitive impairment or dementia Functional impairment Diabetes mellitus Stroke Parkinson's disease	Institutional & community-dwelling older adults	Cross-sectional	Nursing home utilisation

1997	Brody *et al*. (258)	*Health Status Form*	Age ADL disability	Older inpatients	Prospective	Discharge data Pharmacy dispensing data
1998	Carlson *et al*. (259)	*Functional homeostasis*	Changes in the Functional Independence Measure (FIM)	Older inpatients	Prospective	Hospital readmissions Medical adverse outcomes
1998	Dayhoff *et al*. (260)	*Balance and lower limb strength*	Dorsiflexion strength Balance (including visual contribution)	Community-dwelling aged ≥ 60	Cross-sectional	Self-reported functional status Perceived health
1999	Rockwood *et a*l. (261)	*Brief clinical instrument*	Walking assistance ADL Continence Cognition	Community-dwelling aged ≥ 65	Prospective	Nursing home utilisation Mortality
2001	Schuurmans *et al*. (220)	*Groningen Frailty Indicator*	Mobility Physical fitness Vision Hearing Nutrition Morbidity Cognition Psychosocial	Community-dwelling aged ≥ 65	Cross-sectional	Self-Management Ability scale
2001	Nourhashémi *et al*. (262)	*IADL disability* (≥ 1)	IADLs	Community-dwelling women aged ≥ 75	Cross-sectional	Co-morbidities Cognition Falls
2004	Matthews *et al*. (263)	*Strawbridge questionnaire*	>1 functional difficulty: physical, cognitive, sensory, nutritive	Community-dwelling geriatric outpatients	Cross-sectional and prospective	TUG Sit-to-stand test Bimanual dexterity Cognition Nursing home utilisation Mortality

2004	Studenski *et al*. (264)	*Clinical Global Impression of Change in Physical Frailty*	Appearance Healthcare utilisation Medical complexity Muscle strength Balance Nutrition Stamina Neuromotor performance Mobility Perceived health ADL Emotional status Social status	Geriatric patients	Cross-sectional	Geriatrician's impression of frailty
2005	Rockwood *et al*. (265)	*CSHA Clinical Frailty Scale (7-point)*	Clinical judgement	Community-dwelling aged ≥ 65	Cross-sectional and prospective	Nursing home utilisation Mortality
2006	Rolfson *et al*. (266)	*Edmonton Frail Scale*	Cognition, General health Functional independence Social support Medication use Nutrition Mood Continence Functional performance	Outpatients aged ≥ 65	Cross-sectional	Geriatrician's impression of frailty

2008	Ravaglia *et al*. (267)	*Self-reported frailty score*	Age Gender Physical activity Comorbidity Sensory deficits calf circumference IADL Gait Health pessimism	Community-dwelling aged ≥ 65	Prospective	Fractures Hospitalisation Mortality
2009	Pijpers *et al*. (268)	*Frailty Risk Score*	Age Gender Living alone Body mass index Cardiovascular disease Elderly mobility score Medications Impaired motor and process skills	Psycho-geriatric outpatients	Prospective	Mortality
2010	Shinkai *et al*. (269)	*Kaigo-Yobo Checklist*	Questionnaire	Community-dwelling aged ≥ 70	Cross-sectional and prospective	Nutrition Falls Homebound Nursing home utilisation
2010	Lucicesare *et al*. (270)	*Self-rated health deficits index*	Questionnaire	Community-dwelling aged ≥ 65	Cross-sectional and prospective	Hospital admissions Mortality
2010	Gobbens *et al*. (271)	*Tilburg Frailty Indicator*	Self-report: Physical, Psychological and Social components	Community-dwelling aged ≥ 75	Cross-sectional	Physical, cognitive and psychosocial scales Healthcare utilisation Quality of life

2010	Freiheit *et al*. (272)	*Frailty index for patients with coronary artery disease*	Balance Body mass index Trail-Making Test Part B Depressive symptoms Living alone	Inpatients aged ≥ 60 undergoing cardiac ca-theterisation	Cross-sectional and prospective	Disability Health-related quality of life

(I)ADL: (independent) activities of daily living; **TUG**: time to get up and go.

Fried's phenotypic approach

The US group led by Fried uses a *frailty phenotype* approach to operationalise frailty (2), and their approach has attracted considerable scientific interest internationally (229, 273-277). The main advantage of Fried's method is that it requires the measurement of only five variables, namely *weight loss*, *exhaustion*, *grip strength*, *walking speed* and *physical activity* (2). In Fried's definition, frailty is defined in terms of three categories, each of which is defined by the sum of the number of individual criteria present (0: *non-frail*; 1 or 2: *pre-frail*; and 3, 4 or 5: *frail*). The dichotomisation of individual criteria that are measured on a continuous scale (i.e. grip strength, walking speed and physical activity) is done retrospectively according to the lowest twentieth percentile rule, and there are further criteria stratifications (2).

Fried's phenotype is underpinned by a *biological* model where weakness may be the most common first manifestation, and occurrence of weakness, slowness, and low physical activity precede exhaustion and weight loss in subjects who are non-frail at baseline (278). Fried's model is also based on the hypothesis that the accumulation of physiological dysregulations is associated with increasing *allostatic load*, which may be

related to the loss of reserve characterised by frailty (279, 280). According to Fried's model, the likelihood of frailty increases *nonlinearly* in relationship to the number of physiological systems that are abnormal (281).

Rockwood's frailty index (cumulative deficits) approach

A Canadian group led by Rockwood uses a *Frailty Index* (FI) approach, which is based on the *accumulation of deficits* (i.e. from a given list where each of them is defined as present or absent), in relation to age (234, 282-285). While the FI is based on the same biological principle as Fried's phenotype (i.e. multiple physiological systems dysregulation), the FI does not necessarily include exactly the same deficit variables or the same number of variables each time, allowing researchers to construct customised frailty indices tailored to the data available to them, which normally derive from a comprehensive geriatric assessment (CGA). In the published studies by Rockwood *et al*., between 20 and 70 deficit variables from various datasets have been applied (1, 265, 286-289).

To be included in the FI, each deficit variable needs to satisfy three basic criteria: to be biologically sensible, to accumulate with age, and not to saturate too early (i.e. develop too high a prevalence at younger ages, e.g., presbyopia, which is almost universal at age 55) (234). To calculate the FI, data are coded so that 1 represents the presence of a deficit and 0 represents its absence. Continuous variables may be categorised according to the problem's severity (e.g. mild: one third of the deficit; moderate: two thirds of the deficit; severe: full deficit). For a given individual, the FI is calculated as the number of deficits present divided by the number of deficits considered. The FI is a gamma-

distributed continuous variable correlated with age, and cut-offs can be applied to classify the sample into subgroups with increasing levels of frailty: non-frail (i.e. FI ≤ 0.08), pre-frail, and frail (i.e. FI ≥ 0.25) (234). The FI approach has been applied by various groups internationally (290, 291).

The clinical significance of frailty

As suggested by the validation endpoints used for the various frailty measurement tools summarised in Table 2.1, frailty has multiple negative correlates and poor prognostic implications, not only in terms of chronic disability, institutionalisation, injurious falls, and death, but also from a psychosocial perspective (226, 292).

Frailty: molecular associations

There is evidence of generalised oxidative (293), endocrine (294) and immune systems (295-297) dysregulation in frailty. A strong association of frailty with inflammation has been demonstrated (298-311), and there is increasing evidence of a link between frailty and vitamins D (312-315) and B (316, 317) deficiencies. Interestingly, similar vitamin deficiencies have also been implicated in OH (318-327).

Frailty and sarcopenia

According to the recent Report *of the European Working Group on Sarcopenia in Older People* (328), sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death. According to the Working Group, *frailty and sarcopenia overlap*; most frail older people exhibit sarcopenia, and

some older people with sarcopenia are also frail. Despite the overlap, it is accepted that the general concept of frailty goes *beyond physical factors* to encompass psychological and social dimensions as well, including cognitive status, social support and other environmental factors (328-334). Interestingly, a postulated defence against OH and OI (orthostatic intolerance) is the 'skeletal muscle pump', whereby contractions of the leg and gluteal muscles during the active stand help propel venous blood back to the heart (335).

Frailty and chronic renal disease

Frailty is significantly associated with chronic kidney disease, and particularly with its moderate and severe stages; the potential underlying mechanisms remain elusive (336, 337). Interestingly, OH is also linked with severe chronic renal failure (especially in patients on haemodialysis) (338-341).

Frailty: association with falls

Falls are the hallmark of frailty (4), and frailty is a very strong independent predictor of falls and fall-related fractures (5, 6, 342). Similarly to frailty, falls are multifactorial, so the factors underlying falls are now being investigated as part of the increasing attention being paid to the evolution of frailty in older people (343). Frailty is becoming the best paradigm to predict falls and adverse fall-related outcomes in older people, as frailty not only encapsulates the physical, cognitive (344) and psychological (345) causes of falls, but also the increased vulnerability to adverse outcomes (e.g. injuries, fractures, and their down-spiralling consequences).

Frailty: association with cognition

Frailty has been associated with increased risk of cognitive impairment and dementia, and a rapid rate of cognitive decline (346-351).

Frailty: psychological and psychiatric associations

Frailty has been associated with sleep disturbances (352, 353), reduced psychological well-being (354) and impaired quality of life (355, 356). It has been proposed that the onset of frailty may be associated with a psychological stage of adult development termed the *frailty identity crisis* (192). Frailty is also associated with higher levels of *health anxiety* (357) and other psychiatric (including depressive) symptoms (358-360). Interestingly, a longitudinal study found that high positive affect may significantly lower the risk of frailty in older adults (361).

Frailty: socioeconomic correlates

Frailty in older adults is independently associated with individual and neighbourhood socioeconomic factors (362, 363). Rockwood *et al*. operationalised *social vulnerability* according to a deficit accumulation approach, in recognition to the fact that as people age and become more vulnerable, their social circumstances particularly impact their health (364). Indeed, availability of social support and access to care resources become critical when frailty manifests as disability (365, 366) and constricted life space (367).

Frailty: correlation with the utilisation of health and social care services

Frail older people are frequent users of healthcare services at all levels (i.e. primary, secondary and tertiary); they are also frequent users of social care services and have a high risk of institutionalisation (227, 368-371).

Frailty: risk of death

Frailty significantly increases the risk of death (234, 372-380). In a proportional hazards model controlling for age, gender, education and baseline frailty, each 1-unit increase in annual change in a continuous composite measure of frailty (ranging -2 to 2) was associated with an almost 5-fold higher risk of mortality per year (374). In the Cardiovascular Health Study, Fried *et al*. found that frail subjects had an adjusted hazard ratio for mortality at 3 years of 2.24 (2). Using the FI, Rockwood *et al*. showed that each unit increase in deficits increased the hazard rate for mortality by 4% per year (378).

Chapter 3

Research Questions

This chapter presents the observation from the literature reviews that orthostatic hypotension and frailty have epidemiological similarities. The main research question is posed, namely: *is orthostatic hypotension a manifestation of frailty in older people?* Some previous suggestions of that question are reviewed, and the current knowledge gap to answer it is highlighted. Three secondary questions are posed, namely: (1) *Which orthostatic hypotension definition has the closest association with frailty?* (2) *Is orthostatic hypotension an independent predictor of falls in the face of frailty?* and (3) *Could orthostatic hypotension be a screening tool for frailty in older people?*

Similarities between orthostatic hypotension and frailty

From the preceding literature reviews, one could say that OH and frailty have a number of similarities (Table 3.1.). *Firstly*, they occur commonly, have similar prevalences in community-dwelling older people, and often coexist together; *secondly*, unresolved issues remain concerning their definition, with various definitions being available for each entity; *thirdly*, they both have similar adverse epidemiological associations. Both are associated with ageing and increased physical and psychological morbidity, and with increased risk of mortality. Of special clinical interest is their commonality as predictors of falls; however, frailty appears more strongly linked with falls than OH.

Table 3.1. Epidemiological similarities between orthostatic hypotension (OH) and frailty.

	OH	**Frailty**
Various definitions available	✓	✓
Prevalence in community-dwelling older people	5 – 34%	5 - 27%
Prevalence increases with age and comorbidities	✓	✓
Associations with cardiovascular and cerebrovascular disease	✓	✓
Psychosocial associations	✓	✓
Association with falls	(✓)	✓
Increased mortality risk	✓	✓

✓: yes; (✓): yes, but less consistent.

Main question: is orthostatic hypotension a manifestation of frailty in older people?

Whilst frailty is a geriatric *giant*, OH could be one of its missed *footprints* (381). Biologically, it is plausible that OH, reflecting disordered hemodynamic equilibrium, could be one of the manifestations of a wider process of multisystem dysregulation. In fact, cardiovascular disease (of which OH is a manifestation) is increasingly being associated with frailty in epidemiological studies (7, 8, 379, 382-385).

As such, the hypothesis that *OH* may be *a marker of frailty* is not novel and has been previously suggested. In 1998, Masaki *et al*. were probably the first group to suggest that '*OH may be a marker for physical frailty*', in light of their results that OH was a powerful predictor of mortality in the *Honolulu Heart Program* (174, 175). In 2000, Eigenbrodt *et al*. argued that the fact that OH was found as an independent risk factor for stroke in their study '*does not exclude the possibility that OH acts as a measure of disease severity, frailty, or cardiac dysfunction or is in the causal pathway of these other risk factors*' (138). In 2005, Tabara *et al*. referred to OH as '*a potent predictor of cardiovascular frailty*' (386, 387), and in 2007, Ejaz *et al*. argued that '*it is perhaps not surprising that OH is more prevalent in frail individuals, because frailty is the cumulative effect of age, disease, disuse, and reduction in various physiologic reserves*' (110). Recently, Wieling defined OH as '*a physical sign that reflects a final common pathway of various forms of disordered physiology*' (15).

Despite the above suggestions in the research literature and a general impression among practising clinicians that OH may be a sign of frailty in older people, no studies to date had attempted to test this hypothesis with methodological rigour, and that was the main

aim of the present investigation. Importantly, in order to answer the main question, a *generic* conceptual approach to OH was adopted, which considers the latter as a drop in systolic and/or diastolic blood pressure on standing, which in a given subject could be regarded as abnormal on the basis of its magnitude, clinical consequences, or both. Therefore, the *clinical-epidemiological* question was whether (1) *hemodynamic* OH is a *sign* of frailty; (2) *clinical* OH (i.e. orthostatic intolerance) is a *symptom* of frailty; (3) both hemodynamic and clinical OH are linked with frailty or (4) none of them are.

Secondary questions

As reviewed in Chapter 1, OH has various definitions, and as reviewed in Chapter 2 the same applies to frailty. Since this investigation endeavoured to *explore* the association between various OH and frailty definitions, a secondary question arose as to *which OH definition(s) has(have) the closest association with frailty*.

Another question of clinical interest is whether *OH is an independent predictor of falls in the face of frailty*. The majority of falls in older people are *multifactorial*, and the exact cause can often be difficult to determine (388). In a prospective descriptive study evaluating those over 65 years of age presenting to an emergency department with falls, Davies and Kenny found a median number of *three* risk factors for falls in these subjects, with falls being readily explainable in less than one third of cases (389). In a study establishing the prevalence of cardioinhibitory carotid sinus hypersensitivity in patients 50 years or over presenting to the emergency department with 'unexplained' or 'recurrent' falls (N = 4,051 fallers), Richardson *et al*. found a clear attributable medical diagnosis for the fall in only 871 (21.5%) cases (390). Even in a specialised syncope

clinic setting, sixty per cent of older patients with vasodepressor carotid sinus syndrome also had OH or vasodepressor vasovagal syncope, suggesting a *common aetiology* for these entities (391). Indeed, systematic reviews on falls prevention or assessment are underpinned by the attribution of falls to multiple interacting factors rather than one identifiable cause (392-394), in keeping with the frailty paradigm (5, 395). In that light, Nowak and Hubbard argued that falls are '*a manifestation of complex system failure*' (4). The frailty paradigm helps understand why systematic reviews and meta-analyses evaluating the effectiveness of interventions to reduce falls in older people have reached conflicting conclusions (4, 396).

In Geriatric Medicine research, considerable uncertainty remains as to the independent contribution of OH to falls in older people (13). In clinical practice, OH is often implicated in the aetiology of falls, but concerns have been expressed that the direct attribution of falls to OH may be *over-simplistic* and unlikely to be useful in predicting future risk of falling (167). In addition, there have been concerns that withdrawing antihypertensives on the basis of OH (i.e. assuming that this will prevent future falls) has less evidence than their beneficial effects in the prevention of vascular events (397, 398). However, if OH is a marker of frailty, and frailty is a better predictor of falls than OH, then OH could be a useful indicator of the need for *multifaceted interventions* to target frailty (and, in turn, falls) (399). In that light, a question is *whether OH could be useful as a screening tool for frailty* rather than an end diagnosis in itself.

Chapter 4

Research setting and subjects

In this chapter, the Technology Research for Independent Living (TRIL) Clinic at St James's Hospital Dublin is presented as the research setting on which this investigation is based, with particular attention to the scope of the clinic, role of the candidate within the multidisciplinary research team, general inclusion criteria, sources of recruitment, ethical approval, good clinical practice and sources of funding.

Description and scope of the research setting

The clinical data collection for this Ph.D. project was conducted at the Technology Research for Independent Living (TRIL) Clinic in St James's Hospital, Dublin (www.trilcentre.org) between August 2007 and May 2009.

The TRIL Clinic is a partnership between the TRIL Centre and the Mercer's Institute for Successful Ageing at St James's Hospital, Dublin (http://www.misa.ie). The TRIL Centre is an active collaboration between Intel and University College Dublin, Trinity College Dublin and National University of Ireland Galway with support from IDA (Industrial Development Agency) Ireland and GE Healthcare.

The TRIL Clinic (http://www.trilcentre.org/tril-clinic.html) was created in 2007 as a clinical research platform to test and inform the development of new technologies aimed at maintaining and enhancing the independent living of older people. The TRIL Clinic offers a free outpatient clinical service to community-dwelling people aged 60 and over, based on principles of *comprehensive geriatric assessment* (CGA) (400) and incorporating the use of existing and experimental technologies to measure risk factors for falls, cognitive decline and lack of social connectedness.

The specific objectives of the TRIL Clinic are:

- To apply existing and innovative technologies within the setting of a CGA clinic in order to identify risk factors for falls, cognitive decline and social isolation.
- To provide a model of an efficient, patient-centred service that provides a detailed, one-stop multi-disciplinary assessment in multiple domains (which otherwise would

take multiple appointments over a long period of time) and makes this information available to those involved in the continuity of care of the patients.

- To provide a model of excellence in conducting CGA of older people by employing technologies that deliver reliable, objective and clinically meaningful data.
- To discover and deliver technology solutions that support independent ageing with the ultimate aim of improving the quality of life of older citizens while reducing the burden on carers and on the healthcare system.

The research team and the role of the candidate within it

The TRIL Clinic team is highly multidisciplinary and includes doctors, nurses, physiotherapists, psychologists, anthropologists, ethnographers, engineers and various administrators. The TRIL Centre is divided into five interconnected research strands (Ethnography, Falls Prevention, Cognitive Function, Social Connection, and Technology Platform), which comprise more than 50 individual researchers. The research setting was shared with many other TRIL projects and was not designed for the exclusive purpose of this Ph.D. project. The TRIL Clinic research protocol was a 'closed' one (i.e. it had already been developed by the time the candidate joined the research group). The Ph.D. candidate worked as one of the doctors in the TRIL Clinic throughout the entire period of data collection and had an active role in database design and coordination of data inputting.

General inclusion criteria

The generic *inclusion criteria* for participation in the TRIL Clinic assessment were the following:

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

The participants' journey through the TRIL Clinic

In the TRIL Clinic, we designed an integral assessment process in a one-site, one-stop fashion. The complete assessment for each participant took about three to four hours, with regular breaks throughout the assessment. The participants' assessments at the TRIL Clinic included the following:

1) Welcome and obtainment of written informed consent for research (by doctor).
2) Cognitive battery (by psychologists).
3) Medical assessments (by doctors and nurse), including anthropometric data, past medical history, medications, nutritional status, physical exam, electrocardiogram, blood tests, screening for OH, assessment of vision and hearing, and functional and gait assessments.
4) Physiotherapy assessments (by physiotherapist or doctors/nurse), including balance and handgrip strength.
5) Social connection interviews (by psychologists), including socioeconomic data, and assessment of mood, personality, loneliness, sleep quality and social support.

The specific measures used in this investigation will be described as they appear in the following chapters.

The TRIL Clinic is a *clinical research facility* as well as an *outpatient clinical service* and a *health screening service* for older people, which is free at the point of delivery. Therefore, the physician-led assessment at the TRIL Clinic included *medical care* to the participants. On completion of each assessment, the doctor offered feedback to each participant (including explanation of any abnormal results) and appropriate treatment and/or follow-up were agreed as necessary. For example, following identification of significant OH, interventions included medical advice, lifestyle modifications (e.g. advice on fluid intake), feedback and advice to General Practitioners (GPs), and, if clinically indicated, referral to St James's Hospital *Falls and Blackouts Unit* for further investigations. Subject to participants' consent, their GP and, if applicable, the referring health professional were sent a summary of the participants' assessment. Participants who requested a copy of their own assessment summary were sent one.

Recruitment sources

The TRIL Clinic has a national scope and welcomes referrals from the following sources:

- *Self-referrals* for health check by people attracted by our leaflet (Appendix 1), website (http://www.trilcentre.org) and/or articles in the media (401-403). The TRIL Clinic leaflet was distributed around public areas of St James's Hospital and also sent to primary care centres around the hospital catchment area. Amongst self-referred participants, a *snowball* (i.e. word of mouth) recruitment (404) was present.

- *Referrals from health professionals* for comprehensive geriatric assessment of 'at risk' subjects. A number of participants were referred by St James's Hospital *Emergency Department* (ED) following presentation with a fall; a specific referral form was supplied to the ED for that purpose (Appendix 2). Some participants were referred by local *General Practitioners*, following receipt of the TRIL Clinic leaflet or their patient attending the ED (Appendix 3). Health professionals from other St James's Hospital facilities (e.g. outpatient clinics such as the *Falls and Blackouts Unit* and the *Robert Mayne Day Hospital*) also referred patients, as did some other community practitioners who were aware of the TRIL Clinic service.

These recruitment practices resulted in a *convenience* sample *not* representative of the general population of Irish people aged 60 and over. Following receipt of a referral from a health professional, the TRIL Clinical Nurse Manager contacted the patient in a structured manner and offered a TRIL Clinic appointment (Appendix 4). Not all participants for whom a health professional referral was received ended up attending (e.g. unable to contact, declined offer, failed to attend); for example, the attendance rate for ED referrals was 58.3%. Self-referrals contacted the TRIL Clinic themselves and in general kept the appointment given. On arrival to the TRIL Clinic, a physician obtained written informed consent on each participant prior to the assessments (Appendix 5).

Characteristics of the total TRIL Clinic sample

Between August 2007 and May 2009, 624 community-dwelling subjects aged 60 years and over registered as TRIL Clinic participants. The mean age (standard deviation) was 73.0 (7.4) years and 69% were females. Table 4.1 shows their referral sources:

Table 4.1. Referral sources for the total TRIL Clinic sample ($N = 624$).

	Number	Percent
Self referral	417	66.8
Emergency Department	91	14.6
Falls & Blackouts Unit, St James's Hospital	58	9.3
General Practitioner	32	5.1
Other outpatients, St James's Hospital	18	2.9
Community allied health professionals (e.g. physiotherapy, occupational therapy, public health nurse)	7	1.1
Other outpatients (not St James's Hospital)	1	0.2
Total	**624**	**100.0**

Self-referrals (67%) were different from health professional referrals (33%) in terms of their health status, with clinical evidence of a *healthy volunteer effect* among self-referrals. For example, while 26.0% of health professional referrals had had a fall in the 6 months preceding the assessment, only 8.2% of self-referrals had (Chi-squared test: $p < 0.001$). Chapter 6 expands on this difference with a focus on frailty.

Ethics approval

All TRIL Clinic activities were carried out in compliance with the 1964 World Medical Association *Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects* (405), as last amended in 2008 (406). Local Research Ethics Committee approval was obtained via St James's Hospital and Adelaide and Meath Hospital inc. National Children's Hospital (SJH/AMNCH) Research Ethics Committee (approval Reference Number: 2007/06/13). All persons gave written informed consent prior to their inclusion in the study.

Good Clinical Practice and data quality assurance

Registration of all participants in the TRIL Clinic was carried out through their official registration as patients of St James's Hospital; therefore, they were assigned a unique Medical Record Number (MRN), if they did not have one already. All medical records and clinical data were stored confidentially in St James's Hospital in accordance with the hospital's Data Protection Policy and relevant national law. Formal on-site *Good Clinical Practice* training was provided by the TRIL Centre to all its researchers, and it was delivered by trainers of the Irish Clinical Research Infrastructure Network.

Over the period, data entry and internal database audits were conducted by the TRIL Clinic team in five structured '*data retreats*', under the coordination of the candidate. An external data verification and investigational site audit was carried out in October 2009 at the request of the TRIL Centre Manager by Java Clinical Research Limited (http://www.javacr.com), which resulted in detection and correction of remaining data entry errors.

Sources of funding

The TRIL Clinic is funded by Intel Corporation, the Industrial Development Agency (IDA) Ireland and GE Healthcare, with operational support from the Mercer's Institute for Successful Ageing at St James's Hospital, Dublin (www.misa.ie). The financial sponsors played no role in the design, execution, analysis and interpretation of data, or writing of this study.

Chapter 5

Methods for the assessment of orthostatic hemodynamics and final sample selection criteria

In this chapter, the candidate describes the equipment (i.e. Finometer®) and the protocol (i.e. active stand) used for the assessment of the participants' orthostatic hemodynamic responses, and explains the exclusion criteria applied to the initial sample in order to minimise possible confounding of the correlations between orthostatic hypotension and frailty.

Blood pressure monitoring equipment

For the assessment of orthostatic hemodynamic responses, subjects underwent a lying-to-standing orthostatic test (active stand) with non-invasive beat-to-beat blood pressure monitoring by the Finometer® Pro device (Finapres Medical Systems BV, Amsterdam, The Netherlands, www.finapres.com).

The Finometer® measures finger blood pressure non-invasively on a beat-to-beat basis and gives waveform measurements similar to intra-arterial recordings. The Finometer® received an A/B grading according to the *British Hypertension Society* protocol and satisfied the validation criteria of the *Association for the Advancement of Medical Instrumentation* (407). Various studies have favourably compared the beat-to-beat non-invasive blood pressure recordings by the Finometer® with those obtained from intra-arterial recordings, although the latter remain as the gold standard (408-411).

Active stand protocol

As per ethics approval, subjects were not asked to stop any of their usual medications, fast or modify their lifestyle habits prior to or during the TRIL Clinic assessments. Participants did not have familiarisation visits, but prior to attendance they had a telephone conversation with the Clinical Nurse Manager explaining the content of their scheduled visit. Studies were performed in a quiet clinical laboratory room (Hospital 4, top floor, St James's Hospital) at ambient temperature (21–23°C) by the physician and/or the Clinical Nurse Manager. None of the members of staff were uniformed. Active stands were conducted between 9am and 5pm on weekdays.

A proper sized cuff was applied to the finger as recommended by the manufacturer (412, 413). Warming of the hand was occasionally necessary to improve signal pick-up. Prior to standing, subjects were resting in the supine position for at least ten minutes, with the monitored arm (left) resting extended by their side.

The blood pressures measured by the Finometer® Pro device were calibrated at baseline (at least two minutes before the active stand) using the *Return to Flow* (RTF) calibration system, which involves the use of an oscillometric pressure cuff on the ipsilateral upper arm for an individual calibration of the reconstruction of the finger pressure signal to brachial level (410). The hydrostatic height correction system was used throughout the study to compensate for hand movements with respect to heart level, and a height nulling procedure (with the zero mark at the level of the right atrium) was performed on each participant in the supine position as recommended by the manufacturer (412).

The automatic *Physiocal* function, which intermittently calibrates the finger arterial size at which finger cuff air pressure equals finger arterial blood pressure (414) was used to assess the signal quality prior to the active stand. We used the published criterion that when the number of beats between physiocals reaches 40, the signal can be considered of good quality (37). Just prior to standing, the *Physiocal* function was switched off to ascertain a continuous recording during the transient orthostatic blood pressure changes, and it remained switched off during the remainder of the test. Despite a theoretical danger of signal 'drift' after a prolonged period without the *Physiocal*, advice was received from the manufacturer that signal drift was very unlikely to occur

before three minutes, provided that the departing signal prior to stand was of acceptable quality. As explained below, an independent quality check of the active stand files was also carried out, resulting in the exclusion of some files with protocol violations and/or excessive signal fluctuation.

We aimed for subjects to complete the change from supine to standing within three seconds, and we provided help when this could not be achieved independently. After standing, the blood pressure was monitored for three minutes with subjects standing motionless and the monitored arm resting extended by the side; therefore, differences in arm position were relatively minor in supine and standing positions (415), with the hydrostatic height correction system taking care of the remaining differences. However, some authors prefer the method of avoiding hydrostatic pressure effects by holding the finger cuff fixed at right atrial level (37), which avoids reliance on the height correction system. In our active stand protocol, we followed the manufacturer's advice on the use of the height correction system (412), and all subjects followed the same protocol.

Immediately after the test, subjects were asked to report whether they had felt dizziness, faintness or light-headedness, and the latter symptoms were defined as *orthostatic intolerance* (OI: yes or no).

Active stand data processing

Active stand data were exported to Microsoft Excel® spreadsheets with the BeatScope® 1.1a software according to the five-second averages method, as a previous Finometer®-based study demonstrated that this time average (as compared to beat-to-beat and 1, 10,

15, 20 and 30 s averages) showed the best association between OH and history of falls (416), the latter being an important frailty-related outcome. The full 5-second-averaged data (-60 seconds to +180 seconds around active stand) for SBP, DBP and heart rate (HR) were saved for each participant in the database (SPSS 16.0).

Missing data

Of 624 community-dwelling subjects aged 60 and over who registered as participants over the period, 608 had a continuous non-invasive measurement of finger arterial blood pressure as described above. Active stand data could not be saved for 10 subjects, resulting in a sample of $N = 598$ available for analyses.

Exclusion criteria

All 598 active stands were independently reviewed and 11 excluded due to poor quality signals (i.e. artefacts, excessive signal fluctuation) and/or violation of the active stand protocol (e.g. *Physiocal* not switched off before stand leading to signal interruptions). Appendix 6 shows examples of such excluded files.

To maximise the reliability of self-reported OI (58), falls (417) and other self-reported parameters of importance for the correlations with frailty, subjects with a Mini-Mental State Examination (MMSE) score of < 23 were excluded, as the latter cut-off has been proven as optimal when screening for dementia in an Irish community setting (418).

This investigation departed from the pathophysiological premise that OH and frailty may share a background of *multiple* system dysregulation. Therefore, the candidate was

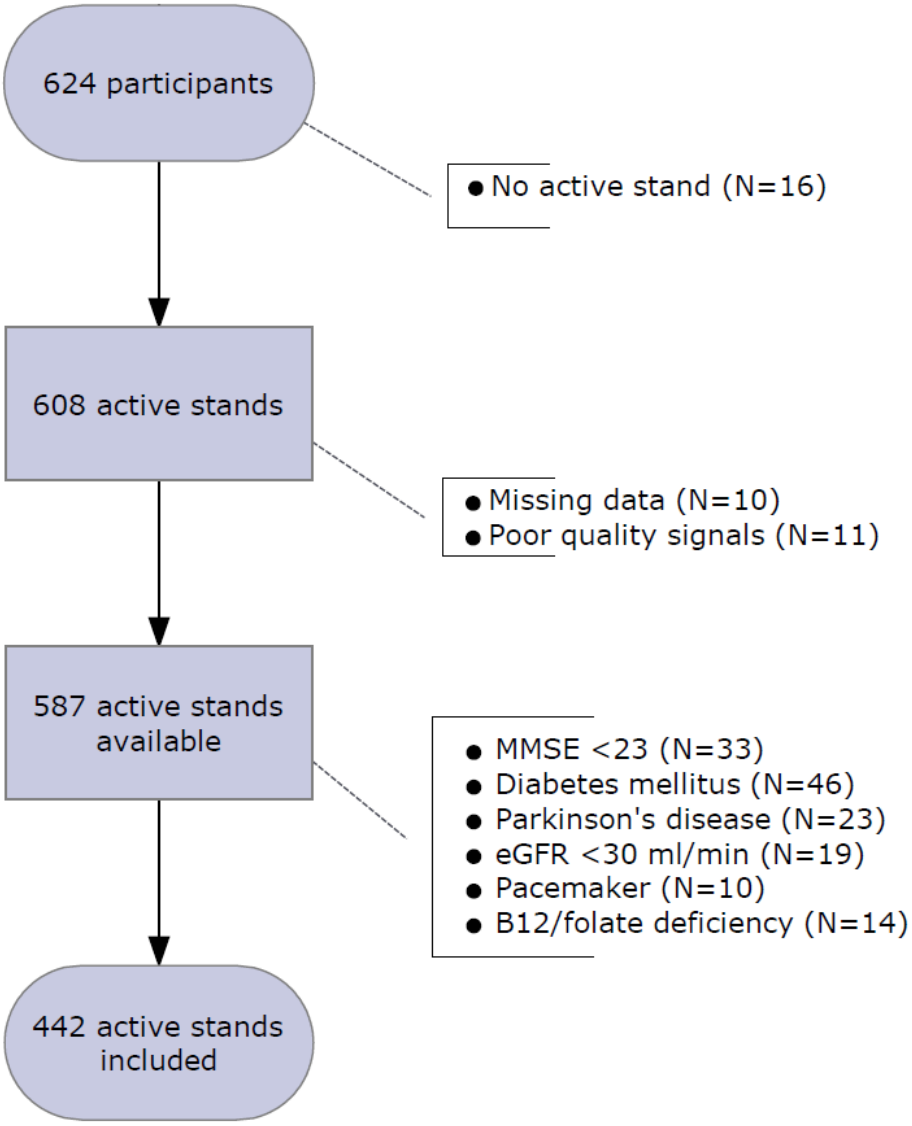
of the opinion that an association between OH and frailty would be more consistent with that premise if it was found in a sample where OH could not be attributable to conditions with a strong, well-known link to autonomic neuropathy. That is not to say that those conditions may not be part of the frailty syndrome; however, if an excessive burden of *identified* risk factors for autonomic neuropathy had been found in the frail group, a link between OH and frailty could have been interpreted as easily explainable by the overrepresentation of such dysautonomic subjects in the frail group. For that reason, the candidate excluded subjects with any of the following conditions: Diabetes mellitus (419-428), Parkinson's disease (429-441), severe chronic kidney disease (defined as a Cockcroft-Gault estimated Glomerular Filtration Rate < 30 mL/min) (338, 339, 341), and serum vitamin B_{12} (319-327) or red cell folate deficiency (442).

The above argument could also apply to the burden of vasoactive medications, which was expected to be greater in the frail group. However, if all subjects on those medications had been *a priori* excluded, that would have reduced the sample size to an unacceptably small number and led to underpower for multivariable statistical analyses. The potential confounding effect of medications was therefore left to *post-hoc* analyses.

Subjects with permanent cardiac pacemaker were also excluded to avoid confounding by possible pacemaker-induced alterations in orthostatic cardiac reactivity (443).

Figure 5.1 summarises the participants' flowchart. The final sample was composed by 442 subjects, mean age 72.1 years (SD 7.1); 317 (71.7%) were females.

Figure 5.1. Participants' flowchart.



Chapter 6

Orthostatic hypotension definitions: hemodynamic and clinical characterisation

The *consensus* (COH), *Fedorowski-modified* (FOH) and *morphological* (MOH) are pure *hemodynamic* definitions; *orthostatic intolerance* (OI) is a pure *clinical* definition, and *initial* (IOH) is a *mixed* hemodynamic and clinical definition of OH. In this chapter, these definitions are applied to the sample and their respective subgroups are characterised in terms of demographics (i.e. age and gender), orthostatic hemodynamic profiles (i.e. systolic and diastolic blood pressure, and heart rate) and clinical correlates (i.e. orthostatic intolerance and previous history of falls). The chapter concludes with a hemodynamic and clinical comparison of the five definitions.

Pure hemodynamic OH definitions

Three *pure hemodynamic* OH definitions were applied to the 5-second-averaged active stand data in the sample of $N = 442$: *consensus* (COH), *Fedorowski-modified* (FOH) and a novel *morphological* classification (MOH).

Classical (or consensus) OH (COH)

It is defined as a drop of at least 20 mmHg in systolic (SBP) and/or 10 mmHg in diastolic blood pressure (DBP) within the first three minutes of orthostasis (14). This definition was originally intended for the sphygmomanometer (444) and not for beat-to-beat data, so it was not supposed to capture the initial orthostatic hemodynamic changes (i.e. those occurring within the first 30 seconds) post-stand. However, for the purpose of this investigation (which aimed at illustrating the application of the COH definition to beat-to-beat data), the BP drops as per COH definition were defined as the difference between baseline BP (i.e. average between 60 and 30 seconds pre-stand, corresponding to *seven* 5-second averages) and the lowest of the *thirty-six* 5-second averages (i.e. 3 minutes) after stand. Notably, 94.8% of the SBP nadirs and 95.9% of the DBP nadirs occurred within 15 seconds (i.e. first three averages) after standing. These early nadirs would not have been captured by the routine sphygmomanometer method.

Fedorowski OH definition (FOH)

It is defined in the same way as COH, but applies a 30 mmHg cut-off in SBP drop in subjects with baseline supine SBP $\geq$ 160 mmHg and a cut-off of 15 mmHg in subjects with SBP $<$ 120 mmHg (DBP criterion is the same as in COH) (35). As in COH, this definition was also intended for the sphygmomanometer and not for beat-to-beat data.

A novel morphological classification of OH (MOH)

The candidate created this classification as a means to capture and characterise the three known morphological patterns of orthostatic blood pressure recovery: *quick* recovery, *slow* recovery, and *failure* to recover (30, 36, 37). The candidate felt it was necessary to have an OH classification based on the pattern of blood pressure recovery, as none of the other two pure hemodynamic OH definitions explicitly captures it. For the purpose of creating a morphological OH classification, *systolic* (as opposed to diastolic or mean arterial) blood pressure changes were used, as previous studies suggested that they are more clinically relevant (in terms of epidemiological associations) than diastolic blood pressure changes (128, 445). The MOH classification was developed as a research tool for the purpose of the present study and it was not intended to have immediate clinical applicability for the purpose of individual patient diagnosis. That is because the MOH classification results from the application of a statistical technique (which is explained below) on a reference sample; in a similar way, the original Fried's frailty classification requires the use of statistics on a reference sample, so it is not immediately applicable in clinical practice (274).

To *automatically* classify the present sample into three morphological orthostatic blood pressure groups based on SBP recoverability, the *K-means Cluster Analysis* technique was employed (SPSS 16.0), which assigns cases to a fixed number of groups (clusters) whose characteristics are not yet known but are based on a set of specified (clustering) variables. The K-means algorithm is internally programmed in SPSS 16.0 and the only active steps required by the user are to specify the clustering variables (i.e. clustering criteria) and the number of clusters to be obtained (i.e. three). K-means cluster analysis

has been used in analogous exploratory cross-sectional studies in Gerontology (446-448). Prior to the cluster analysis, the order of the cases in the dataset was randomised. The following clustering variables were entered:

- *Delta SBP*: difference between *baseline* (average SBP between 60 and 30 seconds before stand) and *nadir* (lowest SBP point reached *within 30 seconds* following active stand).
- *Percentage of SBP recovery*: maximum percentage of baseline SBP recovered by *30 seconds* (i.e. highest of six 5-second averages: +5 to + 30 seconds), *1 minute* (6 averages: +35 to + 60 seconds), and *2 minutes* (12 averages: +65 to +120 seconds) after stand.

Maximum percentage of SBP recovery by 3 minutes was not included based on the results of a pilot K-means cluster analysis showing that it did not significantly contribute to the solution in the face of the other four variables. This is consistent with the clinical views by Wieling *et al*. that analysis of the beat-to-beat blood pressure changes in the early phases after standing provides almost all the information that is necessary to determine abnormalities in orthostatic circulatory control (449).

Based on the above four clustering variables, three clusters were requested and their initial centres were determined automatically. The cluster membership variable was then saved to the dataset for characterisation purposes. Figure 6.1 shows a graphic matrix with the scatter plots of the variables used in the K-means clustering; Table 6.1 shows the inter-correlations between the clustering variables.

Figure 6.1. Graphic matrix with the scatter plots of the variables used in the K-means clustering (morphological OH classification).

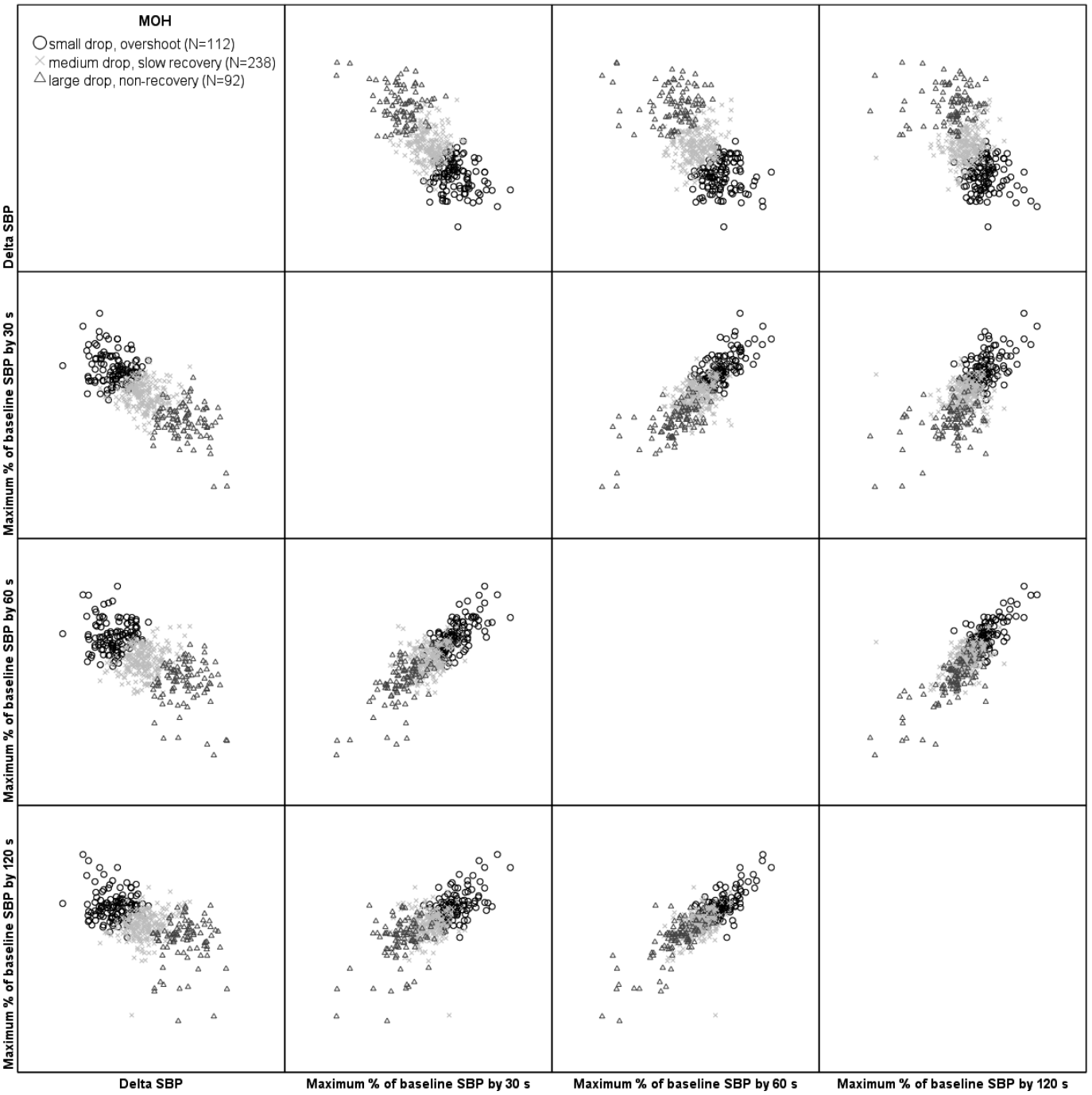


Table 6.1. Inter-correlations between the variables underlying the morphological OH classification.

		Delta SBP	Maximum % of baseline SBP by 30 s	Maximum % of baseline SBP by 60 s	Maximum % of baseline SBP by 120 s
Delta SBP	Correlation coefficient		-0.70	-0.54	-0.45
	P value (2-tailed)		<0.001	<0.001	<0.001
Maximum % of baseline SBP by 30 s	Correlation coefficient	-0.70		0.74	0.60
	P value (2-tailed)	<0.001		<0.001	<0.001
Maximum % of baseline SBP by 60 s	Correlation coefficient	-0.54	0.74		0.75
	P value (2-tailed)	<0.001	<0.001		<0.001
Maximum % of baseline SBP by 120 s	Correlation coefficient	-0.45	0.60	0.75	
	P value (2-tailed)	<0.001	<0.001	<0.001	

Listwise $N = 442$. Spearman's *rho* correlation coefficients are shown.

Pure clinical OH definition: orthostatic intolerance (OI)

This investigation took the view of the American *Joint National Committee* (JNC) *on Prevention, Detection, Evaluation and Treatment of High Blood Pressure*, namely that retinal and cerebral hypoperfusion symptoms occurring during a drop in blood pressure on standing should be considered as expressions of *possible* OH (47).

In our protocol, OI was defined as symptoms of dizziness, faintness or light-headedness at any point after standing during the active stand test. Subjects were asked to answer 'yes' or 'no' in response to whether or not they had felt any of the aforementioned symptoms. None of the subjects were unable to provide an answer to the question.

Mixed hemodynamic and clinical OH definition: initial OH (IOH)

For the purpose of this investigation, IOH is defined as a drop, within 15 seconds after standing, of > 40 mmHg in SBP and/or > 20 mmHg in DBP, *with symptoms* of cerebral hypoperfusion (i.e. orthostatic intolerance). The BP drop as per IOH definition was calculated as the difference between baseline (as defined for COH) and the lowest of the *three* 5-second averages (i.e. 5, 10 and 15 s) after stand.

The original IOH definition by Wieling *et al*. requires that the blood pressure fall upon standing is *transient*, that is, that it does not persist beyond the initial orthostatic phase. IOH was defined by Wieling *et al*. as a '*transient BP decrease within 15 seconds* after standing, of > 40 mmHg in SBP and/or > 20 mmHg in DBP, with symptoms of cerebral hypoperfusion' (31). However, only 81 out of 442 subjects (18.3%) had a transient BP decrease, the latter defined as the maximum SBP and DBP between 5 and 15 seconds after stand (i.e. three averages) being *equal to or greater* than the baseline SBP and DBP, respectively. Of those 81 subjects, only 7 had (within 15 seconds after standing) a SBP drop of > 40 mmHg, and 21 had a DBP drop of > 20 mmHg. Of those 21 'eligible' transient SBP or DBP drops, only 4 subjects had complaints of orthostatic intolerance, reducing the prevalence of 'transient' IOH in the total sample ($N = 442$) to 0.9%.

In view of the above preliminary finding, in this investigation the *transient* character of the original IOH definition was not taken into account, so a modified IOH definition is, in fact, used. IOH is hereafter defined as a drop, within 15 seconds after standing, of > 40 mmHg in SBP and/or > 20 mmHg in DBP, *with symptoms* of cerebral hypoperfusion (i.e. orthostatic intolerance).

Characterisation of the orthostatic hypotension classifications

Hemodynamic characterisation of the OH classifications

The following variables were used for SBP and DBP:

- *Baseline*: average between 60 and 30 seconds before stand (average of 7 averages).
- *Delta*: as defined above for the MOH classification (i.e. difference between baseline and nadir, with the latter being the lowest BP point reached within *30 seconds*, i.e. *six* 5-second averages, following active stand). Delta for COH, FOH and IOH were *calculated* as per their respective definitions; however, Delta BP was *characterised* for all OH definitions in the same way (i.e. considering nadir within 30 seconds) for uniformity purposes.

For heart rate (HR), *baseline* was defined as above; *delta* was defined as the difference between the maximum HR achieved within 30 seconds after stand and the baseline (36, 37).

The hemodynamic characterisation of the OH definitions was complemented by plots of the 5-second-averaged hemodynamic profiles of the orthostatic subgroups for SBP, DBP and HR. The SPSS 16.0 *Chart Builder* was used to that effect. In the figures, the horizontal axis indicates the time period from 60 seconds *pre-* (negative numbers) to 120 seconds *post-* (positive numbers) active stand (indicated as 0). In each figure, *thirty-seven* five-second means (each of them with a 95% confidence interval, CI) are represented for each subgroup. For a given mean or short means series, lack of overlap between 95% CIs *suggests* statistically significant differences between subgroups.

The plots data were used to statistically assess subgroup differences in hemodynamic *recoverability*. To that effect, the two-minute post-stand period was arbitrarily divided into four consecutive recovery phases (R1 to R4 in Figure 6.2; table 6.2):

- *Phase 1 recovery*: defined as the period between 16 and 30 seconds after stand (i.e. three 5-second averaged datapoints).
- *Phase 2 recovery*: period between 31 and 60 seconds post-stand (6 datapoints).
- *Phase 3 recovery*: period between 61 and 90 seconds post-stand (6 datapoints).
- *Phase 4 recovery*: period between 91 and 120 seconds post-stand (6 datapoints).

Figure 6.2. Illustration of the orthostatic blood pressure recovery phases on a Beatscope® output.

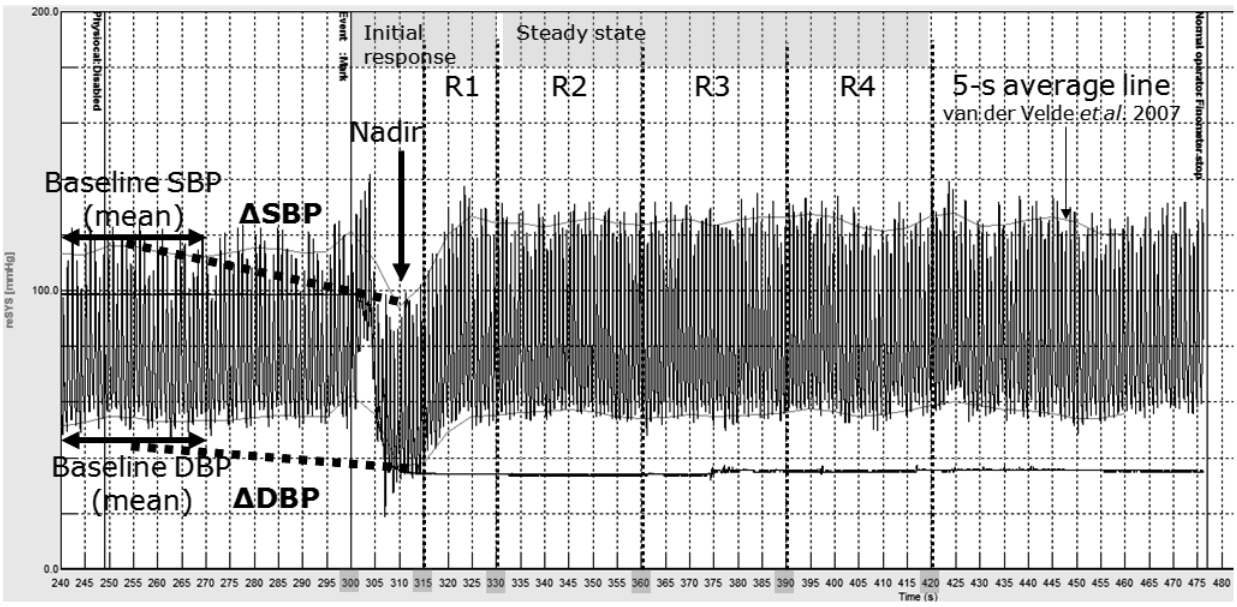


Table 6.2. Correspondence between the recovery phases and the nomenclature by Wieling *et al*. (450).

Recovery phase	Wieling *et al*. (450)
R1 (<30 s)	Initial response (< 30 s)
R2 (< 60 s)	Early steady state (< 120 s)
R3 (< 90 s)	
R4 (< 120 s)	

Demographic characterisation of the OH classifications

The age and the gender of the subjects were included in the characterisation.

Clinical characterisation of the OH classifications

A clinical characterisation of the OH classifications was conducted, using the following variables:

- *OI*: only relevant to COH, FOH and MOH (as OI is included in the IOH definition).
- *History of one or more falls in the previous six months* (i.e. yes or no). In the TRIL Clinic, we defined fall as per 2004 National Institute for Clinical Excellence (NICE) *Clinical practice guideline for the assessment and prevention of falls in older people*, namely 'an event whereby an individual comes to rest on the ground or another lower level with or without loss of consciousness' (451). In relation to the recall period (i.e. six months), a 2005 systematic review highlighted the substantial heterogeneity in the literature, with recall periods ranging from 1 week to 4 years in retrospective studies (452). The authors of the systematic review recommended that in order to maximise accuracy, the recall period over which participants report the absence or presence of a fall event must be short. In that light, and also in view of the dementia exclusion criterion, 6 months was chosen as a reasonable compromise.

Statistical analyses

All statistical analyses were performed with SPSS 16.0. Descriptives for dichotomous variables were given as percentages (%). Continuous variables were described as mean with standard deviation (SD) or standard error (SE). All statistical tests used for

between-group comparisons were 2-sided. The normality of continuous variables was assessed with the one-sample Kolmogorov-Smirnov test.

For comparisons between two groups on dichotomous variables, the Chi-squared or Fisher's exact test were used as appropriate. For continuous variables, the independent samples t-test (parametric) or the Mann-Whitney U test (non-parametric) were used as appropriate. For overall comparisons between three groups on continuous variables, the one-way ANOVA test (parametric) or the Kruskal-Wallis test (non-parametric) were used as appropriate, and where an *overall* significant difference was found, *post-hoc* pairwise multiple comparisons were requested with Bonferroni (equal variances) or Tamhane's T2 (unequal variances) adjustment, as appropriate, to determine which group pairs were different. To test for a linear trend (i.e. gradient) across the three groups, the Chi-squared for trend test was used for dichotomous variables, and the Spearman's rank correlation coefficient was used for continuous variables.

To statistically assess subgroup differences in hemodynamic recoverability at each of the four recovery phases, repeated measures ANOVA was used, using the sequential five-second-averaged hemodynamic datapoints as within-subjects variable and the OH classification as the between-subjects variable. For more than two OH groups, post-hoc multiple comparisons were performed with Bonferroni (equal variances) or Tamhane's T2 (unequal variances) as appropriate.

To adjust for multiple comparisons (453), the level of significance (alpha) was set at $P < 0.01$ throughout. Statistical trend was defined as $P < 0.05$.

Consensus definition of orthostatic hypotension: prevalence, hemodynamic profiles, demographics and association with orthostatic intolerance and falls

The consensus definition of OH (COH) classified the vast majority of subjects (N = 416, 94.1%) as having OH. Table 6.3 compares COH – and COH + subjects according to hemodynamic markers and subgroup prevalences of OI and falls. Figures 6.3a-c show the 5-second-averaged hemodynamic profiles of the two subgroups for SBP, DBP and HR, respectively.

Systolic blood pressure (SBP) profiles

COH – and COH + groups were not significantly different in baseline, but COH – had a very small delta (6.9 mmHg on average) in comparison with COH + (37.6 mmHg) (P < 0.001). In terms of recoverability, the only significant difference was in phase 1, where COH – had a mean SBP (i.e. mean of three datapoints) of 166.0 mmHg *vs*. 150.6 mmHg in COH + (P = 0.006) (Table 6.3). Figure 6.3a visually suggests the differences, in the form of lack of overlap between 95% confidence intervals around delta and first recovery phase.

Diastolic blood pressure (DBP) profiles

COH – and COH + groups were not significantly different in baseline, but COH – had a very small delta (3.6 mmHg) in comparison with COH + (25.1 mmHg) (P < 0.001). In terms of recoverability, the only significant difference was in phase 1, where COH – had a mean DBP of 83.0 mmHg *vs*. 70.6 mmHg in COH + (P < 0.001). There was a trend towards a recoverability difference in phase 2 (80.3 mmHg in COH – vs. 74.5 mmHg in COH +, P = 0.032) (Table 6.3). Figure 6.3b visually suggests the differences,

in the form of lack of overlap between 95% confidence intervals around delta and first recovery phase.

Heart rate (HR) profiles

There were no significant differences between the COH – and COH + groups (Table 6.3, Figure 6.3c).

Age and gender

There were no significant differences between COH – and COH + (Table 6.3).

Orthostatic intolerance (OI) and falls

There were no significant differences between COH – and COH + (Table 6.3).

Table 6.3. Consensus definition of orthostatic hypotension (COH): sample prevalence, hemodynamic profiles, demographics and association with orthostatic intolerance (OI) and falls.

	COH – ($N = 26$)	COH + ($N = 416$)	P value for difference
Systolic blood pressure (SBP)			
Baseline SBP (mmHg) (SD)	153.5 (23.1)	160.8 (24.4)	0.139^{Ω}
Delta SBP (mmHg) (SD)	6.9 (8.3)	37.6 (17.5)	$\mathbf{<0.001}^{\prod}$
Recovery 1: mean SBP (mmHg) (SE)	166.0 (5.4)	150.6 (1.4)	$\mathbf{0.006}^{\infty}$
Recovery 2: mean SBP (mmHg) (SE)	161.2 (5.4)	153.6 (1.3)	0.171^{∞}
Recovery 3: mean SBP (mmHg) (SE)	162.3 (5.4)	156.5 (1.3)	0.295^{∞}
Recovery 4: mean SBP (mmHg) (SE)	161.8 (5.5)	156.1 (1.4)	0.312^{∞}
Diastolic blood pressure (DBP)			
Baseline DBP (mmHg) (SD)	75.3 (8.7)	78.7 (11.5)	0.141^{Ω}
Delta DBP (mmHg) (SD)	3.6 (4.9)	25.1 (11.0)	$\mathbf{<0.001}^{\Omega}$
Recovery 1: mean DBP (mmHg) (SE)	83.0 (2.8)	70.6 (0.7)	$\mathbf{<0.001}^{\infty}$
Recovery 2: mean DBP (mmHg) (SE)	80.3 (2.6)	74.5 (0.6)	$\mathit{0.032}^{\infty}$
Recovery 3: mean DBP (mmHg) (SE)	80.6 (2.6)	75.6 (0.6)	0.061^{∞}
Recovery 4: mean DBP (mmHg) (SE)	80.2 (2.5)	75.3 (0.6)	0.059^{∞}
Heart rate (HR)			
Baseline HR (bpm) (SD)	70.3 (9.2)	68.5 (10.6)	0.409^{Ω}
Delta HR (bpm) (SD)	16.0 (6.7)	14.4 (8.8)	$0.133^{\prod}$
Recovery 1: mean HR (bpm) (SE)	80.6 (2.4)	75.9 (0.6)	0.060^{∞}
Recovery 2: mean HR (bpm) (SE)	79.6 (2.5)	76.4 (0.6)	0.210^{∞}
Recovery 3: mean HR (bpm) (SE)	79.1 (2.4)	75.6 (0.6)	0.163^{∞}
Recovery 4: mean HR (bpm) (SE)	77.9 (2.4)	74.9 (0.6)	0.227^{∞}
Demographics			
Age (years): mean (SD)	74.2 (6.4)	71.9 (7.2)	$0.120^{\prod}$
Female gender (%)	84.6	70.9	0.132^{χ}
Orthostatic intolerance (OI) and falls			
OI symptoms (%)	15.4	29.5	0.123^{χ}
≥ 1 fall in the last 6 months (%)	7.7	13.5	$0.556^{\int}$

$^{\Omega}$ Independent samples t-test; $^{\prod}$ Mann-Whitney U test; $^{\infty}$ Repeated measures ANOVA; $^{\chi}$ Chi-squared test; $^{\int}$ Fisher's exact test (2-sided); SD: standard deviation; SE: standard error. Significant P values ($P < 0.01$) are highlighted in bold; statistical trends ($P < 0.05$) are in italics.

Figure 6.3a. Comparison of orthostatic systolic blood pressure (SBP) profiles between the consensus definition of orthostatic hypotension (COH) subgroups: COH – (N = 26); COH + (N = 416).

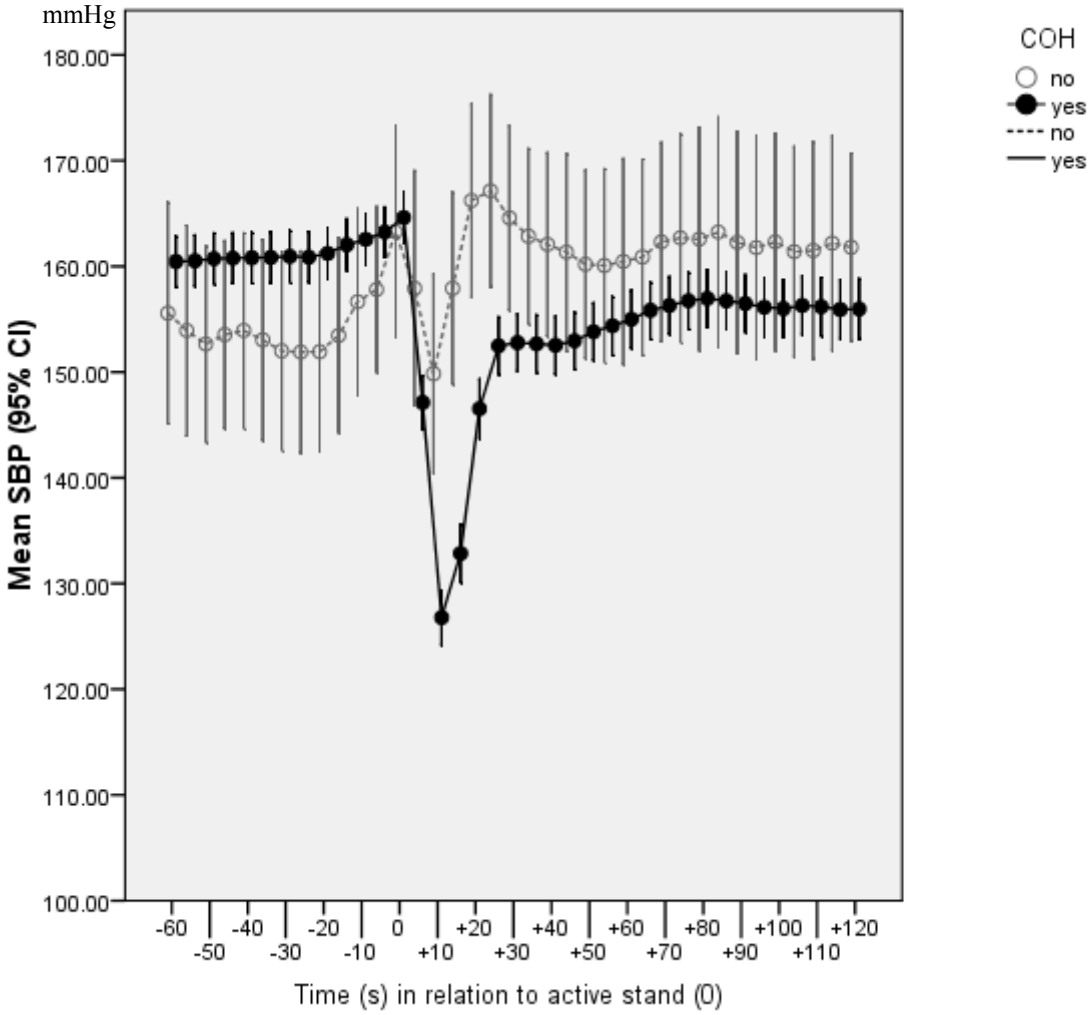


Figure 6.3b. Comparison of orthostatic diastolic blood pressure (DBP) profiles between the consensus definition of orthostatic hypotension (COH) subgroups: COH – (*N* = 26); COH + (*N* = 416).

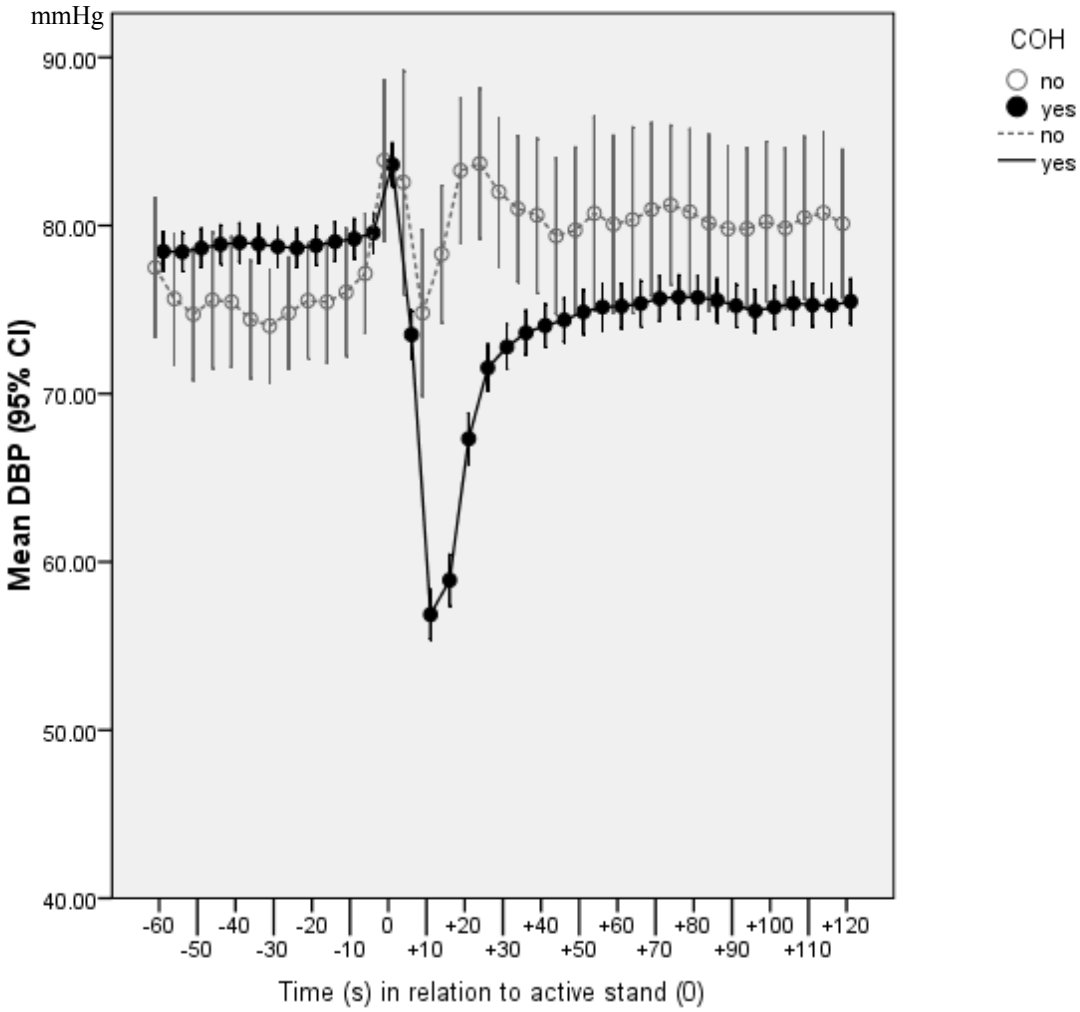
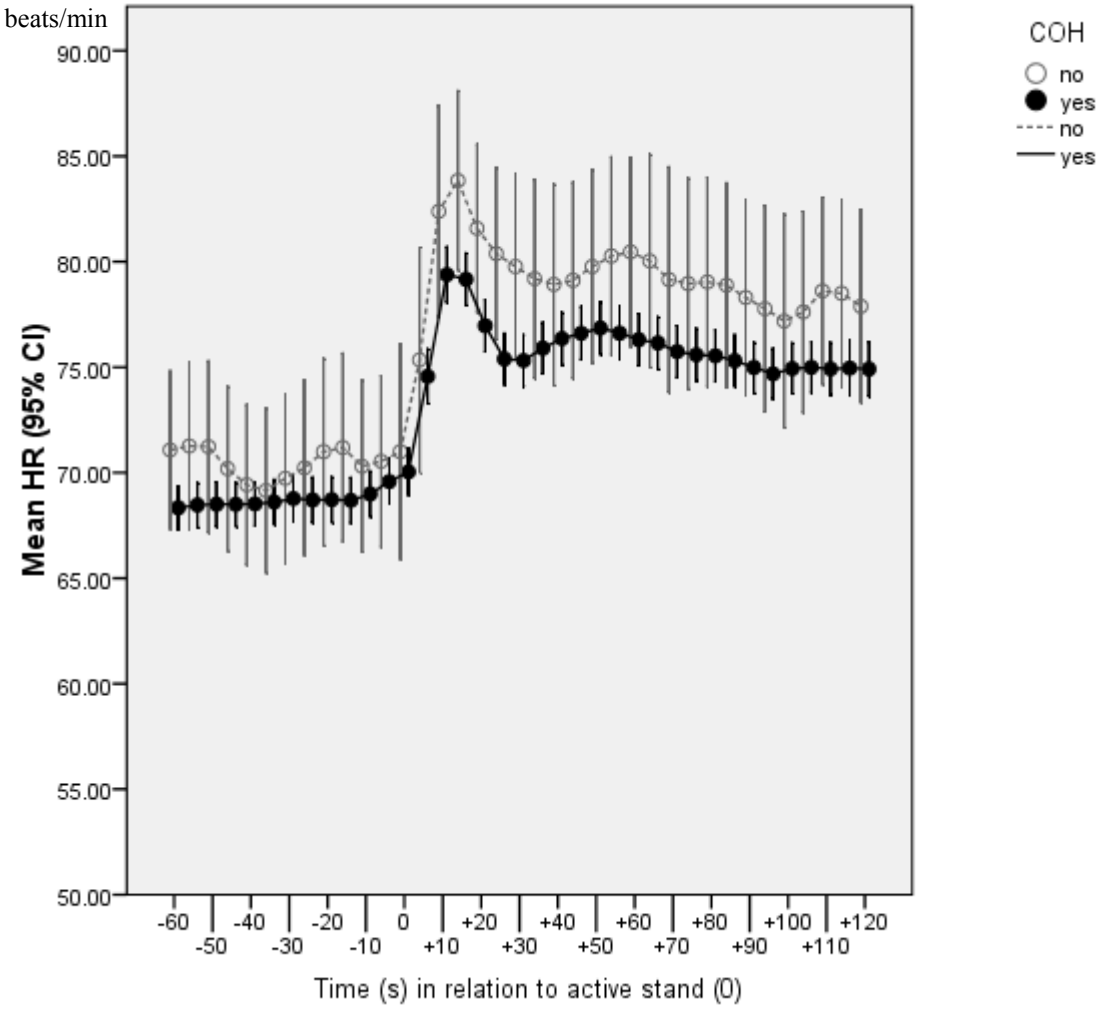


Figure 6.3c. Comparison of orthostatic heart rate (HR) profiles between the consensus definition of orthostatic hypotension (COH) subgroups: COH – (*N* = 26); COH + (*N* = 416).



Fedorowski *et al*.'s modification of the consensus definition of orthostatic hypotension (FOH): prevalence, hemodynamic profiles, demographics and association with orthostatic intolerance and falls

As in COH, FOH classified the vast majority of subjects (N = 412, 93.2%) as having OH. Table 6.4 compares FOH – and FOH + subjects according to hemodynamic markers and subgroup prevalences of OI and falls. Figures 6.4a-c show the 5-second-averaged hemodynamic profiles of the two subgroups for SBP, DBP and HR, respectively.

Applying Fedorowski *et al*.'s SBP criterion adjustment, 30 cases that were positive for the traditional SBP criterion were classified as negative by the modified SBP criterion. However, when combining the SBP-modified and the traditional DBP criteria, only 4 cases were reclassified as OH –.

Systolic blood pressure (SBP) profiles

FOH – and FOH + groups were not significantly different in baseline, but FOH – had a very small delta (9.4 mmHg) in comparison with FOH + (37.7 mmHg) ($P < 0.001$). In terms of recoverability, the only significant difference was in phase 1, where FOH – had a mean SBP of 167.2 mmHg *vs*. 150.4 mmHg in FOH + ($P = 0.001$) (Table 6.4). Figure 6.4a visually suggests these differences, in the form of lack of overlap between 95% confidence intervals around delta and first recovery phase.

Diastolic blood pressure (DBP) profiles

FOH – and FOH + groups were not significantly different in baseline, but FOH – had a very small delta (3.9 mmHg) in comparison with FOH + (25.3 mmHg) ($P < 0.001$). In terms of recoverability (FOH – *vs*. FOH +), there were significant differences in phase 1 (82.5 mmHg *vs*. 70.5 mmHg, $P < 0.001$) and phase 2 (80.9 mmHg *vs*. 74.4 mmHg, $P = 0.009$), and trends towards recoverability differences in phase 3 (81.4 mmHg *vs*. 75.4 mmHg, $P = 0.017$) and phase 4 (80.5 mmHg *vs*. 75.2 mmHg, $P = 0.032$) (Table 6.4). Figure 6.4b visually suggests these differences, in the form of lack of overlap between 95% confidence intervals around delta and first and second recovery phases.

Heart rate (HR) profiles

There were no significant differences between FOH – and FOH + (Table 6.4, Figure 6.4c).

Age and gender

There were no significant differences between FOH – and FOH + (Table 6.4).

Orthostatic intolerance (OI) and falls

There were no significant differences between FOH – and FOH + (Table 6.4).

Table 6.4. Fedorowski *et al.*'s modification of the consensus definition of orthostatic hypotension (FOH): sample prevalence, hemodynamic profiles, demographics and association with orthostatic intolerance (OI) and falls.

	FOH – (N = 30)	FOH + (N = 412)	P value for difference
Systolic blood pressure (SBP)			
Baseline SBP (mmHg)	156.9 (23.8)	160.6 (24.4)	0.419$^{\Omega}$
Delta SBP (mmHg)	9.4 (10.1)	37.7 (17.5)	**<0.001**$^{\prod}$
Recovery 1: mean SBP (mmHg) (SE)	167.2 (5.0)	150.4 (1.4)	**0.001**$^{\infty}$
Recovery 2: mean SBP (mmHg) (SE)	163.4 (5.0)	153.3 (1.4)	0.051$^{\infty}$
Recovery 3: mean SBP (mmHg) (SE)	165.4 (5.0)	156.2 (1.3)	0.078$^{\infty}$
Recovery 4: mean SBP (mmHg) (SE)	164.4 (5.1)	155.8 (1.4)	0.108$^{\infty}$
Diastolic blood pressure (DBP)			
Baseline DBP (mmHg)	75.5 (9.2)	78.7 (11.5)	0.128$^{\Omega}$
Delta DBP (mmHg)	3.9 (4.9)	25.3 (10.9)	**<0.001**$^{\Omega}$
Recovery 1: mean DBP (mmHg) (SE)	82.5 (2.6)	70.5 (0.7)	**<0.001**$^{\infty}$
Recovery 2: mean DBP (mmHg) (SE)	80.9 (2.4)	74.4 (0.6)	**0.009**$^{\infty}$
Recovery 3: mean DBP (mmHg) (SE)	81.4 (2.4)	75.4 (0.6)	*0.017*$^{\infty}$
Recovery 4: mean DBP (mmHg) (SE)	80.5 (2.4)	75.2 (0.6)	*0.032*$^{\infty}$
Heart rate (HR)			
Baseline HR (bpm)	69.8 (8.9)	68.6 (10.7)	0.543$^{\Omega}$
Delta HR (bpm)	15.0 (7.1)	14.5 (8.8)	0.470$^{\prod}$
Recovery 1: mean HR (bpm) (SE)	79.2 (2.3)	75.9 (0.6)	0.165$^{\infty}$
Recovery 2: mean HR (bpm) (SE)	78.4 (2.3)	76.5 (0.6)	0.424$^{\infty}$
Recovery 3: mean HR (bpm) (SE)	78.0 (2.3)	75.6 (0.6)	0.305$^{\infty}$
Recovery 4: mean HR (bpm) (SE)	76.9 (2.3)	75.0 (0.6)	0.415$^{\infty}$
Demographics			
Age (years): mean (SD)	73.3 (6.5)	72.0 (7.2)	0.366$^{\prod}$
Female gender (%)	83.3	70.9	0.143$^{\chi}$
Orthostatic intolerance (OI) and falls			
OI symptoms (%)	16.7	29.5	0.133$^{\chi}$
≥ 1 fall in the last 6 months (%)	6.7	13.6	0.403$^{\int}$

$^{\Omega}$ Independent samples t-test; $^{\prod}$ Mann-Whitney U test; $^{\infty}$ Repeated measures ANOVA; $^{\chi}$ Chi-squared test; $^{\int}$ Fisher's exact test (2-sided); SD: standard deviation; SE: standard error. Significant P values ($P < 0.01$) are highlighted in bold; statistical trends ($P < 0.05$) are in italics.

Figure 6.4a. Comparison of orthostatic systolic blood pressure (SBP) profiles between the Fedorowski *et al.*'s modification of the consensus definition of orthostatic hypotension (FOH) subgroups: FOH – (N = 30); FOH + (N = 412).

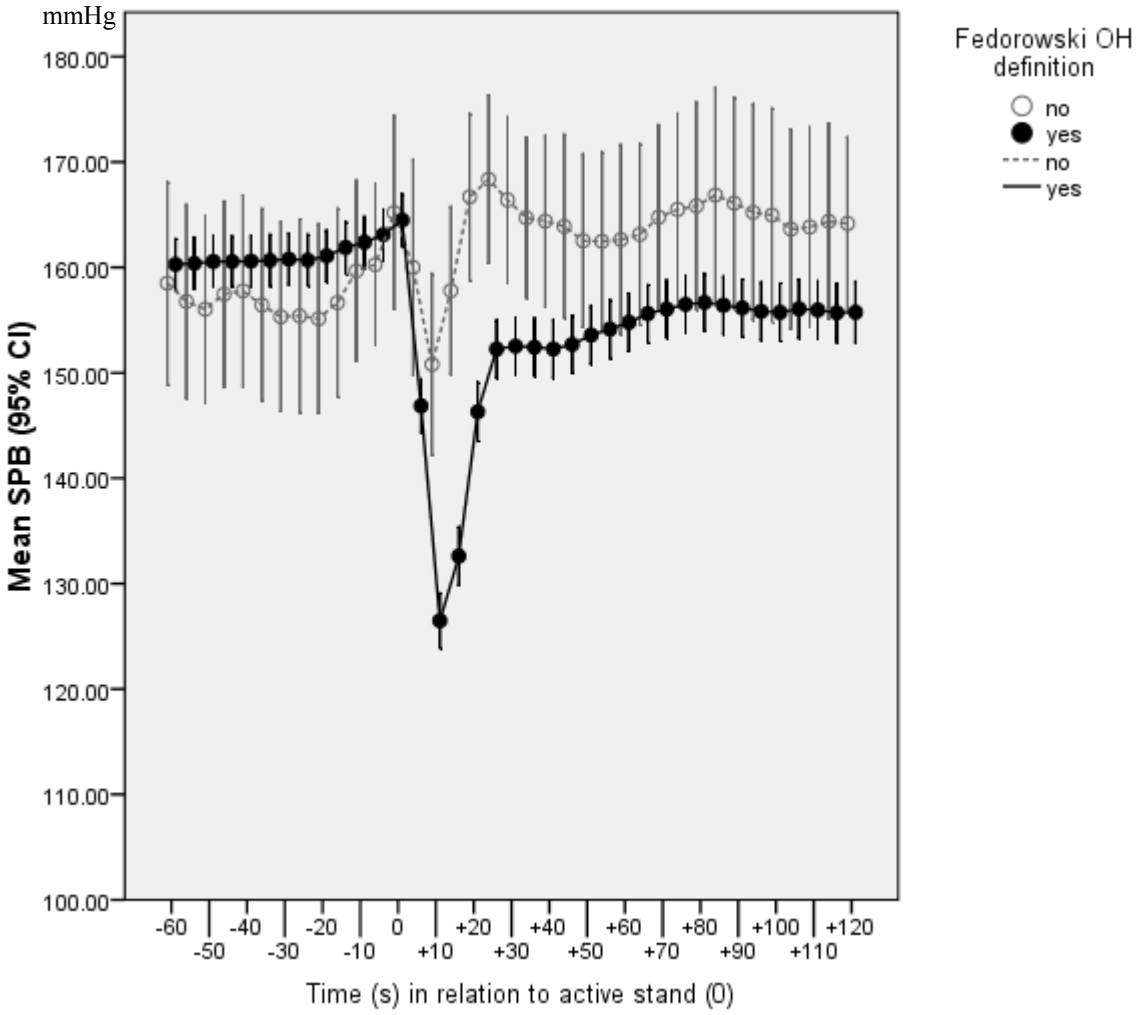


Figure 6.4b. Comparison of orthostatic diastolic blood pressure (DBP) profiles between the Fedorowski *et al*.'s modification of the consensus definition of orthostatic hypotension (FOH) subgroups: FOH – (*N* = 30); FOH + (*N* = 412).

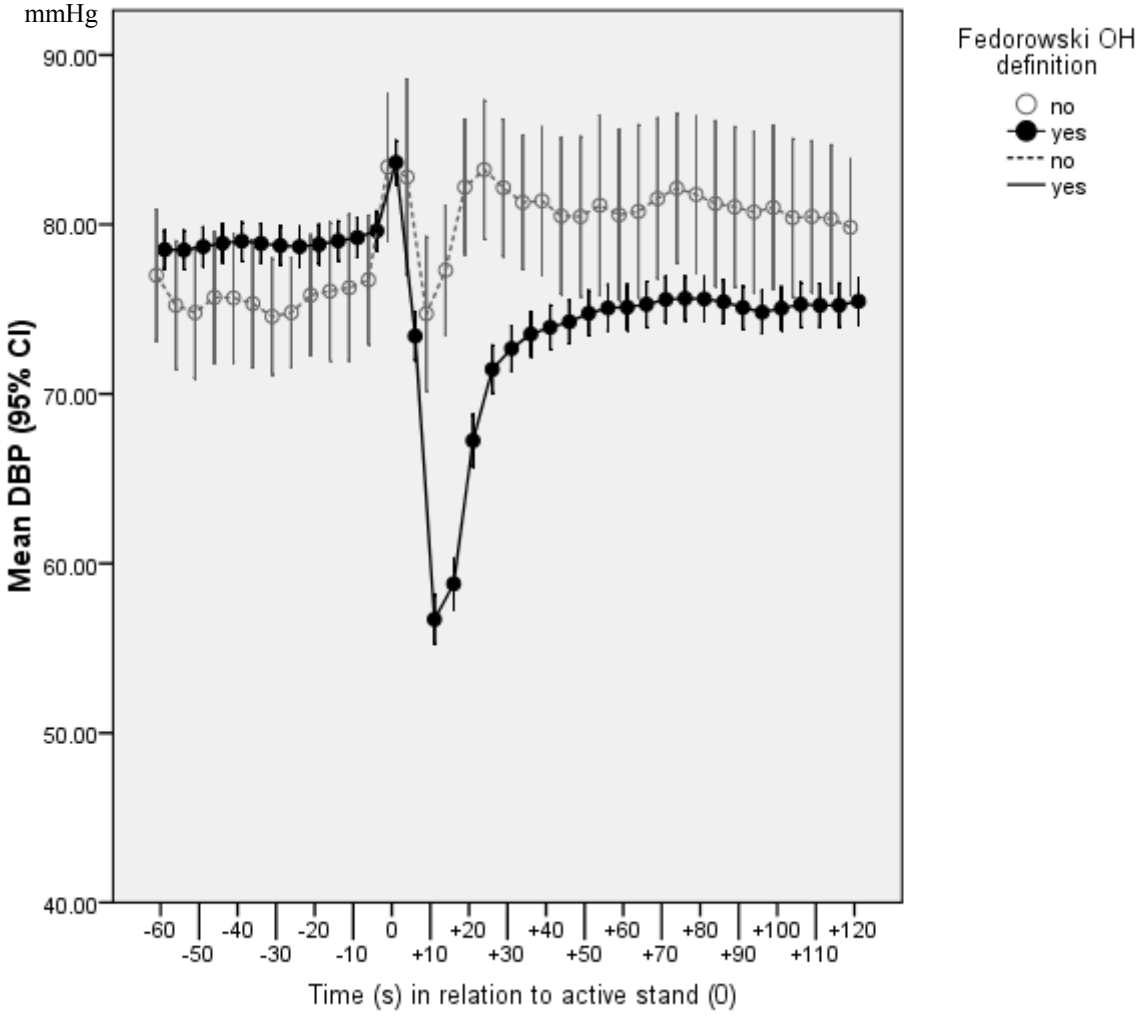
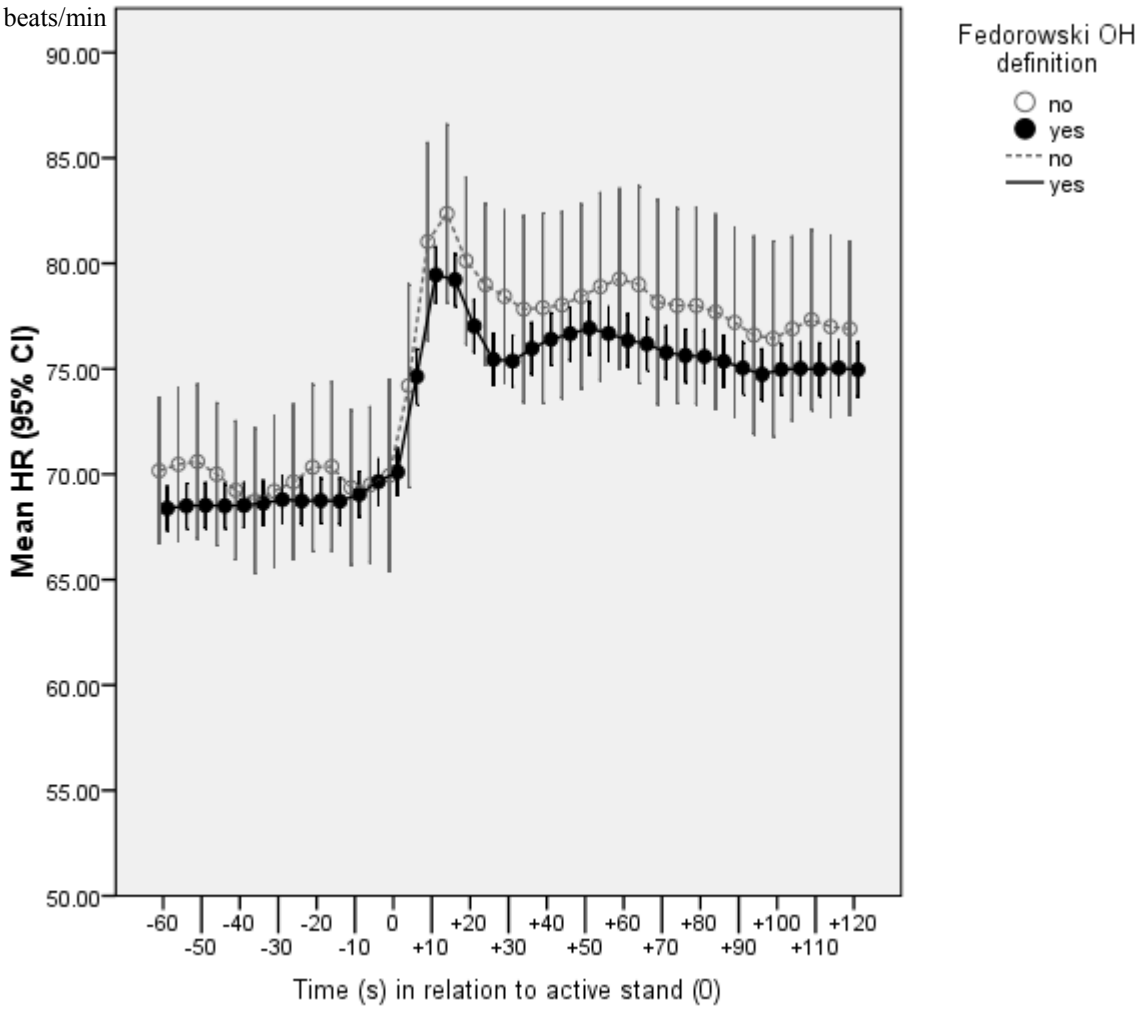


Figure 6.4c. Comparison of orthostatic heart rate (HR) profiles between the Fedorowski *et al.*'s modification of the consensus definition of orthostatic hypotension (FOH) subgroups: FOH – (N = 30); FOH + (N = 412).



Morphological classification of orthostatic hypotension (MOH): prevalence, hemodynamic profiles, demographics and association with orthostatic intolerance (OI) and falls

All four clustering variables significantly contributed to the solution ($P < 0.001$). Of the 442 cases assigned to clusters, 112 (25.3%) were assigned to the first cluster, 238 (53.8%) to the second, and 92 (20.8%) to the third. Table 6.5 compares the MOH groups according to hemodynamic markers and subgroup prevalences of OI and falls. Figures 6.5a-c show the 5-second-averaged hemodynamic profiles of the three MOH subgroups for SBP, DBP and HR, respectively.

Cluster 1 was characterised by relatively small BP drops and quick *overshoot* (over-recovery) of the baseline BP: both for SBP and DBP, the mean BP at the first phase of recovery was higher than at baseline, and remained higher than at baseline at the fourth recovery phase. *Cluster 2* was characterised by intermediate BP drops and slower recovery of the baseline BP: for both SBP and DBP, the mean BP by the fourth phase of recovery was close to that at baseline, but had not fully recovered. *Cluster 3* was characterised by relatively large BP drops and clear under-recovery of the baseline BP.

Systolic blood pressure (SBP) profiles

For baseline, there was a significant overall difference between the clusters ($P < 0.001$, all pairwise comparisons with $P < 0.01$), conforming to a *gradient of increasing hypertension*: 153.0 mmHg in Cluster 1 < 160.8 mm Hg in Cluster 2 < 168.2 mmHg in Cluster 3 ($P < 0.001$). For delta, there was a significant overall difference between the clusters ($P < 0.001$, all pairwise comparisons with $P < 0.01$), conforming to a *gradient*

of increasing SBP drop: 15.9 mmHg in Cluster 1 < 35.2 mm Hg in Cluster 2 < 61.6 mmHg in Cluster 3 ($P < 0.001$). Analogous results were found for the four recovery phases, all conforming to *gradients of increasingly impaired recoverability* (all with $P < 0.001$) (Table 6.5). Figure 6.5a suggests these statistically significant differences as a generalised lack of overlap between 95% confidence intervals.

Diastolic blood pressure (DBP) profiles

For baseline, there were no statistically significant differences between the clusters. For delta, there was a significant overall difference between the clusters ($P < 0.001$, all pairwise comparisons with $P < 0.01$), conforming to a *gradient of increasing DBP drop*: 14.2 mmHg in Cluster 1 < 23.4 mm Hg in Cluster 2 < 36.6 mmHg in Cluster 3 ($P < 0.001$). Analogous significant results were found for the four recovery phases, all conforming to *gradients of increasingly impaired recoverability* (all with $P < 0.001$) (Table 6.5). Figure 6.5b visually suggests these differences, manifesting as lack of overlap between 95% confidence intervals around delta and the four recovery phases.

Heart rate (HR) profiles

For baseline, the statistic for overall difference between the clusters did not reach significance ($P = 0.068$), but there was a *trend towards a gradient of decreasing baseline HR*: 70.3 bpm in Cluster 1 > 68.5 bpm in Cluster 2 > 66.9 bpm in Cluster 3 ($P = 0.035$). For delta, there was a *trend towards a gradient of decreasing cardiac chronotropic response*: 15.5 bpm in Cluster 1 > 14.5 bpm in Cluster 2 > 13.3 bpm in Cluster 3 ($P = 0.033$). In the first phase of recovery there was a *trend towards a gradient of decreasing HR*: 78.6 bpm in Cluster 1 > 75.7 bpm in Cluster 2 > 74.5 bpm

in Cluster 3 (P = 0.020) (Table 6.5). Figure 6.5c shows considerable overlap between 95% confidence intervals, supporting the finding of trends rather than significant differences.

Age and gender

For age, the statistic for overall difference between clusters did not reach significance (P = 0.089), and there was no suggestion of an age gradient (P = 0.206). There were no statistically significant differences in gender across MOH clusters (Table 6.5).

Orthostatic intolerance (OI) and falls

Across MOH clusters, there was a progressive increase in the prevalence of OI, conforming to a statistically significant gradient (P < 0.001). For history of falls, neither the overall difference nor the trend statistic reached statistical significance, despite the suggestion of increasing prevalences: 9.8% in Cluster 1, 13.0 in Cluster 2, and 17.4 in Cluster 3 (Table 6.5).

Table 6.5. Morphological orthostatic hypotension (MOH) classification: sample prevalence, hemodynamic profiles, demographics and association with orthostatic intolerance (OI) and falls.

	Small drop, overshoot $N = 112$	Medium drop, slow recovery $N = 238$	Large drop, non-recovery $N = 92$	*P* value (overall difference)	*P* value (linear trend)
Systolic blood pressure (SBP)					
Baseline SBP (mmHg)	153.0 (23.9)	160.8 (23.0)	168.2 (25.9)	**<0.001**§	**<0.001**$^{\Sigma}$
Delta SBP (mmHg)	15.9 (10.0)	35.2 (9.8)	61.6 (11.6)	**<0.001**$^{\#}$	**<0.001**$^{\Sigma}$
Recovery 1: mean SBP (mmHg) (SE)	165.8 (2.4)	152.1 (1.7)	132.7 (2.7)	**<0.001**$^{\infty}$	**<0.001**$^{\Sigma}$
Recovery 2: mean SBP (mmHg) (SE)	166.4 (2.5)	153.7 (1.7)	139.8 (2.7)	**<0.001**$^{\infty}$	**<0.001**$^{\Sigma}$
Recovery 3: mean SBP (mmHg) (SE)	167.9 (2.5)	156.6 (1.7)	144.0 (2.7)	**<0.001**$^{\infty}$	**<0.001**$^{\Sigma}$
Recovery 4: mean SBP (mmHg) (SE)	167.2 (2.6)	155.7 (1.8)	145.1 (2.8)	**<0.001**$^{\infty}$	**<0.001**$^{\Sigma}$
Diastolic blood pressure (DBP)					
Baseline DBP (mmHg)	77.4 (11.9)	78.4 (11.0)	80.3 (11.6)	0.177§	0.073$^{\Sigma}$
Delta DBP (mmHg)	14.2 (7.2)	23.4 (9.0)	36.6 (11.4)	**<0.001**§	**<0.001**$^{\Sigma}$
Recovery 1: mean DBP (mmHg) (SE)	79.4 (1.2)	71.1 (0.9)	61.8 (1.4)	**<0.001**$^{\infty}$	**<0.001**$^{\Sigma}$
Recovery 2: mean DBP (mmHg) (SE)	81.0 (1.2)	74.5 (0.8)	68.3 (1.3)	**<0.001**$^{\infty}$	**<0.001**$^{\Sigma}$
Recovery 3: mean DBP (mmHg) (SE)	81.7 (1.2)	75.3 (0.8)	70.2 (1.3)	**<0.001**$^{\infty}$	**<0.001**$^{\Sigma}$
Recovery 4: mean DBP (mmHg) (SE)	81.1 (1.2)	74.8 (0.8)	70.7 (1.3)	**<0.001**$^{\infty}$	**<0.001**$^{\Sigma}$
Heart rate (HR)					
Baseline HR (bpm)	70.3 (11.2)	68.5 (9.8)	66.9 (11.3)	0.068§	*0.035*$^{\Sigma}$
Delta HR (bpm)	15.5 (6.7)	14.5 (9.8)	13.3 (7.4)	0.100$^{\#}$	*0.033*$^{\Sigma}$
Recovery 1: mean HR (bpm) (SE)	78.6 (1.2)	75.7 (0.8)	74.5 (1.3)	*0.041*$^{\infty}$	*0.020*$^{\Sigma}$
Recovery 2: mean HR (bpm) (SE)	77.9 (1.2)	76.4 (0.8)	75.6 (1.3)	0.413$^{\infty}$	0.186$^{\Sigma}$
Recovery 3: mean HR (bpm) (SE)	77.5 (1.2)	75.0 (0.8)	75.5 (1.3)	0.230$^{\infty}$	0.120$^{\Sigma}$
Recovery 4: mean HR (bpm) (SE)	76.4 (1.2)	74.6 (0.8)	74.5 (1.3)	0.405$^{\infty}$	0.113$^{\Sigma}$
Demographics					
Age (years): mean (SD)	72.0 (7.1)	71.5 (7.0)	73.6 (7.5)	0.089$^{\#}$	0.206$^{\Sigma}$
Female gender (%)	74.1	71.0	70.7	0.808$^{\chi}$	0.569$^{\chi t}$
Orthostatic intolerance (OI) and falls					
OI symptoms (%)	17.9	27.5	44.6	**<0.001**$^{\chi}$	**<0.001**$^{\chi t}$
≥ 1 fall in the last 6 months (%)	9.8	13.0	17.4	0.280$^{\chi}$	0.113$^{\chi t}$

§ One way ANOVA test; $^{\#}$ Kruskal-Wallis test; $^{\infty}$ Repeated measures ANOVA; $^{\Sigma}$ Spearman's rank correlation coefficient. Significant *P* values ($P < 0.01$) are highlighted in bold, and statistical trends ($P < 0.05$) are indicated in italics.

Figure 6.5a. Comparison of orthostatic systolic blood pressure (SBP) profiles between the morphological orthostatic hypotension (MOH) subgroups.

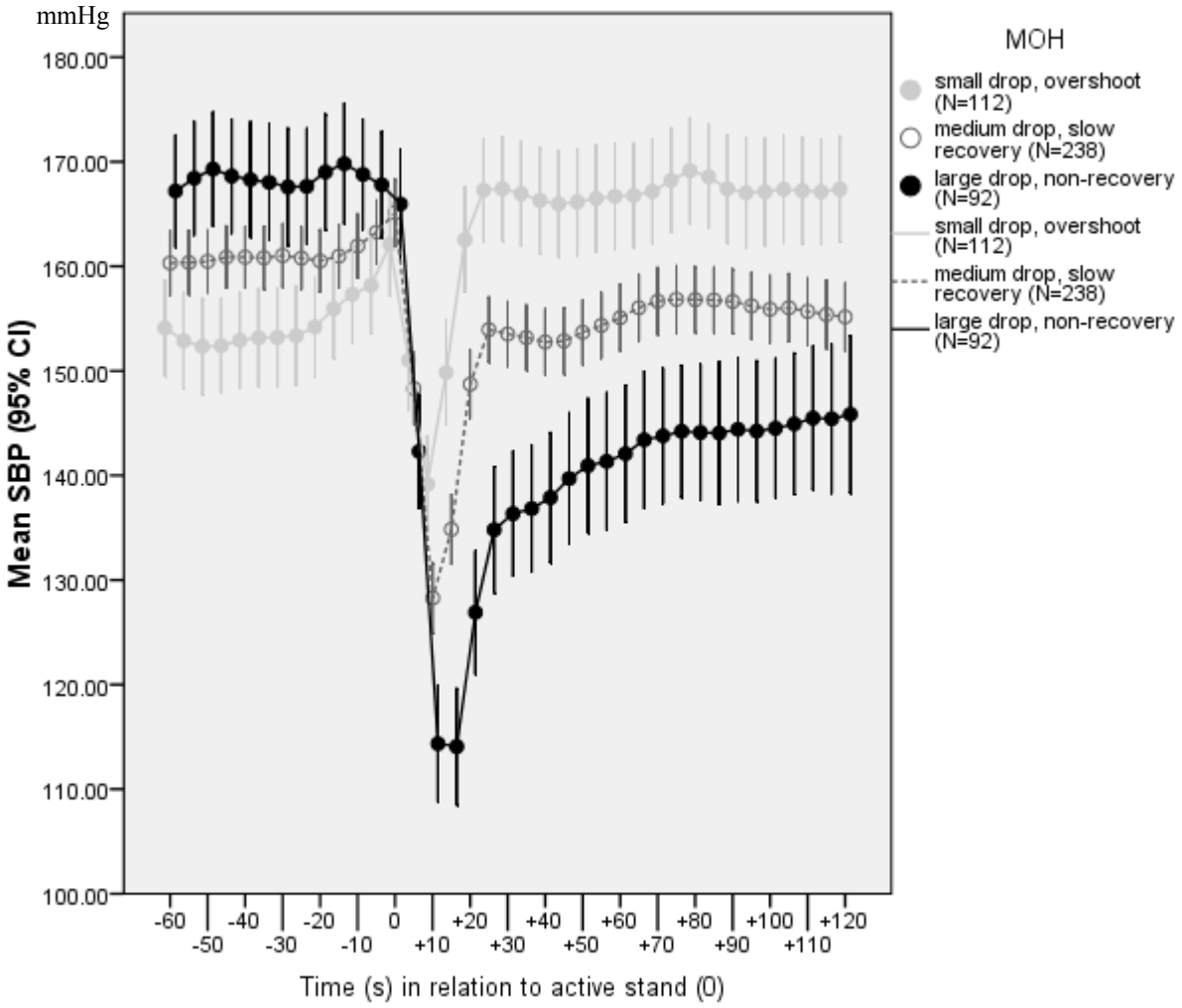


Figure 6.5b. Comparison of orthostatic diastolic blood pressure (DBP) profiles between the morphological orthostatic hypotension (MOH) subgroups.

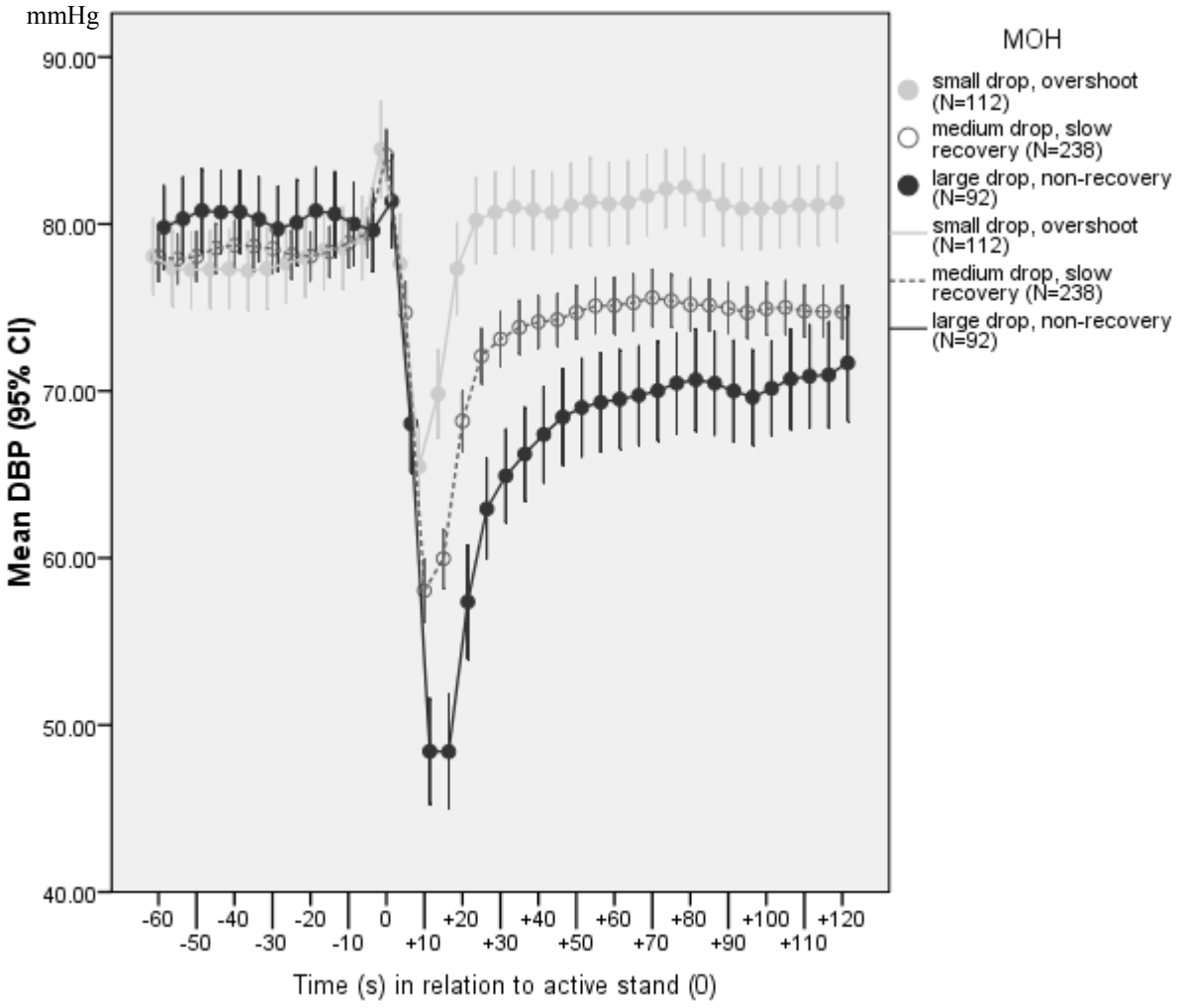
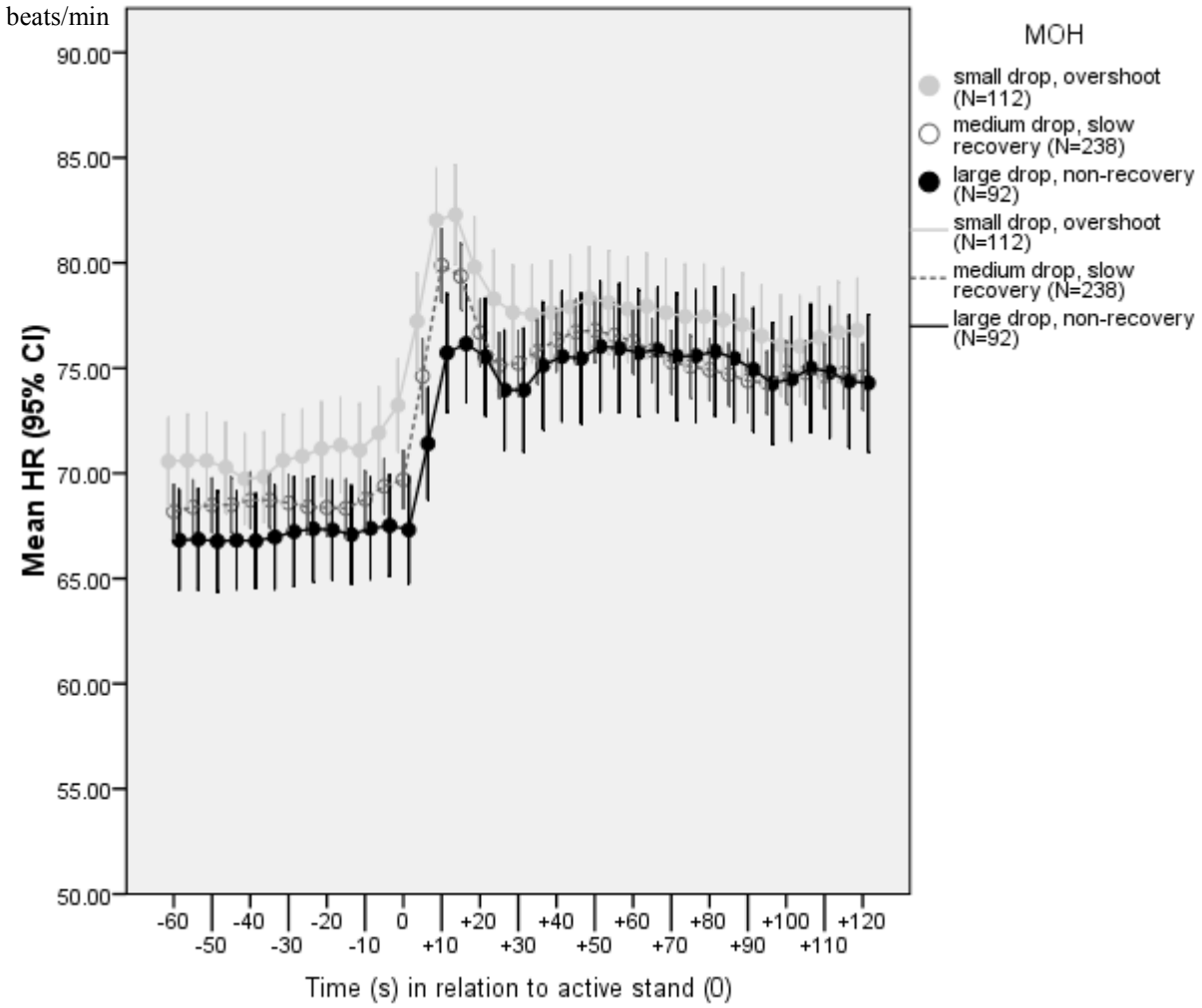


Figure 6.5c. Comparison of orthostatic heart rate (HR) profiles between the morphological orthostatic hypotension (MOH) subgroups.



Orthostatic intolerance (OI): prevalence, hemodynamic profiles, demographics and association with falls

OI, used as an OH definition, classified 126 subjects (28.5%) as having OH. Table 6.6 compares OI – and OI + subjects according to hemodynamic markers and subgroup prevalences of falls. Figures 6.6a-c show the 5-second-averaged hemodynamic profiles of the two subgroups for SBP, DBP and HR, respectively.

Systolic blood pressure (SBP) profiles

OI – and OI + groups were not significantly different in baseline, but OI – had a significantly smaller delta (34.0 mmHg) than OI + (40.4 mmHg) ($P < 0.001$). In terms of recoverability (OI – *vs*. OI +), there were significant differences in phase 1 (154.4 mmHg *vs*. 144.7 mmHg, $P = 0.001$), phase 2 (156.5 mmHg *vs*. 148.2 mmHg, $P = 0.004$), phase 3 (159.2 mmHg *vs*. 151.6 mmHg, $P = 0.009$), and phase 4 (159.1 mmHg *vs*. 150.4 mmHg, $P = 0.003$) (Table 6.6). Figure 6.6a visually suggests the differences, in the form of lack of overlap between 95% confidence intervals around delta and all four recovery phases.

Diastolic blood pressure (DBP) profiles

OI – and OI + groups were not significantly different in baseline, but OI – had a trend towards smaller delta (22.9 mmHg) than OI + (26.0 mmHg) ($P = 0.015$). There were no other statistically significant differences in DBP (Table 6.6). Figure 6.6b shows generalised overlap between 95% confidence intervals.

Heart rate (HR) profiles

There were no significant differences between OI – and OI + (Table 6.6, Figure 6.6c).

Age and gender

There were no significant differences between OI – and OI + (Table 6.6).

Falls

In terms of the presence of falls in the last 6 months (OI – *vs*. OI +), there was a statistically significant difference between the two subgroups (9.9% *vs*. 21.4%, $P < 0.001$) (Table 6.6).

Table 6.6. Orthostatic intolerance (OI): sample prevalence, hemodynamic profiles, demographics and association with falls.

	OI – (N = 316)	OI + (N = 126)	P value for difference
Systolic blood pressure (SBP)			
Baseline SBP (mmHg)	160.9 (24.6)	159.6 (23.7)	0.615$^{\Omega}$
Delta SBP (mmHg)	34.0 (18.2)	40.4 (18.8)	**<0.001**$^{\prod}$
Recovery 1: mean SBP (mmHg) (SE)	154.4 (1.6)	144.7 (2.5)	**0.001**$^{\infty}$
Recovery 2: mean SBP (mmHg) (SE)	156.5 (1.5)	148.2 (2.4)	**0.004**$^{\infty}$
Recovery 3: mean SBP (mmHg) (SE)	159.2 (1.5)	151.6 (2.4)	**0.009**$^{\infty}$
Recovery 4: mean SBP (mmHg) (SE)	159.1 (1.6)	150.4 (2.5)	**0.003**$^{\infty}$
Diastolic blood pressure (DBP)			
Baseline DBP (mmHg)	78.6 (11.4)	78.6 (11.5)	0.992$^{\Omega}$
Delta DBP (mmHg)	22.9 (11.9)	26.0 (11.5)	*0.015*$^{\Omega}$
Recovery 1: mean DBP (mmHg) (SE)	72.1 (0.8)	69.5 (1.3)	0.094$^{\infty}$
Recovery 2: mean DBP (mmHg) (SE)	75.6 (0.7)	73.3 (1.2)	0.095$^{\infty}$
Recovery 3: mean DBP (mmHg) (SE)	76.6 (0.7)	74.2 (1.2)	0.083$^{\infty}$
Recovery 4: mean DBP (mmHg) (SE)	76.2 (0.7)	74.0 (1.2)	0.107$^{\infty}$
Heart rate (HR)			
Baseline HR (bpm)	68.8 (10.7)	68.4 (10.2)	0.705$^{\Omega}$
Delta HR (bpm)	14.2 (7.0)	15.3 (11.7)	0.790$^{\prod}$
Recovery 1: mean HR (bpm) (SE)	76.1 (0.7)	76.5 (1.1)	0.756$^{\infty}$
Recovery 2: mean HR (bpm) (SE)	76.5 (0.7)	77.1 (1.1)	0.635$^{\infty}$
Recovery 3: mean HR (bpm) (SE)	75.7 (0.7)	76.1 (1.1)	0.728$^{\infty}$
Recovery 4: mean HR (bpm) (SE)	75.0 (0.7)	75.4 (1.1)	0.799$^{\infty}$
Demographics			
Age (years): mean (SD)	72.0 (7.0)	72.5 (7.4)	0.596$^{\prod}$
Female gender (%)	72.0	72.2	0.958$^{\chi}$
Falls			
≥ 1 fall in the last 6 months (%)	9.9	21.4	**0.001**$^{\chi}$

$^{\Omega}$ Independent samples t-test; $^{\prod}$ Mann-Whitney U test; $^{\infty}$ Repeated measures ANOVA; $^{\chi}$ Chi-squared test; SD: standard deviation; SE: standard error. Significant P values ($P < 0.01$) are highlighted in bold; statistical trends ($P < 0.05$) are in italics.

Figure 6.6a. Comparison of orthostatic systolic blood pressure (SBP) profiles between the orthostatic intolerance (OI) subgroups: OI – (*N* = 316); OI + (*N* = 126).

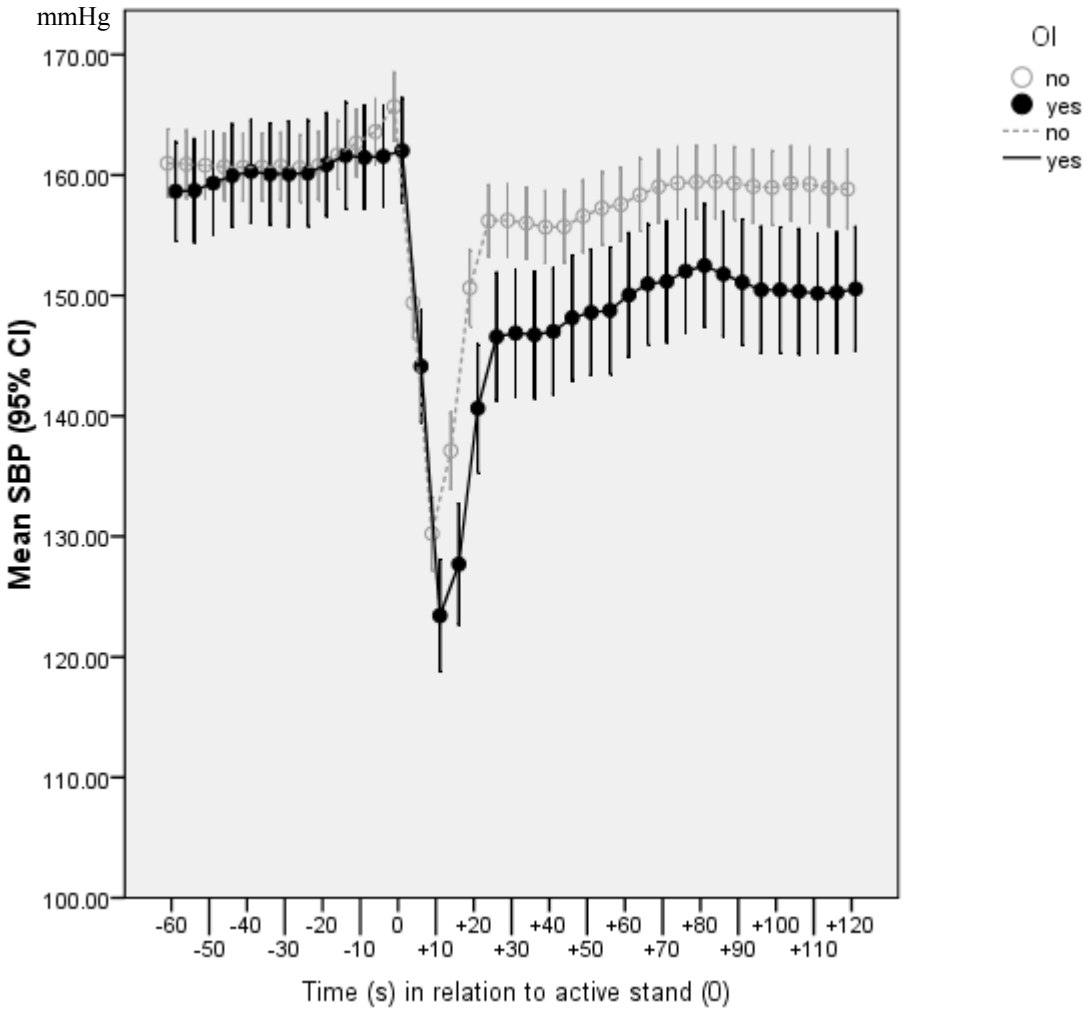


Figure 6.6b. Comparison of orthostatic diastolic blood pressure (DBP) profiles between the orthostatic intolerance (OI) subgroups: OI – (*N* = 316); OI + (*N* = 126).

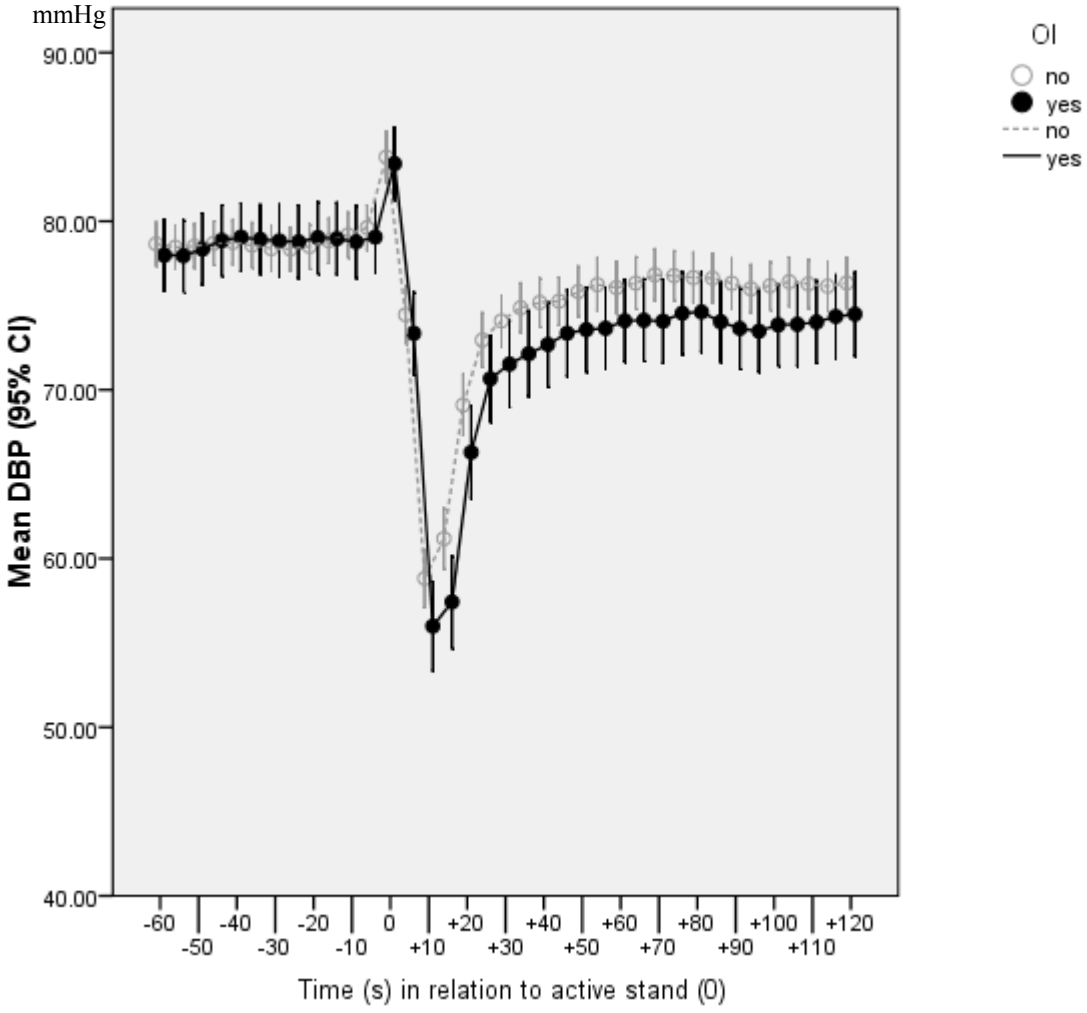
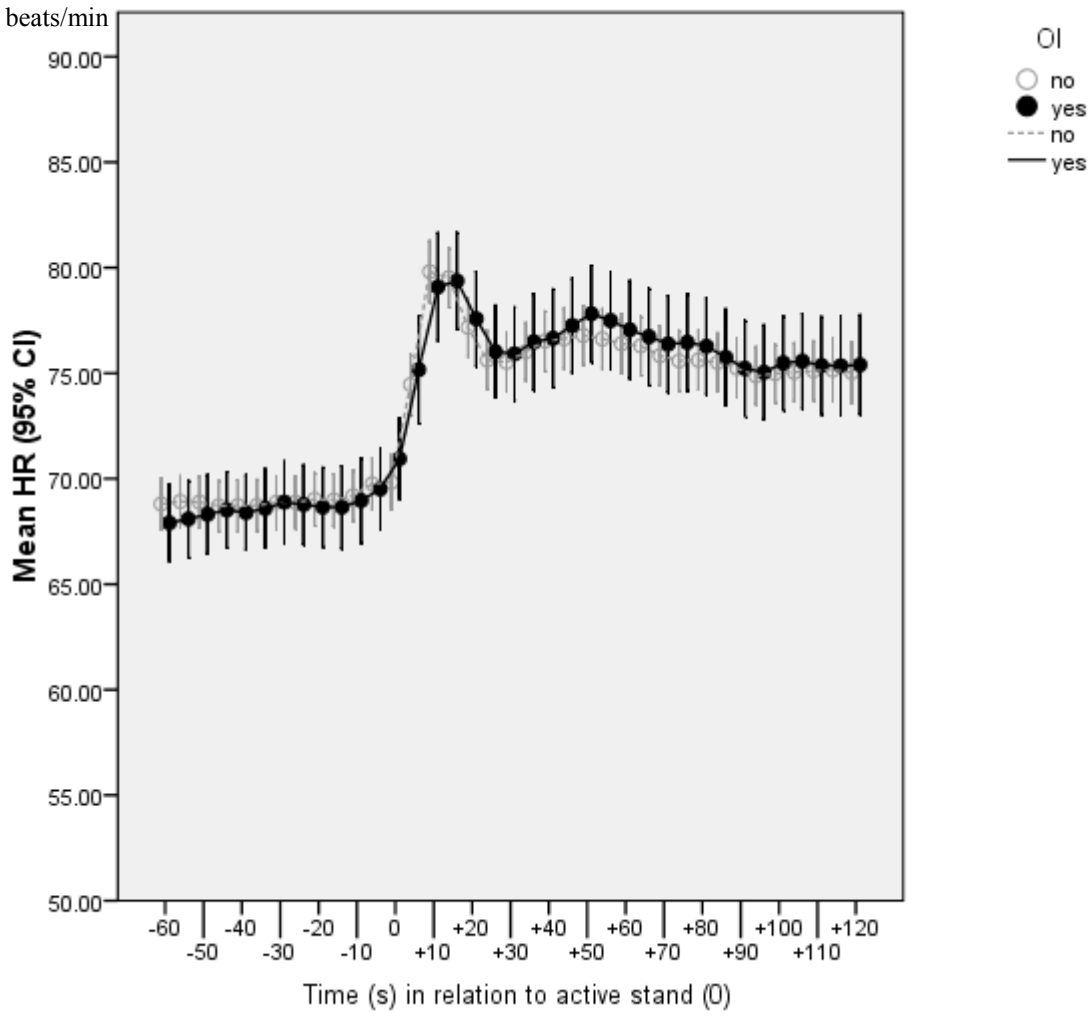


Figure 6.6c. Comparison of orthostatic heart rate (HR) profiles between the orthostatic intolerance (OI) subgroups: OI – (*N* = 316); OI + (*N* = 126).



Initial orthostatic hypotension (IOH) definition: prevalence, hemodynamic profiles, demographics and association with falls

IOH classified 85 subjects (19.2%) as having OH. Table 6.7 compares IOH – and IOH + subjects according to hemodynamic markers and subgroup prevalences of falls. Figures 6.7a-c show the 5-second-averaged hemodynamic profiles of the two subgroups for SBP, DBP and HR, respectively.

Systolic blood pressure (SBP) profiles

IOH – and IOH + groups were not significantly different in baseline, but IOH – had a significantly smaller delta (32.8 mmHg) than IOH + (48.6 mmHg) ($P < 0.001$). In terms of recoverability (IOH – *vs*. IOH +), there were significant differences in phase 1 (153.9 mmHg *vs*. 141.8 mmHg, $P < 0.001$) and phase 2 (155.9 mmHg *vs*. 146.7 mmHg, $P = 0.005$), and trends towards recoverability differences in phase 3 (158.6 mmHg *vs*. 150.5 mmHg, $P = 0.014$) and phase 4 (158.2 mmHg *vs*. 149.7 mmHg, $P = 0.012$) (Table 6.7). Figure 6.7a visually suggests these differences, in the form of lack of overlap between 95% confidence intervals around delta and first and second recovery phases.

Diastolic blood pressure (DBP) profiles

IOH – and IOH + groups were not significantly different in baseline, but IOH – had a significantly smaller delta (22.0 mmHg) than IOH + (31.3 mmHg) ($P < 0.001$). In terms of recoverability (IOH – *vs*. IOH +), there were significant differences in phase 1 (72.5 mmHg *vs*. 66.3 mmHg, $P < 0.001$), phase 2 (75.9 mmHg *vs*. 71.0 mmHg, $P = 0.002$), and phase 3 (76.7 mmHg *vs*. 72.4 mmHg, $P = 0.006$), and a trend towards recoverability difference in phase 4 (76.3 mmHg *vs*. 72.6 mmHg, $P = 0.020$) (Table

6.7). Figure 6.7b visually suggests these differences, in the form of a lack of overlap between 95% confidence intervals around delta and first, second and third recovery phases.

Hear rate (HR) profiles

There were no significant differences between IOH – and IOH + (Table 6.7, Figure 6.7c).

Age and gender

There were no significant differences between IOH – and IOH + (Table 6.7).

Orthostatic intolerance (OI) and falls

11.5% of IOH – had OI, while 100% of IOH + had OI as required by the definition ($P < 0.001$). In terms of the presence of falls in the last 6 months (IOH – *vs*. IOH +), there was a statistically significant difference between the two subgroups (10.4% *vs*. 24.7%, $P < 0.001$) (Table 6.7).

Table 6.7. Initial orthostatic hypotension (IOH) definition: sample prevalence, hemodynamic profiles, demographics and association with falls.

	IOH – (N = 357)	IOH + (N = 85)	P value for difference
Systolic blood pressure (SBP)			
Baseline SBP (mmHg)	159.6 (24.2)	164.3 (24.5)	0.113$^{\Omega}$
Delta SBP (mmHg)	32.8 (18.2)	48.6 (14.2)	**<0.001**$^{\prod}$
Recovery 1: mean SBP (mmHg) (SE)	153.9 (1.5)	141.8 (3.0)	**<0.001**$^{\infty}$
Recovery 2: mean SBP (mmHg) (SE)	155.9 (1.4)	146.7 (3.0)	**0.005**$^{\infty}$
Recovery 3: mean SBP (mmHg) (SE)	158.6 (1.4)	150.5 (3.0)	*0.014*$^{\infty}$
Recovery 4: mean SBP (mmHg) (SE)	158.2 (1.5)	149.7 (3.0)	*0.012*$^{\infty}$
Diastolic blood pressure (DBP)			
Baseline DBP (mmHg)	78.3 (11.5)	79.9 (10.7)	0.222$^{\Omega}$
Delta DBP (mmHg)	22.0 (11.9)	31.3 (8.5)	**<0.001**$^{\Omega}$
Recovery 1: mean DBP (mmHg) (SE)	72.5 (0.8)	66.3 (1.5)	**<0.001**$^{\infty}$
Recovery 2: mean DBP (mmHg) (SE)	75.9 (0.7)	71.0 (1.4)	**0.002**$^{\infty}$
Recovery 3: mean DBP (mmHg) (SE)	76.7 (0.7)	72.4 (1.4)	**0.006**$^{\infty}$
Recovery 4: mean DBP (mmHg) (SE)	76.3 (0.7)	72.6 (1.4)	*0.020*$^{\infty}$
Heart rate (HR)			
Baseline HR (bpm)	69.0 (10.6)	67.4 (10.4)	0.227$^{\Omega}$
Delta HR (bpm)	14.3 (7.0)	15.5 (13.6)	0.930$^{\prod}$
Recovery 1: mean HR (bpm) (SE)	76.4 (0.7)	75.4 (1.3)	0.498$^{\infty}$
Recovery 2: mean HR (bpm) (SE)	76.7 (0.7)	76.5 (1.4)	0.856$^{\infty}$
Recovery 3: mean HR (bpm) (SE)	75.9 (0.7)	75.6 (1.4)	0.830$^{\infty}$
Recovery 4: mean HR (bpm) (SE)	75.1 (0.7)	75.2 (1.3)	0.983$^{\infty}$
Demographics			
Age (years): mean (SD)	71.9 (6.9)	73.2 (7.8)	0.231$^{\prod}$
Female gender (%)	72.1	71.8	0.949$^{\chi}$
Falls			
≥ 1 fall in the last 6 months (%)	10.4	24.7	**<0.001**$^{\chi}$

$^{\Omega}$ Independent samples t-test; $^{\prod}$ Mann-Whitney U test; $^{\infty}$ Repeated measures ANOVA; $^{\chi}$ Chi-squared test; $^{\int}$ Fisher's exact test (2-sided); SD: standard deviation; SE: standard error. Significant P values ($P < 0.01$) are highlighted in bold; statistical trends ($P < 0.05$) are in italics.

Figure 6.7a. Comparison of orthostatic systolic blood pressure (SBP) profiles between initial orthostatic hypotension (IOH) subgroups: IOH – (*N* = 357); IOH + (*N* = 85).

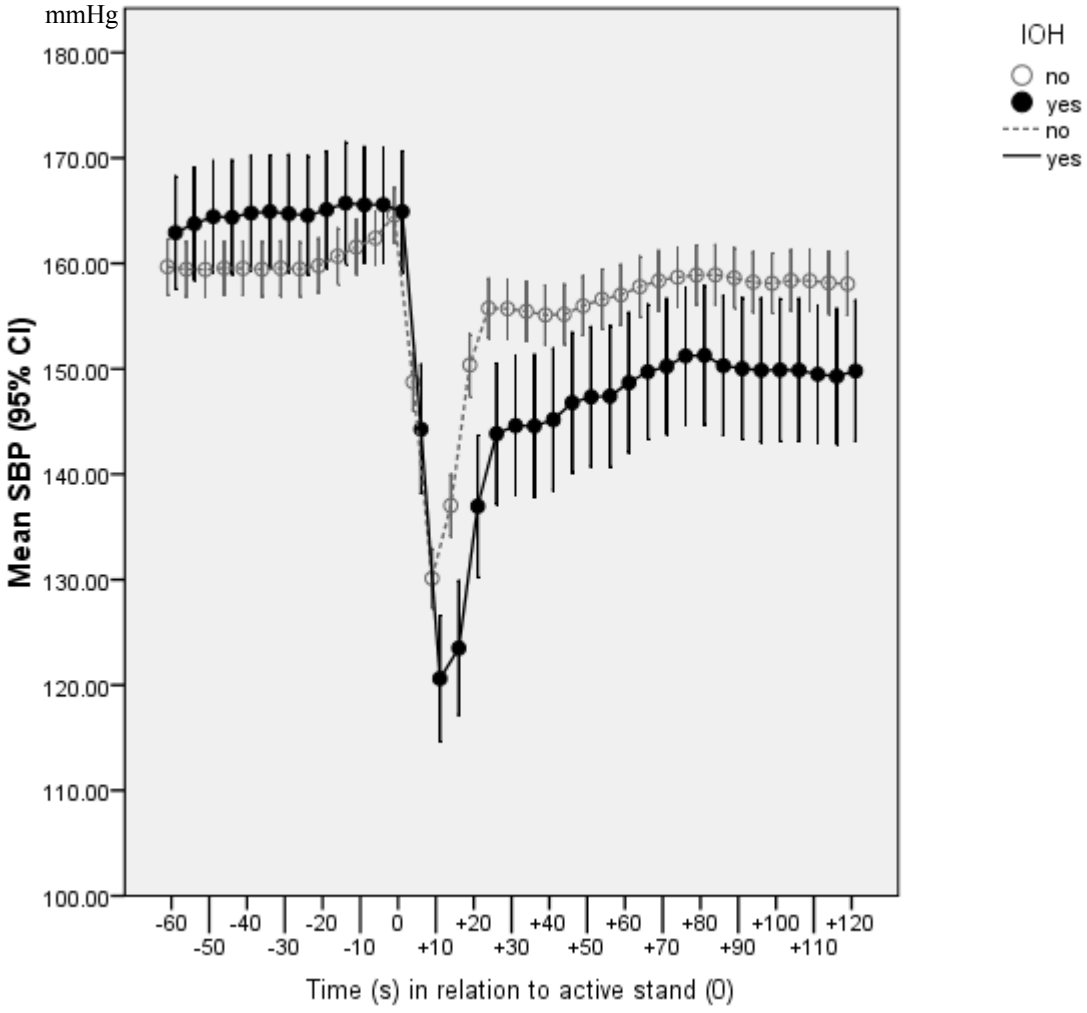


Figure 6.7b. Comparison of orthostatic diastolic blood pressure (DBP) profiles between initial orthostatic hypotension (IOH) subgroups: IOH – (*N* = 357); IOH + (*N* = 85).

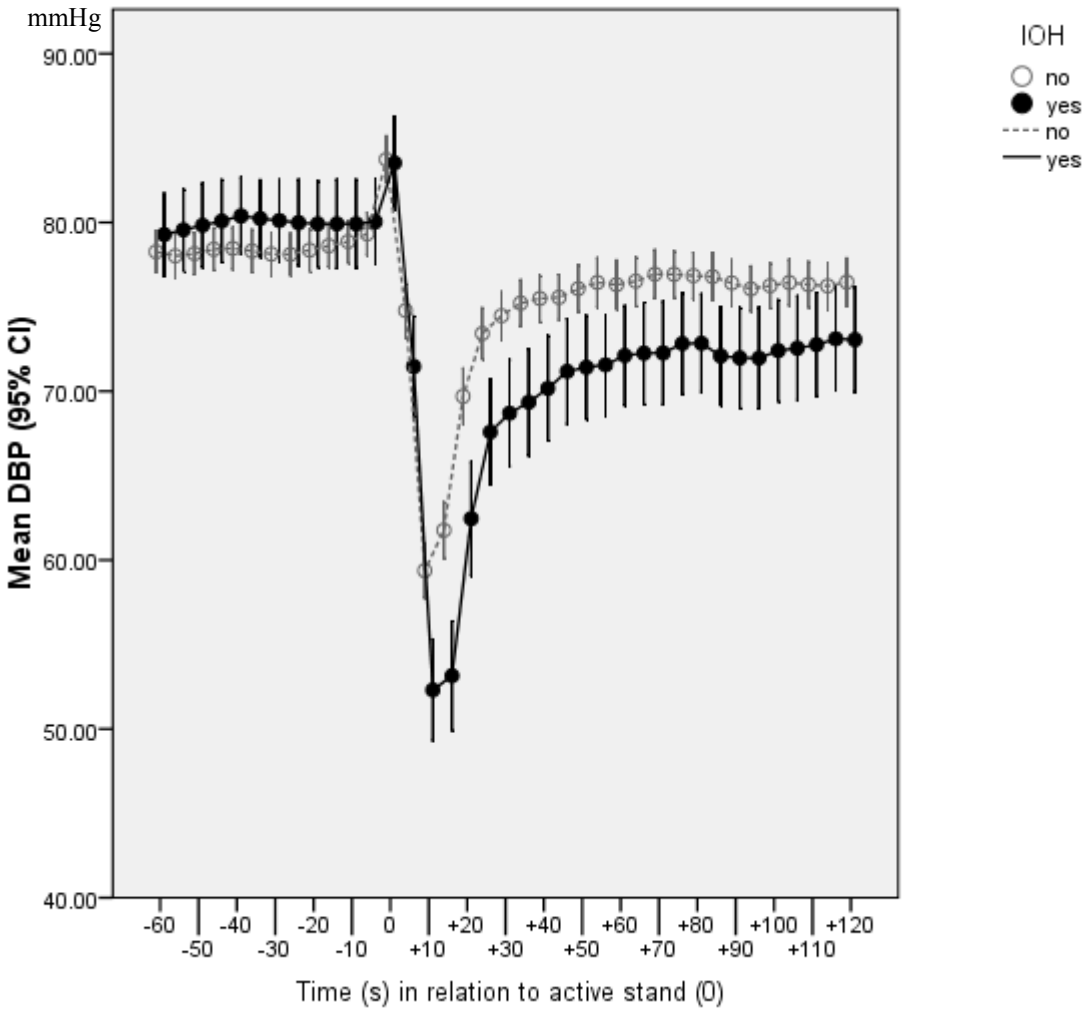
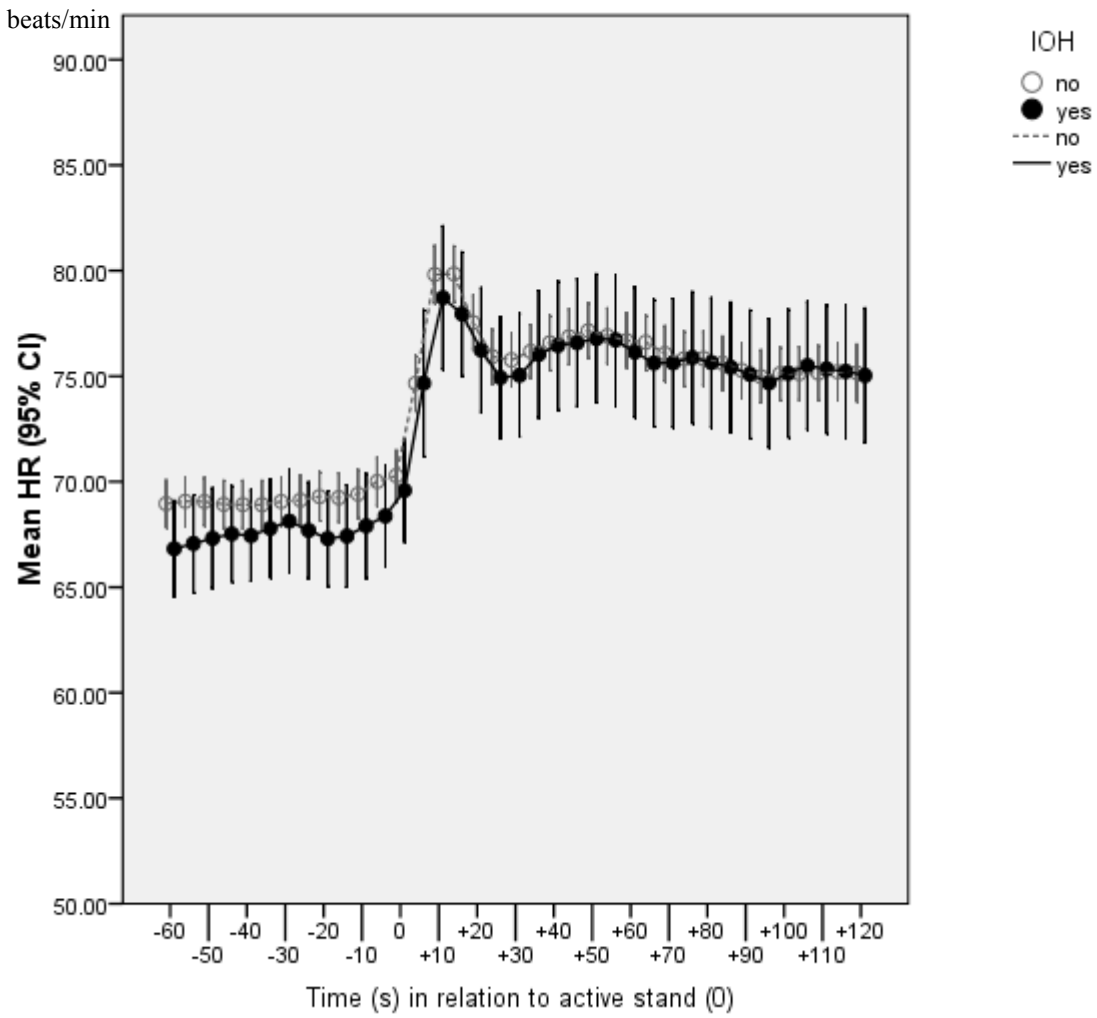


Figure 6.7c. Comparison of orthostatic heart rate (HR) profiles between initial orthostatic hypotension (IOH) subgroups: IOH – (*N* = 357); IOH + (*N* = 85).



Comparison of the five orthostatic hypotension (OH) classifications

Prevalences of OH

The prevalence of OH in the sample was *highly variable* according to the definition considered: 19.2% (IOH), 20.8% (MOH-Cluster 3), 28.5% (OI), 74.6% (MOH-Clusters 2+3), 93.2% (FOH), and 94.1% (COH).

The application of the COH/FOH definitions to beat-to-beat orthostatic data resulted in labelling as *pathological* over 90% of subjects in this sample of relatively healthy older people, suggesting a *lack of specificity* for the diagnosis of OH. This echoes previous concerns as to the usefulness of the COH definition when orthostatic responses are obtained via continuous non-invasive measurement of finger arterial blood pressure (15, 16).

IOH, MOH-Cluster 3 and OI had sample prevalences in keeping with the reported prevalence of OH in population-based samples (17-19). However, the assessment of the sample prevalences found in this study is difficult in the absence of an accepted gold standard for the definition of OH when continuous non-invasive measurement of finger arterial blood pressure is used.

Comparison of systolic blood pressure (SBP) profiles

Of the five OH definitions considered, MOH was the only one that captured differences in baseline SBP, and this is interesting because baseline SBP was *not* used as a *K*-means clustering criterion. The increasing baseline SBP gradient across MOH clusters,

together with the increasing gradient in delta SBP (NB: the latter *was* a clustering criterion), is consistent with previous research reporting a significant correlation between baseline blood pressure and orthostatic blood pressure drop (35, 454, 455). In the overall sample (N = 442), baseline and delta SBP were significantly correlated: r (440) = 0.26, $P < 0.001$.

In terms of delta SBP, all five OH definitions captured highly significant differences between their orthostatic subgroups (all with $P < 0.001$). The absolute delta differences between positive and negative subgroups were 45.7 mmHg (MOH Cluster 3–Cluster 1) 30.7 mmHg (COH), 28.3 mmHg (FOH), 15.8 mmHg (IOH), and 6.4 mmHg (OI).

Another common feature of all OH definitions was that they established statistically significant subgroup differences in the *first phase* of SBP recovery (i.e. 16 – 30 seconds after stand), with all OH + groups having lower mean SBP; the absolute differences were 33.1 mmHg (MOH Cluster 1–Cluster 3), 16.8 mmHg (FOH), 15.4 mmHg (COH), 12.1 mmHg (IOH), and 9.7 mmHg (OI).

Beyond recovery phase 1 (i.e. beyond 30 seconds post-stand), the only definitions that established subgroup differences in SBP recovery were MOH (all recovery phases significantly different), OI (all recovery phases significantly different), and IOH (significant difference in phase 2 and trends towards significance in phases 3 and 4).

Comparison of diastolic blood pressure (DBP) profiles

None of the OH definitions captured differences in baseline DBP. For delta DBP, all definitions but one (OI) captured significant differences between orthostatic subgroups ($P < 0.001$), with OI having a trend towards significance ($P = 0.015$). The absolute delta DBP differences between OH + and OH – subgroups were 22.4 mmHg (MOH Cluster 3–Cluster 1), 21.5 mmHg (COH), 21.4 mmHg (FOH), 9.3 mmHg (IOH), and 3.1 mmHg (OI).

OI was the only OH definition where differences in DBP recoverability could not be demonstrated. The other four definitions established statistically significant subgroup differences in the *first phase* of DBP recovery, with all OH + groups having lower mean DBP; the absolute differences were 17.6 mmHg (MOH Cluster 1–Cluster 3), 12.4 mmHg (COH), 12.0 mmHg (FOH), and 6.2 mmHg (IOH).

Beyond recovery phase 1 (i.e. beyond 30 seconds post-stand), the only definitions that established subgroup differences in DBP recoverability were MOH (all recovery phases), IOH (phases 2 and 3 and a trend in phase 4), FOH (phase 2 and trends in phases 3 and 4), and COH (only a trend in phase 2).

Comparison of heart rate (HR) profiles

MOH was the only definition suggesting differences in orthostatic HR dynamics, which is again interesting as HR variables were not used for clustering (N.B. clustering variables are *expected* to be different between clusters, because the K-means clustering algorithm aims at maximising between-cluster differences on the clustering variables).

Demographic comparison

None of the five OH definitions considered revealed statistically significant differences in age or gender. Interestingly, in this sample there was a lack of gender differences in OI despite previous reports that OI may be more prevalent in women than in men (456, 457).

Comparison of clinical parameters (i.e. orthostatic intolerance and falls)

Neither COH nor FOH had significant associations with OI or falls. This is consistent with previous reports that COH was not found to be an independent predictor of falls in frail nursing home residents (458, 459).

The MOH classification resulted in an *increasing gradient of OI* across subgroups ($P < 0.001$), and although the prevalences of falls across subgroups seemed to conform to an increasing gradient (9.8%, 13.0%, 17.4%), the trend statistic did not reach significance ($P = 0.113$). The observation that MOH (based on SBP variables) was associated with OI is consistent with a published pilot study by the candidate (based on part of the same sample) that OI during an active stand test is specially related to the rate of recovery of SBP (i.e. as modelled in the MOH definition) during the first 30 seconds after active stand (49). In the present sample ($N = 442$), 24 out of 45 (53.3%) subjects not recovering at least 80% of their baseline SBP by 30 seconds after stand complained of OI; among those who did recover at least 80% of their SBP baseline by 30 seconds ($N = 395$), a significantly lower proportion ($N = 102$, 25.8%) reported OI (Chi-squared = 14.96, df = 1, $P < 0.001$). Interestingly, the IOH definition (which includes OI) also revealed an SBP *recovery deficit* in IOH + subjects (Table 6.7, Figure 6.7a), which

could perhaps explain why so few subjects had *transient* IOH as per original Wieling *et al*.'s definition.

To replicate the previous interim finding that SBP recoverability is the best predictor of OI in the face of delta and nadir SBP, age, gender and Mini-Mental State Examination (MMSE) score (49), the multivariate binary logistic regression model shown in Table 6.8 was computed.

When all six predictor variables were considered together, they significantly predicted whether or not a subject was symptomatic, $\chi^2 = 18.49$, $df = 6$, $N = 442$, $P = 0.005$. The Nagelkerke "pseudo" R^2 estimate was 0.059 indicating that approximately 6% of the variance in whether or not subjects were symptomatic can be predicted from the linear combination of the independent variables. Overall, 71.2% of the subjects were predicted correctly; however, the model was much better at predicting who would be asymptomatic (94.6% correct) than who would be symptomatic (13.5% correct).

An examination of the variables in the equation revealed that only the variable indicating *at least 80% of the baseline SBP recovered by 30 seconds* after stand was significant, $B = -0.81$, $SE = 0.37$, 95% CI for Odds Ratio = 0.22 – 0.92, $P = 0.030$.

Table 6.8. Multivariate binary logistic regression predicting orthostatic intolerance (OI).

	B	S.E.	Wald	*P*	Odds Ratio	95.0% C.I. for Odds Ratio	
						Lower	Upper
Delta SBP	0.008	0.007	1.407	0.236	1.008	0.995	1.022
Nadir SBP	-0.006	0.005	1.697	0.193	0.994	0.984	1.003
At least 80% baseline SBP recovery by 30 s.	-0.806	0.371	4.727	*0.030*	0.447	0.216	0.924
Gender	0.097	0.246	0.156	0.693	1.102	0.681	1.783
Age	0.003	0.016	0.036	0.849	1.003	0.972	1.035
MMSE	-0.007	0.060	0.012	0.913	0.993	0.884	1.117
Constant	0.163	2.362	0.005	0.945	1.176		

The above logistic regression finding is consistent with the fact that MOH, which was the only definition not including OI that established differences in SBP recoverability *beyond 30 seconds* post-stand, had significant association with OI (Table 6.9). Another interesting point is that definitions including OI (i.e. OI itself and IOH) had significant associations with previous falls (Table 6.9), suggesting a *clinical-clinical* correlation (i.e. *clinical* OH definitions correlating with *clinical* outcomes) and that *OI could be a mediator between OH and falls*. In the next chapter the candidate introduces *structural equation modelling* as a statistical technique to assess how the data supports causal hypotheses like the latter.

Table 6.9. Summary comparison of the five OH definitions: prevalence, demographics, SBP profiles and association with orthostatic intolerance (OI) and falls.

	Consensus (COH)	Fedorowski (FOH)	Morphological (MOH)	OI	Initial OH (IOH)
Sample prevalence	94.1%	93.2%	20.8% (MOH-3)	28.5%	19.2%
Age	-	-	-	-	-
Gender	-	-	-	-	-
Differences in baseline SBP	-	-	+	-	-
Differences in delta SBP	+	+	+	+	+
Differences in R1 phase (<30s)	+	+	+	+	+
Differences in R2 phase (<60s)	-	-	+	+	+
Differences in R3 phase (<90s)	-	-	+	+	(+)
Differences in R4 phase (<120s)	-	-	+	+	(+)
Differences in OI	-	-	+	+*	+*
Differences in falls history	-	-	-	+	+

+ indicates statistically significant association ($P < 0.01$).
(+) indicates statistical trend towards association ($P < 0.05$).
- indicates no statistically significant association ($P \geq 0.05$).
* OI is included in the OH definition.

Chapter 7

Using structural equation modelling to hypothesise causal relationships between orthostatic hemodynamic and clinical variables

In this chapter, *structural equation modelling* (SEM) is used to explore how the data supports postulated causal relationships between orthostatic hemodynamic and clinical variables. Each of the orthostatic hypotension definitions, i.e. *consensus* (COH), *Fedorowski-modified* (FOH), *initial* (IOH), *morphological* (MOH) and *orthostatic intolerance* (OI) is postulated as a cause of falls (controlling by age) and, as appropriate, of OI. A basic pathophysiological model of postulated relationships between orthostatic systolic blood pressure variables, OI and previous falls is tested.

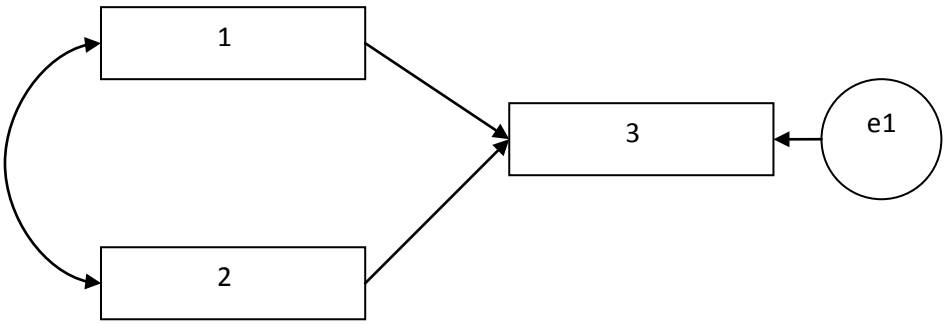
Structural equation modelling (SEM): an existing technique in a new field

Structural equation modelling (SEM), also referred to as *path analysis*, is an advanced, multivariable statistical technique that allows the assessment of the *statistical plausibility* of *postulated* causal relationships in cross-sectional, non-experimental research (460, 461). SEM has been a popular technique in the social and behavioural sciences, but has been less used in medical research. To the knowledge of the candidate, SEM has not been previously applied to the clinical study of orthostatic hemodynamics, so this represents a new methodological contribution to the field.

Although SEM has been referred to as *causal modelling*, it *does NOT* allow the inference of causality. Attributing causality is a design, not a statistical issue (461). The appropriate use of SEM departs from the *postulation* of *clinically plausible* causal relationships, which should be based on substantiated theoretical arguments or preliminary findings. The candidate uses SEM in that light. An advantage of SEM is that it allows the modelling of both *causal* and *correlational* relationships (Figure 7.1).

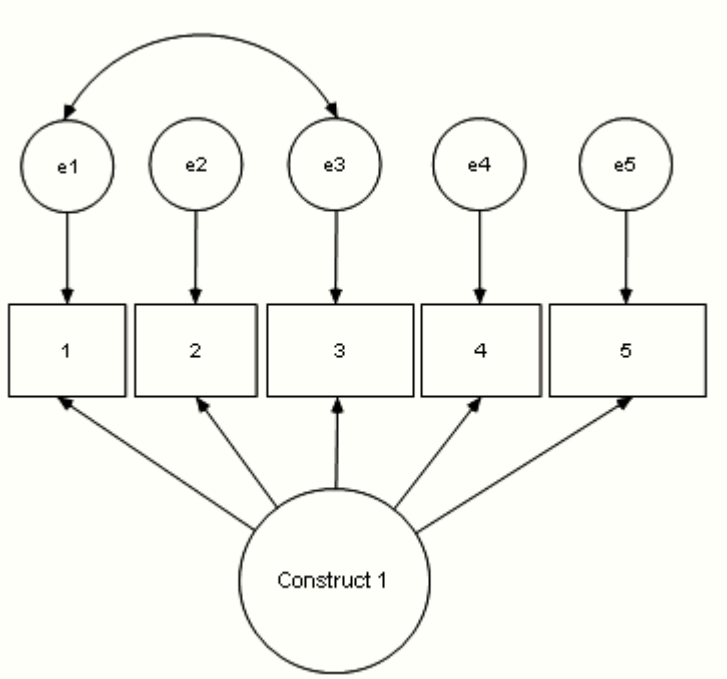
Another advantage of SEM is that it allows both *observed* and *unobserved* variables to be drawn in the models. Observed variables are *measured* variables that are present in the dataset, and are represented by rectangles in the models; unobserved variables are unmeasured and represented by circles. Two types of unobserved variables are used in this investigation: *error terms* and *latent constructs*. An error term (e.g. e1, e2) is drawn as an unobserved 'cause' of an observed variable that has one or more other observed causes; in that context, the error term refers to 'everything else' causing (or explaining) the observed variable in addition to the observed, postulated causes (Figure 7.1).

Figure 7.1. Example of causal model. Observed variables 1 and 2 are postulated as causes of the observed variable 3. Variables 1 and 2 are correlated (i.e. have a covariance). The error term (e1) is 'everything else' that causes variable 3.



Other types of unobserved variables are *latent constructs*, which cannot be measured by one single variable but can be *indicated* by a collection of related measures. In this context, SEM serves the purpose of *confirmatory factor analysis* (461) (Figure 7.2).

Figure 7.2. Example of confirmatory factor analysis using structural equation modelling (SEM). The unobserved construct 1 is postulated as indicated by five observed variables. Each observed variable is indicated by 'everything else' but construct 1. If observed variables 1 and 3 are measured in the same way, their errors may be correlated (i.e. hence the drawn covariance between e1 and e3).



The SEM software used in this investigation is AMOS 16.0 (462). By default, AMOS uses *maximum likelihood* (ML) to compute the parameter estimates, and that method is the one underlying all SEMs presented in the main text of this thesis (with *estimation of means and intercepts* to allow for any missing data). Notably, the ML method does not take into account the measurement level of the observed variables in the model (i.e. treats them all as continuous), resulting in all the standardised regression coefficients deriving from *linear* regression. When the model incorporates categorical *dependent* variables (e.g. dichotomous variables such as falls history: yes or no), an alternative to ML is the *Markov chain Monte Carlo* (MCMC) method, which uses a *probit* model that links the predictor to the categorical response, using a cumulative normal probability function (462, 463). For comparative purposes, the SEMs in this investigation were repeated by the MCMC method and their results are presented in Appendix 7.

Once the causal model has been drawn on the software's screen (AMOS 16.0), ML estimation is run and the programme tests the fit of the model against the data. If the fit indices are favourable, then the model is, *overall*, *supported by the data* (i.e. internally valid); however, the model may not be *externally* valid. External validity is a function of the extent to which the model fits external datasets; but even if it does, causality is not proven if the study design is cross-sectional.

Multiple statistical *fit indices* have been created for ML-SEMs (460). A full review of those indices is outside the scope of this chapter, but Table 7.1 presents a non-statistical summary of the most commonly used ones. The most statistically robust and widely reported are the Chi-squared test and the RMSEA (460).

Table 7.1. Fit indices used for the structural equation models (SEMs) in this investigation.

Fit index name	Fit index type	Fit index values	Value for a good fit
Chi-squared test	Absolute fit measure. The null hypothesis is that the model is correct	Chi-squared statistic with degrees of freedom (df)	$P > 0.05$ (supports the null hypothesis)
NFI (normalised fit index)	Relative fit measure	0.00 – 1.00	> 0.9
IFI (incremental fit index)	Relative fit measure	0.00 – 1.00	> 0.9
TLI (Tucker-Lewis index)	Relative fit measure	0.00 – 1.00	> 0.9
CFI (comparative fit index)	Relative fit measure	0.00 – 1.00	> 0.9
RMSEA (root mean square error of approximation)	Based on the non-central chi-squared distribution. The null hypothesis is that the model is correct	Statistic value with 90% confidence interval and *P* value	RMSEA < 0.05 $P > 0.05$

An important point for the understanding of the SEM outputs is the interpretation of the *standardised regression coefficients* (β) which are shown next to each regression and covariance line in the models. β values range between 0.00 and 1.00, and provide a measure of the *strength* (i.e. effect size) of the regression or correlation. Table 7.2 summarises the approximate effect size of a β coefficient according to its absolute value (464). The sign of a β coefficient can be positive, indicating a direct association (i.e. the higher A, the higher B; or the lower A, the lower B), or negative, indicating an inverse association.

Table 7.2. Effect size (i.e. strength) of a regression/correlation according to the value of the standardised regression coefficient (β).

Standardised regression coefficient values	Effect size
< 0.29	Small
0.30 – 0.59	Medium
≥ 0.6	Large

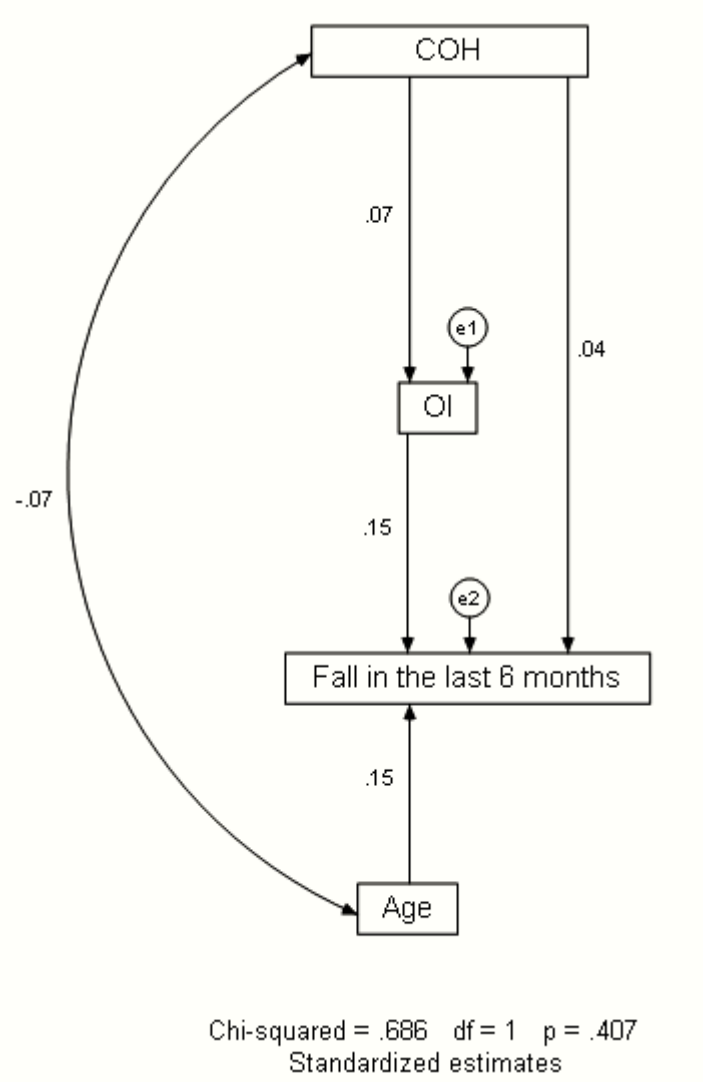
The level of significance for the standardised regression coefficients was established at $P < 0.01$. Trend towards significance was defined as $P < 0.05$.

Modelling causal relationships between orthostatic and clinical variables

To shed light on possible inter-associations between each of the OH definitions, OI and falls, a structural equation model (SEM) was postulated and tested with AMOS 16.0. In the model, it was postulated that OH (differently defined each time) leads to OI, and OI is a cause of being a faller. In addition, OH was postulated as an independent cause of being a faller (i.e. independently of OI). To facilitate the identification of the model and to assess the degree to which OH increases with age (i.e. covariance), age was added to the model. Age was also postulated as an independent influence on being a faller (465). In this model, there were 14 distinct sample moments and 13 distinct parameters to be estimated, allowing for 1 degree of freedom (i.e. 14 – 13). In ML estimation, at least 1 degree of freedom is required to allow computation of probability level (460, 461).

Figure 7.3 shows this causal model for COH. Standardised regression coefficients (β) are shown next to the arrows. The only significant regression coefficients were OI → Faller (β = 0.15, P = 0.002) and Age → Faller (β = 0.15, P = 0.002). The covariance between Age and COH was not significant (β = -0.07, P = 0.118). Overall, the model had a good fit: Chi-squared = 0.686, df = 1, P = 0.407; other fit indices are shown in Table 7.3. The model is consistent with results in Table 6.3 that COH did not have significant bivariate associations with age, OI or falls. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 7.3. Structural equation model (SEM) with postulated relationships between the consensus classification of orthostatic hypotension (COH), orthostatic intolerance (OI), falls and age.



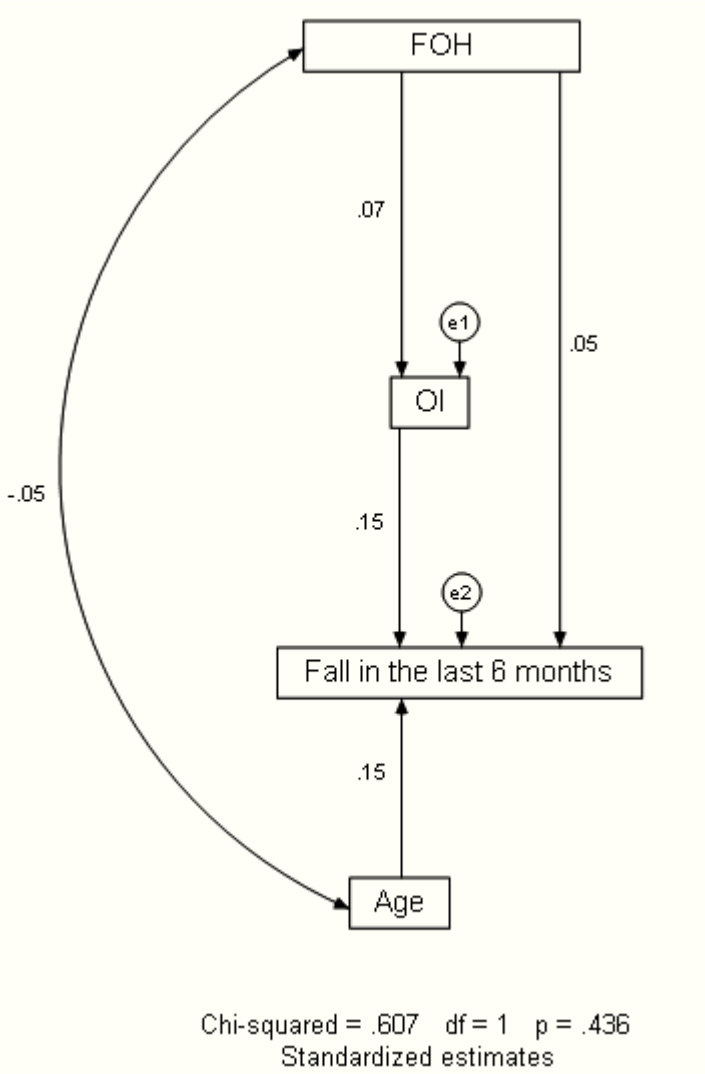
Significant regression coefficients:
OI → Faller (β = 0.15, *P* = 0.002); Age → Faller (β = 0.15, *P* = 0.002).

Table 7.3. Fit indices for the SEM in Figure 7.3.

Fit index	Values
NFI (normalized fit index)	0.97
RFI (relative fit index)	0.74
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.12, *P* = 0.618)

Figure 7.4 shows the same SEM for the Fedorowski-modified orthostatic hypotension definition (FOH). As in the model for COH, the only significant regression coefficients were OI → Faller (β = 0.15, *P* = 0.002) and Age → Faller (β = 0.15, *P* = 0.002). The covariance between Age and COH was not significant (β = -0.05, *P* = 0.340). Overall, the model had a good fit: Chi-squared = 0.607, df = 1, *P* = 0.436; other fit indices are shown in Table 7.4. The model is consistent with results in Table 6.4 that FOH did not have a significant bivariate association with age, OI or falls. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 7.4. Structural equation model (SEM) with postulated relationships between the Fedorowski-modified classification of orthostatic hypotension (FOH), orthostatic intolerance (OI), falls and age.



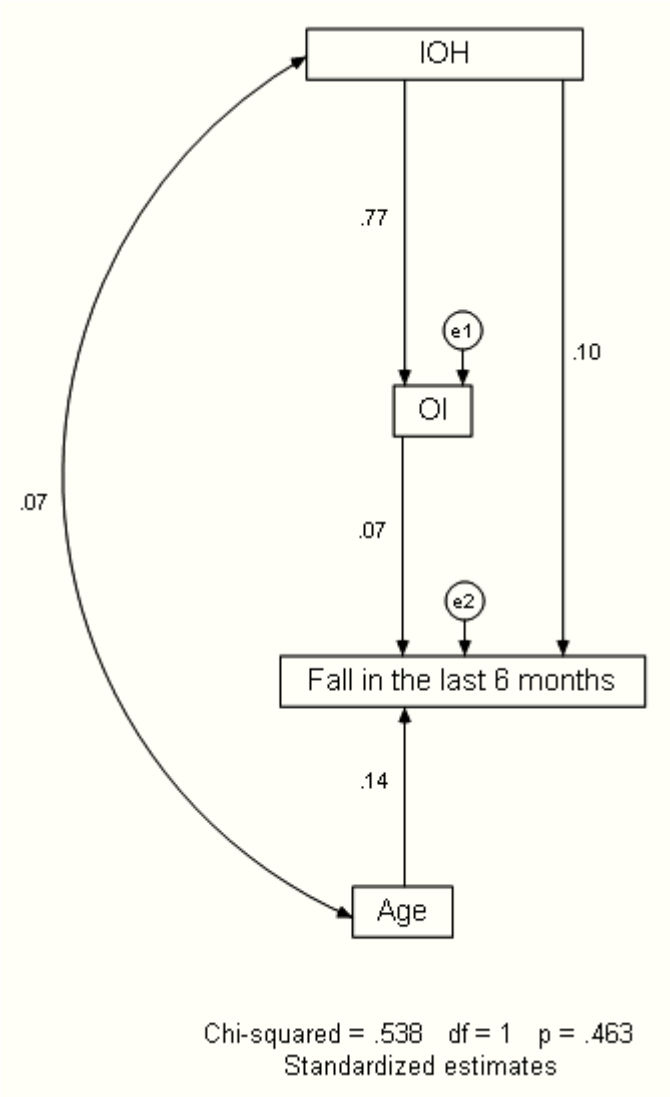
Significant regression coefficients:
OI → Faller (β = 0.15, *P* = 0.002); Age → Faller (β = 0.15, *P* = 0.002).

Table 7.4. Fit indices for the SEM in Figure 7.4.

Fit index	Values
NFI (normalized fit index)	0.98
RFI (relative fit index)	0.76
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.12, *P* = 0.640)

Figure 7.5 shows the SEM for initial orthostatic hypotension (IOH). In this model, the significant regression coefficients were IOH → OI (β = 0.77, $P < 0.001$, as expected from the IOH definition) and Age → Faller (β = 0.14, $P = 0.003$). The covariance between Age and IOH was not significant (β = 0.07, $P = 0.129$). Overall, the model had a good fit: Chi-squared = 0.538, df = 1, $P = 0.463$; other fit indices are shown in Table 7.5. The model does not confirm results in Table 6.7 that IOH had a significant bivariate association with falls. In the SEM model, the regression coefficient IOH → Faller did not reach statistical significance (β = 0.10, $P = 0.167$), in the face of the other predictors included. The MCMC estimation method yielded similar results, but the model fit was poor (posterior predictive $P = 0.00$) (Appendix 7).

Figure 7.5. Structural equation model (SEM) with postulated relationships between the initial orthostatic hypotension classification (IOH), orthostatic intolerance (OI), falls and age.



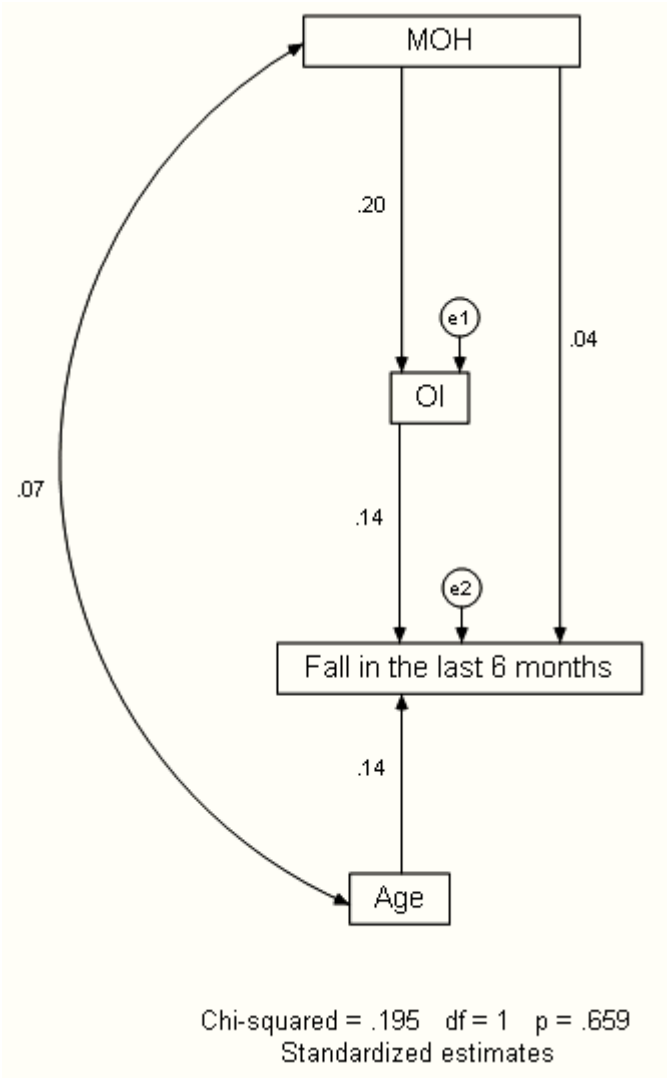
Significant regression coefficients:
IOH → OI ($\beta = 0.77$, $P < 0.001$); Age → Faller ($\beta = 0.14$, $P = 0.003$).

Table 7.5. Fit indices for the SEM in Figure 7.5.

Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	0.99
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.11, $P = 0.662$)

Figure 7.6 shows the SEM for the morphological classification of OH (MOH). The significant regression coefficients were MOH → OI (β = 0.20, $P < 0.001$), OI → Faller (β = 0.14, $P = 0.003$), and Age → Faller (β = 0.14, $P = 0.002$). The covariance between Age and MOH was not significant (β = 0.07, $P = 0.164$). Overall, the model had a good fit: Chi-squared = 0.195, df = 1, $P = 0.659$; other fit indices are shown in Table 7.6. The model supports results in Table 6.5 that MOH had a significant association with OI, but not with falls; it also supports the hypothesis that OI (not included in MOH definition) could be a potential mediator between MOH and falls. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 7.6. Structural equation model (SEM) with postulated relationships between the morphological classification of orthostatic hypotension (MOH), orthostatic intolerance (OI), falls and age.



Significant regression coefficients:
MOH → OI (β = 0.20, $P < 0.001$); OI → Faller (β = 0.14, $P = 0.003$);
Age → Faller (β = 0.14, $P = 0.002$).

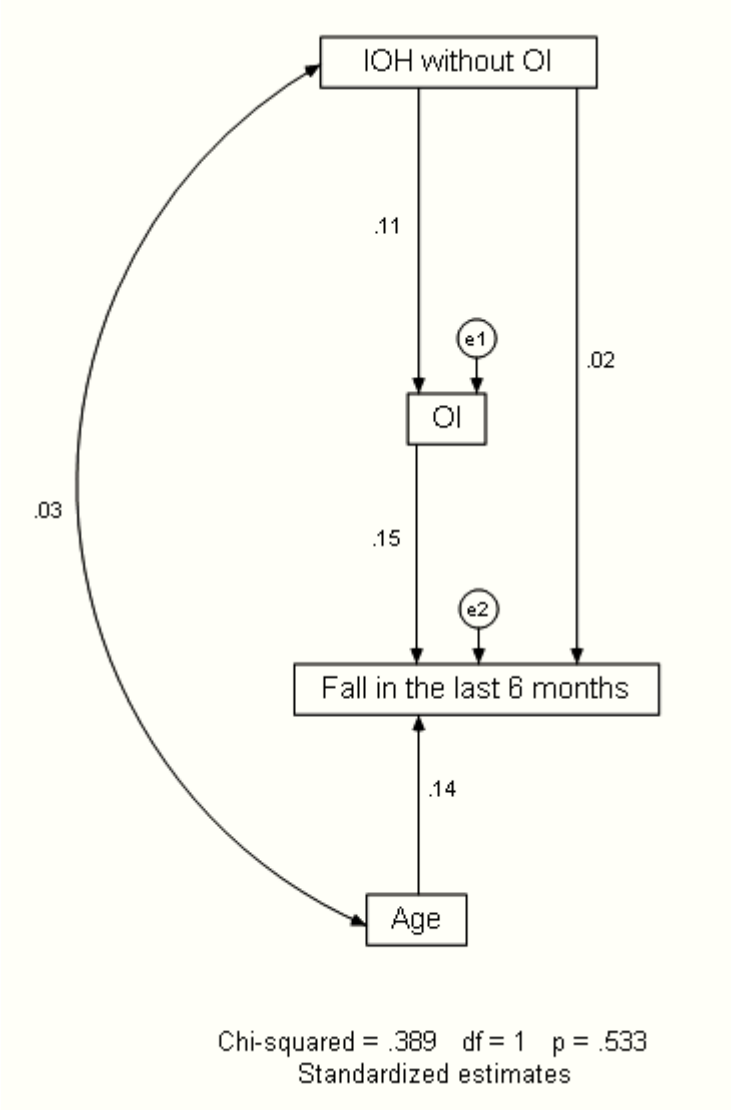
Table 7.6. Fit indices for the SEM in Figure 7.6.

Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	0.95
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.10, $P = 0.796$)

Results from the above models suggest that OI was the best OH definition in terms of the *correlation with falls*, even after adjusting for age. It was also suggested that MOH could have an indirect association with falls *via OI* (Figure 7.6); in addition, a question remained as to whether the significant bivariate association between IOH and falls previously seen in Table 6.7 could have occurred due to the inclusion of OI in the IOH definition.

To shed light on the latter question, a modified IOH definition was created, including the same hemodynamic criteria as in the original IOH definition, but not taking OI into account. The performance of this modified IOH definition in the previously postulated SEM is shown in Figure 7.7. The significant regression coefficients were OI → Faller ($\beta = 0.15$, $P = 0.002$), and Age → Faller ($\beta = 0.14$, $P = 0.002$). IOH-modified → OI had a trend towards significance ($\beta = 0.11$, $P = 0.020$). In the absence of a direct correlation between IOH-modified → Falls ($\beta = 0.02$, $P = 0.725$), it is therefore plausible that, as seen for MOH, the association of IOH with falls could have been mediated by OI. Overall, the model had a good fit: Chi-squared = 0.389, df = 1, $P = 0.533$; other fit indices are shown in Table 7.7. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 7.7. Structural equation model (SEM) with postulated relationships between a modified version of the initial OH classification (i.e. IOH without OI), orthostatic intolerance (OI), falls and age.



Significant regression coefficients:
OI → Faller (β = 0.15, *P* = 0.002); Age → Faller (β = 0.14, *P* = 0.002).
IOH-modified → OI had a trend towards significance (β = 0.11, *P* = 0.020).

Table 7.7. Fit indices for the SEM in Figure 7.7.

Fit index	Values
NFI (normalized fit index)	0.99
RFI (relative fit index)	0.85
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.11, *P* = 0.712)

In view of the suggestion in the above SEMs that OI could be a *mediator* between OH and falls, a further *pathophysiological* SEM was postulated in order to identify the best hemodynamic predictors of OI, and confirm previous preliminary evidence that OI was best predicted by early SBP recoverability in this sample (49). Figure 7.8 shows such a model: baseline SBP determines the degree of SBP drop (delta), and delta influences the percentage of baseline SBP recovered by 30 seconds, OI, and falls. OI is predicted by the percentage of SBP recovered by 30 seconds, and the latter and OI are postulated as causes of being a faller.

In this model, the significant standardised regression coefficients were Baseline SBP → Delta SBP ($\beta = 0.26$, $P < 0.001$), Delta SBP → % Baseline SBP by 30 seconds ($\beta = -0.71$, $P < 0.001$), and OI → Faller ($\beta = 0.14$, $P = 0.003$). The regression coefficient % Baseline SBP by 30 seconds → OI tended towards significance ($\beta = -0.16$, $P = 0.015$). The signs of all the standardised coefficients were as expected (e.g. the higher baseline, the higher delta: positive β; the higher delta, the lower % SBP recovery: negative β). Overall, the model had a good fit: Chi-squared = 3.27, df = 3, $P = 0.351$; other fit indices are shown in Table 7.8. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 7.8. Structural equation modelling (SEM) with postulated relationships between systolic orthostatic hemodynamic variables, orthostatic intolerance (OI), and falls.

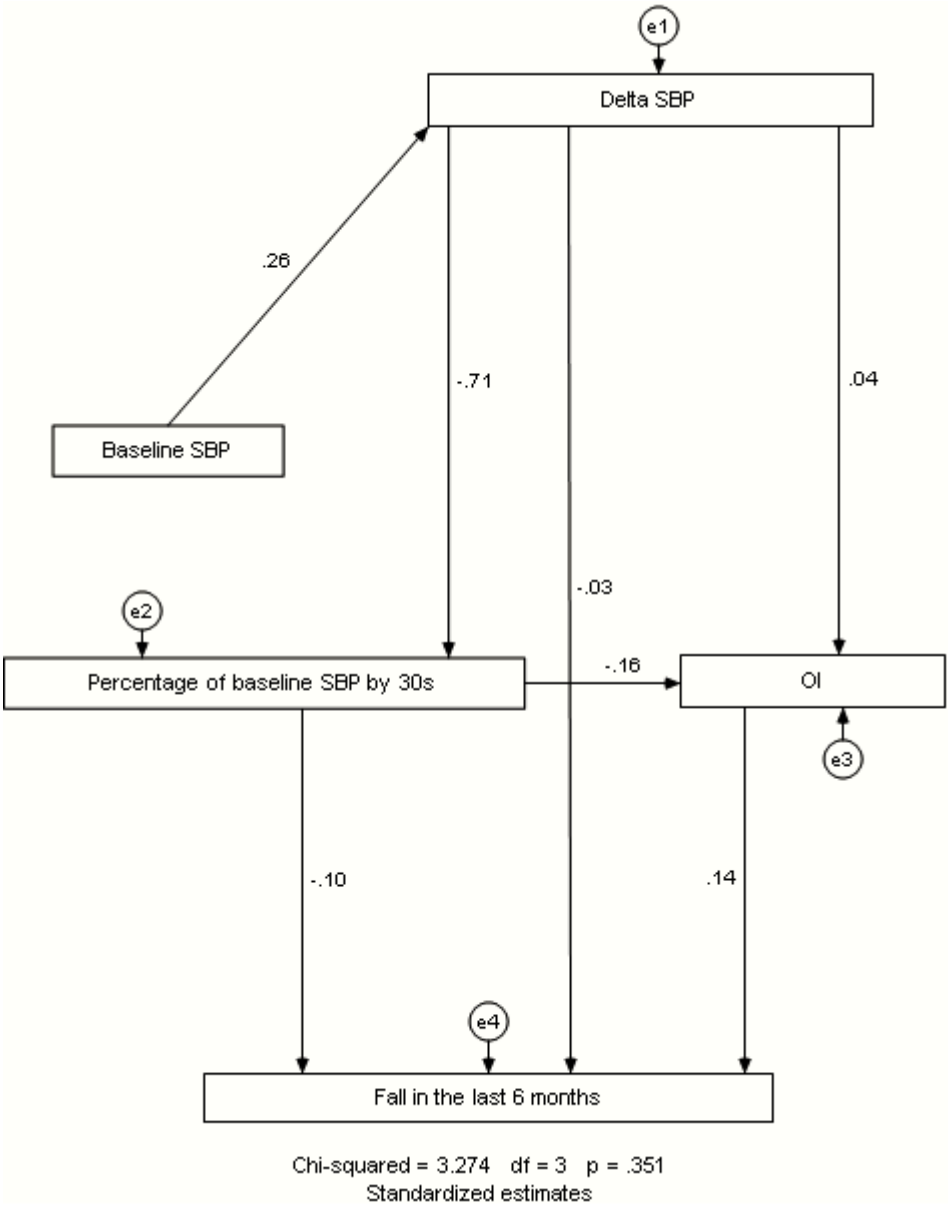


Table 7.8. Fit indices for Figure 7.8.

Fit index	Values
NFI (normalized fit index)	0.99
RFI (relative fit index)	0.96
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.01 (0.00 – 0.08, *P* = 0.723)

Summary of key findings

The results from the SEMs in this chapter suggest the following:

- Of the five OH definitions considered (i.e. consensus, Fedorowski-modified, initial, morphological and orthostatic intolerance), OI was the most consistently associated with previous history of falls.

- OI may be an appropriate OH definition because it has hemodynamic correlates; indeed, the hemodynamic hallmark of OI was a *systolic blood pressure recovery deficit*, which is in keeping with the results of a pilot study by the candidate on part of the same sample, which showed that subjects who recovered at least 80% of their baseline SBP by 30 seconds post-stand were less likely to report OI (49).

- OI could be a *mediator* between a deficit in early SBP recovery and previous falls. The pathophysiological model in Figure 7.8 suggested that delta SBP does not have, *per se*, a direct influence on OI or previous falls. If this model was externally valid, it could have implications for clinical practice, because the clinical assessment of OH is normally focused on delta blood pressure changes and not on the morphology of the blood pressure recovery.

In the following chapter, the concept and operationalisations of frailty are presented, which will be later used to revisit the associations between orthostatic hemodynamic and clinical variables, with a focus on frailty.

Chapter 8

Frailty classifications and their cross-sectional validation

In this chapter, the biopsychosocial concept of frailty is operationalised in the study sample, using two well established methods: Fried's *frailty phenotype* (with some criteria modifications) and Rockwood's *frailty index*. Using each method, the sample is divided into three subgroups of increasing frailty: *non-frail*, *pre-frail* and *frail*. Each classification is cross-sectionally validated in terms of its *concurrent validity* against a wide range of measurements from the comprehensive geriatric assessment. Finally, the level of agreement between the two frailty classifications is assessed.

Modified Fried's frailty classification

Unfortunately, the TRIL Clinic research protocol did not include Fried's criteria according to their original definition (2). However, similar variables were collected and they were used for the construction of a 'modified' Fried's frailty classification.

Modifications of the original Fried's criteria have been previously used to construct frailty classifications based on Fried's approach. For instance, Santos-Eggimann *et al*. employed an approach to Fried's method in the first wave of the *Survey of Health, Ageing and Retirement in Europe* (SHARE), in order to establish the prevalence of frailty in middle-aged and older community-dwelling Europeans (233); since SHARE did not collect Fried's criteria according to their original definition, Santos-Eggimann *et al*. selected the five SHARE variables which, in their view, were the closest to Fried's variables. Using latent class analysis, the candidate subsequently demonstrated that this selection of variables had sufficient construct, concurrent and predictive validity for the construction of a frailty instrument for primary care (274).

Description of the modified Fried's frailty criteria

For the classification of the sample into three increasing frailty categories according to Fried's approach, the following five variables were selected amongst the ones in the TRIL Clinic research protocol as the closest to criteria by Fried *et al*. (2):

- *Exhaustion*: this criterion was present if the subject responded 'yes' to either (or both) of the following questions (based on the CES–D Depression Scale (466)): (a) "In the last week, did you feel on at least 3 days that everything you did was an effort?"; (b) "In the last week, did you feel on at least 3 days that you could not get going?". This criterion is the same as in the original Fried's definition.

- *Grip strength*: it was measured three times in each hand with a hydraulic hand dynamometer (Kg). The three measurements in each hand were averaged, and the higher of the two averages was selected. Subjects were classified as frail by the *weakness* criterion if they were in the lowest 20th percentile of grip strength, stratifying by gender and quartiles of body mass index (BMI). The original Fried's criterion is defined as the maximal grip strength (Kg) in the dominant hand (three measurements averaged), using a Jamar hand-held dynamometer, with stratification by gender and BMI quartiles.

- *Walking speed*: it was measured with the GAITRite® walkway system (CIR Systems, Inc., http://www.gaitrite.com). Participants were asked to walk once along the walkway at their preferred walking speed, with no additional cognitive loading. The GAITRite®-generated height-normalised gait velocity was used (i.e. absolute gait velocity divided by the average leg length [LL] of the subject, in LL/s). Subjects were classified as frail by the *slowness* criterion if they were within the lowest 20th percentile of normalised walking speed, stratifying by gender. The original Fried criterion is based on the time (seconds) to walk 15 feet at usual pace, stratifying by gender and height.

- *Weight loss*: this criterion was present if the subject reported ≥ 1 Kg (i.e. 2.2 pounds) of unintentional weight loss in the last 3 months (this information was taken from the screening section of the Nestlé Mini-Nutritional Assessment, MNA® (467)). In the original Fried's cross-sectional criterion, subjects answering 'yes' to the question: "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" were classified as frail by the weight loss criterion.

- *Physical activity*: number of hours per week spent walking outdoors. Subjects in the lowest 20th percentile (stratifying by gender) were classified as frail by the *low activity* criterion. The original Fried's criterion is based on the short version of the *Minnesota Leisure Time Activity questionnaire* (MLTAQ) (468) (in men, those with < 383 Kcals of physical activity per week are frail; in women, those with < 270 Kcals per week are frail). Although the MLTAQ was not available in the TRIL Clinic protocol, frequency of going outdoors was the closest proxy and there is evidence in the literature that it may be a reliable indicator of frailty (469, 470).

As per Fried *et al*.'s classification method (2), subjects with ≥ 3 of the modified criteria present were defined as *frail*; those with 1 or 2 criteria present were classified as *pre-frail*. The rest were classified as *non-frail*.

Internal (i.e. construct) validation of the Fried's modified criteria

Since modifications of the original criteria by Fried *et al*. were employed to classify the sample according to Fried's approach, an *internal* (construct) *validation* of the modified criteria became necessary in order to demonstrate that the modified variables were still indicators of a single underlying construct (i.e. frailty). For this internal validation, a structural equation model (SEM) was used (AMOS 16.0), which tested the fit of an underlying frailty construct (unobserved variable) indicated by the five above-described (observed) modified frailty variables.

Figure 8.1 shows the results of the validation of the modified frailty definition SEM (in N = 442). The identified model had 15 parameters and 5 degrees of freedom: Chi-squared = 7.44, P = 0.190 (non-significant P value suggests good fit). The standardised regression weights for exhaustion (β = 0.44), grip strength (β = -0.43), walking speed (β = -0.58) and physical activity (β = -0.42) were all highly significant ($P < 0.001$); the regression coefficient for weight loss (β = 0.17) tended towards significance (P = 0.015). The model fit indices were favourable (Table 8.1), supporting the internal validity of this modified Fried's frailty definition. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 8.1. Internal validation of the modified Fried's definition using a structural equation model (AMOS 16.0).

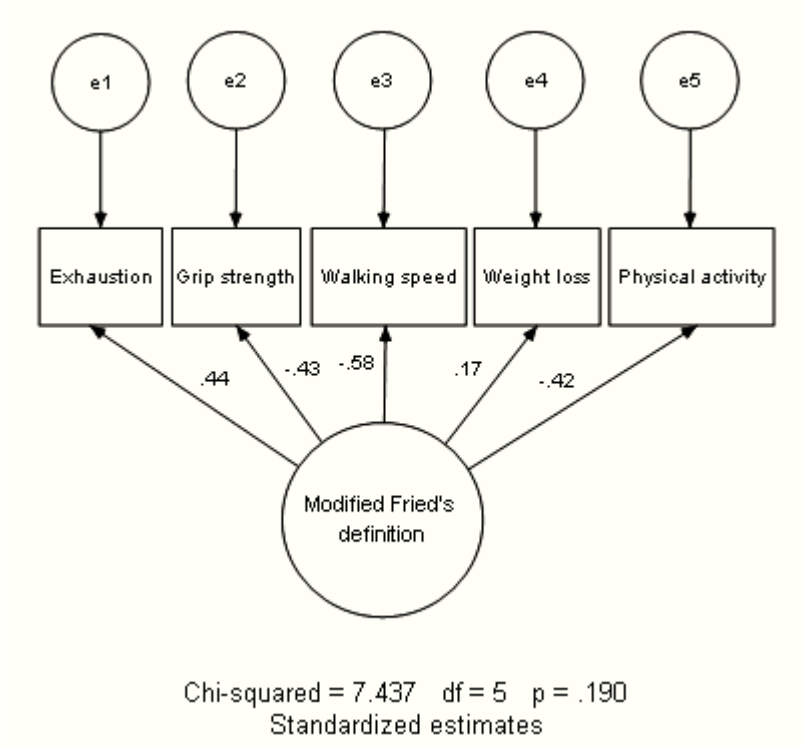


Table 8.1. Fit indices for the SEM in Figure 8.1.

Fit index	Values
NFI (normalized fit index)	0.93
RFI (relative fit index)	0.80
IFI (incremental fit index)	0.98
TLI (Tucker-Lewis index)	0.93
CFI (comparative fit index)	0.98
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.03 (0.00 – 0.08, *P* = 0.665)

Concurrent validity of the modified Fried's frailty categories

The frailty phenotypes as per modified Fried's definition were characterised according to a range of variables collected during the comprehensive geriatric assessments at the TRIL Clinic. *Concurrent validity* refers to the degree to which the operationalisation of a construct correlates with other measures of the same construct that were measured at the same time (471). As reviewed in Chapter 2, frailty is a *biopsychosocial* construct, so a biopsychosocial range of measurements were used to assess the concurrent validity of the modified Fried's frailty definition. The measurements considered are presented below with their respective total ($N = 442$) sample prevalences:

- *Socio-demographic domain*:
    - *Age* (years): mean 72.1 (SD 7.1).
    - *Gender* (71.7% females).
    - *Social class*: subjects were asked their main (previous or current) occupation and then classified into one of the Irish Census social class groups (http://www.cso.ie/Census): 1: Professional workers (20.4%); 2: Managerial and technical (17.5%); 3: Non-manual (26.8%); 4: Skilled manual (14.5%); 5: Semi-skilled (8.5%); 6: Unskilled (10.4%), and 7: all others gainfully occupied and unknown (1.9%). Groups 1 to 3 were classified as non-manual (64.7%) and groups 4-7 as manual (35.3%).
    - *Highest completed education*: 0: no formal education (1.4%); 1: primary (25.5%); 2: Junior Certificate or equivalent (29.7%); Leaving Certificate or equivalent (25.1%); primary university degree (13.2%); postgraduate degree (5.1%). For computational purposes, this variable was treated as ordinal (0 to 5).

- *National Deprivation Score 2006*, which is an objective measurement of material deprivation that results from a weighted combination of four indicators from those available in the Small Area Population Statistics of the Irish Census: *employment*, *social class*, *type of home tenure* and *car ownership* (472) (http://www.sahru.tcd.ie/services/deprivation.php). In the total sample, the lowest score (i.e. least deprivation) was -2.53, and the maximum 8.62 (mean 0.32, SD 2.12).

- *Proportion of self-referrals* to the TRIL Clinic (as opposed to referrals by health professionals).
- *Co-morbidities*:
  - The Charlson Comorbidity Index (CCI) (without age adjustment) was calculated for each participant on the basis of their past medical histories using Hall *et al*.'s electronic calculator (473). CCI encompasses 19 medical conditions weighted 1–6 with total scores ranging from 0 (lowest) to 37 (highest) comorbidity. The sample prevalences for some of its individual items were: ischaemic heart disease (IHD): 14.7%; congestive heart failure (CCF): 28.7%; peripheral vascular disease (PVD): 5.2%; cerebrovascular disease, including transient ischaemic attack (CVD/TIA): 10.9%; stroke: 3.2%; asthma or chronic obstructive pulmonary disease (COPD): 11.3%; connective tissue disease (CTD): 5.0%; peptic ulcer disease (PUD): 8.6%; chronic liver disease (CLD): 4.5%; cancer (solid or haematological): 4.5%.
  - *Hypertension*: history of having been diagnosed or medicated for arterial hypertension (42.3%).

- *Atrial fibrillation*: based on self-reported history or as seen on the 12-lead electrocardiogram (ECG) during the medical assessment (4.1%). The presence of *non-acute ischaemic signs on the ECG* (e.g. Q waves, chronic T wave changes) was also recorded (16.8%).
- *Abnormal nutritional status*: Participants were administered the full version of the Nestlé Mini Nutritional Assessment (467) (MNA®, http://www.mna-elderly.com/forms/MNA_english.pdf), which has three possible outcomes: normal, at risk of malnutrition or malnourished. The latter two were considered as abnormal (6.9%).

- *Medication burden*:
  - *Polypharmacy*: defined as the regular use of 4 or more medications (41.4%). The specific burden of antihypertensive and psychotropic medications was also recorded using the WHO Anatomical Therapeutic Chemical (ATC) classification (http://www.whocc.no) (474). In the total sample, 24.7% of subjects were on two or more antihypertensives, 5.4% on two or more psychotropes, and 15.2% were on regular benzodiazepines.
- *Falls, disability and dependency*:
  - *History of ≥ 1 fall in the past 6 months* (13.1%). History of ≥ 1 fall-related fracture (in the past 5 years) was also recorded (15.2%).
  - *Disability*: assessed by the (self-maintenance) Activities of Daily Living scale (ADL, maximum 24 points indicating least disability) and the Independent Activities of Daily Living (IADL) scale (maximum 27 points indicating least disability) (475). Mean ADL: 22.8 (SD 1.6); mean IADL: 25.9 (SD 1.9).

- Regular use of a *walking aid* (e.g. stick, frame) (7.2%).
- Regular receipt of domestic or personal *home help* (12.0%), or *meals on wheels* (1.1%).

- *Functional assessments*:
  - *Visual acuity*: binocular log of the minimal angle of resolution (logMAR) tested at a distance of 4 metres. Normal vision corresponds to a logMAR of 0.00, with higher (more positive) logMAR indicating worse visual acuity and lower (more negative) indicating better than normal visual acuity (476). The sample mean was 0.11 (SD 0.15).
  - *Hearing ability*: poor hearing (13.4%) *vs*. normal or mildly impaired hearing (86.6%), based on the automated report of a self-administered pure-tone audiogram (Kamplex® BA25 Audiometer, P.C.Werth Ltd.).
  - *Time to get Up and Go* (TUG, in seconds): a test of general mobility asking the participant to stand up from a chair, walk a distance of three metres, turn around, walk back to the chair and sit down again (477). The sample mean was 9.5 seconds (SD 4.0).
  - *Berg Balance Score* (BBS): maximum 56 points (i.e. normal balance), with < 45 points indicating increased risk of falls (478, 479). The sample mean was 52.3 (SD 5.5).
- *Inflammatory markers* (blood tests):
  - *HbA1c* (glycated hemoglobin, %): mean 5.7 (SD 0.5).
  - *Fibrinogen* (g/L): mean 3.3 (SD 0.6).
  - *C-reactive protein* (CRP, mg/L): mean 3.3 (SD 4.4).
  - *Erythrocyte sedimentation rate* (ESR, mm/h): mean 16.4 (SD 12.4).

- *Other biomarkers* (blood tests):
    - *Haemoglobin* (g/dL): mean 13.5 (SD 1.3).
    - Serum 25-hydroxyvitamin D [25(OH)D, in nmol/L] was analyzed at St James's Hospital Biochemistry Department using the DiaSorin LIAISON® 25(OH)D TOTAL (http://www.diasorin.com), a chemiluminescence immunoassay. The sample mean was 49.5 (SD 23.8). Vitamin D supplementation was ascertained from the medication histories; subjects were regarded as supplemented (36.0%) if they reported regular intake of prescription medicines and/or over-the-counter preparations (i.e. cod liver oil or multivitamin preparations) containing vitamin D.
    - *Parathyroid hormone* (PTH, pg/mL): mean 45.7 (SD 17.7).
    - *Albumin* (g/L): mean 41.7 (SD 2.9).
    - *Cockcroft-Gault estimated glomerular filtration rate* (eGFR, mL/min): mean 74.5 (SD 22.6).
    - *N-terminal pro-B-type Natriuretic Peptide* (NT-proBNP, pg/mL): mean 263.2 (SD 475.3) (480).
    - *Serum osmolality* (mOsm/Kg): mean 295.5 (SD 6.5) (481).
- *Cognitive domain*:
    - *Mini-Mental State Examination* (MMSE) (482). Mean 27.8 (SD 1.8).
    - *Delayed word recall* test: mean 3.9 (out of 10 words) (SD 2.0).
    - Tests of executive function: *animal naming* test: mean 17.4 (SD 5.3) words in the allowed time period; and *trail making test B–A*: mean 74.2 (SD 53.7) (higher scores in the latter indicate worse executive function) (483, 484).

- *Psychological domain*:
    - *Eysenck Personality Inventory* (EPI) (485): measures two major personality axes, extraversion (E) and neuroticism (N). Both E and N scores range from 0 (minimum) to 24 (maximum) points. The sample mean was 10.8 (SD 4.0) for E and 9.2 (SD 4.6) for N. The Lie scale (L) is also included in EPI and was initially introduced to detect individuals 'faking good' (dissimulation). However, subsequent research showed that it also measures some stable personality factor related to social desirability, naivety or conformity (486). In the sample, the mean L was 4.5 (SD 1.9).
    - *Self-rated health*: on a verbal rating scale from 0 (worst) to 10 (best) (mean 7.7, SD 1.6).
    - *Pain score*: on a verbal rating scale from 0 (best) to 10 (worst) (mean 2.9, SD 2.6).
    - *Modified Falls Efficacy Scale* (MFES) (487): it ranges from 0 (maximum fear of falling) to 10 (maximum confidence) (mean 9.3, SD 1.2).
    - *Center for Epidemiological Studies Depression scale (8 items)* (CESD-8) (466): it ranges from 0 to 8 with higher scores indicating more depressive symptoms (mean 1.7, SD 1.9).
    - *Hospital Anxiety and Depression Scale (Anxiety subscale)* (HADS) (488): it ranges from 0 to 21; higher scores indicate more anxiety (mean 5.3, SD 3.6).
    - *Lubben Social Network Scale-18* (LSNS-18) (489): it quantifies perceived social support received from relatives, neighbours, and friends outside the neighbourhood. Scores range from 0 (minimum) to 90 (maximum perceived support) (mean 47.4, SD 13.0).

- *Perceived Stress Scale* (PSS) (490): it is a measure of the degree to which situations in one's life are appraised as stressful. Scores range from 0 (minimum) to 40 (maximum perceived stress) (mean 9.2, SD 6.5).
- *De Jong Gierveld Loneliness Scale (6 items)* (491). The social subscale (sum of 3 items) refers to loneliness brought on by the lack of a social network (mean 0.5, SD 0.8); the emotional subscale (3 items) captures feelings of emptiness and social rejection (mean 0.8, SD 0.9).
- *Pittsburgh Sleep Quality Index* (PSQI) (492): assesses sleep quality and disturbances over the past month. Nineteen individual items generate seven 'component' scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score (range 0 to 21). Higher scores indicate worse sleep quality (mean 6.7, SD 4.0).

Results of the modified Fried's classification

Following application of Fried's classification method on the total sample (N = 442), 198 (44.8%) subjects were classified as non-frail, 213 (48.2%) as pre-frail, and 31 (7.0%) as frail. Table 8.2 shows the distribution of the modified Fried's criteria (and their raw variables as applicable) across the frailty subgroups. To test for linear trends (i.e. gradients) across frailty phenotypes, the Chi-squared for trend test was used for dichotomous variables and the Spearman's rank correlation coefficient for continuous variables.

Table 8.2. Distribution of the modified Fried's criteria across the frailty subgroups.

	Non-frail *N* = 198	Pre-frail *N* = 213	Frail *N* = 31	*P* value (linear trend)
Frailty				
Exhaustion criterion present (%)	0.0	31.0	71.0	**<0.001**$^{\chi t}$
Grip strength (Kg): median (IQR)	25.5 (12.6)	18.6 (11.4)	14.2 (6.9)	**<0.001**$^{\Sigma}$
Weakness criterion present (%)	0.0	31.5	51.6	**<0.001**$^{\chi t}$
Height-normalized gait speed (LL/s)	1.37 (0.21)	1.16 (0.31)	0.80 (0.32)	**<0.001**$^{\Sigma}$
Slowness criterion present (%)	0.0	27.4	82.8	**<0.001**$^{\chi t}$
Weight loss criterion present (%)	0.0	24.9	48.4	**<0.001**$^{\chi t}$
Outdoor walking (hours/week)	5.2 (2.0)	3.3 (2.3)	1.3 (1.5)	**<0.001**$^{\Sigma}$
Low activity criterion present (%)	0.0	25.4	71.0	**<0.001**$^{\chi t}$
No. frailty criteria: median (IQR)	0.0 (0.0)	1.4 (0.5)	3.2 (0.5)	**<0.001**$^{\Sigma}$

$^{\Sigma}$ Spearman's rank correlation coefficient; $^{\chi t}$ Chi-squared test for trend; significant *P* values (< 0.01) are highlighted in bold. IQR: interquartile range; LL/s: leg lengths per second.

Concurrent validity of the modified Fried's frailty classification

Tables 8.3a and 8.3b show the results of the correlations between the modified Fried's frailty subgroups and the biopsychosocial range of variables described above.

Table 8.3a. Correlations between the frailty categories (based on the modified Fried's definition) and a biopsychosocial range of variables from the comprehensive geriatric assessment.

	Non-frail *N* = 198	Pre-frail *N* = 213	Frail *N* = 31	*P* value (linear trend)
Socio-demographics				
Age (years)	70.5 (6.3)	72.9 (7.5)	76.6 (7.3)	**<0.001**$^{\Sigma}$
Female gender (%)	66.7	76.1	74.2	0.064$^{\chi t}$
Manual social class (%)	31.9	36.1	55.2	*0.037*$^{\chi t}$
Education level	2.6 (1.3)	2.2 (1.1)	1.8 (1.1)	**<0.001**$^{\Sigma}$
National Deprivation Score 2006	0.01 (2.08)	0.40 (2.04)	1.85 (2.33)	**<0.001**$^{\Sigma}$
Referral source				
Self-referral rate (%)	81.8	70.4	32.3	**<0.001**$^{\chi t}$
Comorbidities				
CCI: median (IQR)	1 (2)	1 (3)	3 (3)	**<0.001**$^{\Sigma}$
Ischaemic heart disease (%)	11.1	16.0	29.0	*0.011*$^{\chi t}$
Chronic ischaemia on ECG (%)	15.2	16.9	25.8	0.216$^{\chi t}$
Congestive heart failure (%)	21.7	30.0	64.5	**<0.001**$^{\chi t}$
Atrial fibrillation (%)	4.1	3.8	6.5	0.761$^{\chi t}$
Peripheral vascular disease (%)	2.5	6.1	16.1	**0.002**$^{\chi t}$
CVD/TIA (%)	5.1	11.3	45.2	**<0.001**$^{\chi t}$
Stroke (%)	1.5	3.3	12.9	**0.005**$^{\chi t}$
Hypertension (%)	39.4	43.2	54.8	0.130$^{\chi t}$
Cockcroft-Gault eGFR < 60 mL/min (%)	23.2	28.2	51.6	**0.005**$^{\chi t}$
Asthma/COPD (%)	9.1	11.7	22.6	0.053$^{\chi t}$
Connective tissue disease (%)	4.5	5.2	6.5	0.640$^{\chi t}$
Peptic ulcer disease (%)	7.1	8.9	16.1	0.138$^{\chi t}$
Chronic liver disease (%)	2.5	5.2	12.9	*0.014*$^{\chi t}$
History of cancer (%)	5.1	3.3	9.7	0.835$^{\chi t}$
Abnormal MNA® (%)	2.0	7.3	35.5	**<0.001**$^{\chi t}$
Medication burden				
Polypharmacy (%)	33.3	45.1	67.7	**<0.001**$^{\chi t}$
On ≥ 2 antihypertensives (%)	20.2	26.8	38.7	*0.018*$^{\chi t}$
On ≥ 2 psychotropics (%)	2.5	5.6	22.6	**<0.001**$^{\chi t}$
On regular benzodiazepines (%)	9.6	16.4	41.9	**<0.001**$^{\chi t}$
Falls, disability and dependency				
≥ 1 fall in the last 6 months (%)	6.6	16.0	35.5	**<0.001**$^{\chi t}$
≥ 1 fall related fracture (last 5 years)	12.0	17.1	23.3	0.057$^{\chi t}$
ADL score	23.1 (1.4)	22.6 (1.7)	22.0 (1.8)	**<0.001**$^{\Sigma}$
IADL score	26.5 (0.9)	25.6 (2.1)	23.4 (2.9)	**<0.001**$^{\Sigma}$
Walking aid (%)	1.9	8.5	33.3	**<0.001**$^{\chi t}$
Receives home help (%)	8.6	12.7	29.0	**0.004**$^{\chi t}$
Receives meals on wheels (%)	0.5	0.9	6.5	*0.034*$^{\chi t}$
Functional assessments				
Vision (Binocular LogMAR)	0.10 (0.13)	0.12 (0.16)	0.20 (0.21)	0.093$^{\Sigma}$
Poor hearing (PTA) (%)	8.6	17.9	12.5	*0.046*$^{\chi t}$
TUG (s)	8.0 (1.8)	10.0 (4.2)	15.8 (5.8)	**<0.001**$^{\Sigma}$
Berg balance score	54.4 (2.3)	51.5 (5.6)	43.7 (9.5)	**<0.001**$^{\Sigma}$

$^{\Sigma}$ Spearman's rank correlation coefficient; $^{\chi t}$ Chi-squared test for trend; significant *P* values (< 0.01) are highlighted in bold; statistical trends ($P < 0.05$) are indicated in italics. CCI: Charlson comorbidity index; CVD/TIA: cerebrovascular disease/transient ischaemic attack; eGFR: estimated glomerular filtration rate; COPD: chronic obstructive pulmonary disease; MNA®: Mini-Nutritional Assessment; (I)ADL: (independent) activities of daily living; PTA: pure tone audiogram; TUG: time to get up and go.

Table 8.3b. Correlations between the frailty categories (based on the modified Fried's definition) and a biopsychosocial range of variables from the comprehensive geriatric assessment.

	Non-frail *N* = 198	Pre-frail *N* = 213	Frail *N* = 31	*P* value (linear trend)
Inflammatory markers				
HbA1c (%)	5.6 (0.3)	5.7 (0.6)	5.8 (0.4)	0.080$^{\Sigma}$
Fibrinogen (g/L)	3.3 (0.6)	3.3 (0.6)	3.3 (0.7)	0.158$^{\Sigma}$
CRP (mg/L)	2.7 (2.7)	3.7 (5.2)	5.3 (6.3)	**0.001**$^{\Sigma}$
ESR (mm/h)	14.5 (10.3)	17.5 (14.0)	20.3 (11.4)	**0.006**$^{\Sigma}$
Other biomarkers				
Haemoglobin (g/dL)	13.7 (1.2)	13.4 (1.4)	12.8 (1.8)	**0.001**$^{\Sigma}$
Vitamin D (nmol/L)	49.5 (21.0)	50.5 (25.6)	42.1 (26.9)	0.392$^{\Sigma}$
On Vitamin D supplements (%)	30.3	39.9	45.2	*0.023*$^{\chi t}$
Vitamin D (nmol/L) (not on supplements)	45.5 (20.3) (*N* = 126)	39.9 (19.8) (*N* = 113)	27.9 (20.1) (*N* = 13)	**0.002**$^{\Sigma}$
PTH (pg/mL)	45.0 (15.2)	45.2 (18.9)	54.9 (22.9)	0.567$^{\Sigma}$
Albumin (g/L)	42.0 (2.6)	41.5 (3.0)	41.3 (3.1)	0.061$^{\Sigma}$
Cockcroft-Gault eGFR (mL/min)	77.2 (21.3)	73.1 (22.3)	66.6 (30.0)	**0.001**$^{\Sigma}$
NT-proBNP (pg/mL)	181.0 (282.8)	306.7 (573.8)	508.4 (625.8)	**<0.001**$^{\Sigma}$
Serum osmolality (mOsm/Kg)	296.2 (5.9)	294.7 (6.5)	295.3 (9.5)	0.062$^{\Sigma}$
Cognitive				
MMSE	28.2 (1.6)	27.6 (1.9)	26.2 (2.2)	**<0.001**$^{\Sigma}$
Delayed word recall	4.2 (1.9)	3.7 (2.0)	3.3 (2.2)	**0.006**$^{\Sigma}$
Animal naming	17.8 (5.1)	17.2 (5.2)	15.3 (6.4)	0.071$^{\Sigma}$
TMT B-A	64.7 (46.4)	80.3 (57.1)	111.6 (65.4)	**<0.001**$^{\Sigma}$
Psychological				
EPI-Extraversion	11.4 (4.1)	10.5 (3.9)	9.6 (3.8)	**0.003**$^{\Sigma}$
EPI-Neuroticism	8.3 (4.6)	9.9 (4.4)	11.1 (4.1)	**<0.001**$^{\Sigma}$
EPI-Lie	4.4 (1.9)	4.6 (1.8)	4.7 (2.1)	0.112$^{\Sigma}$
Self-rated health	8.1 (1.3)	7.5 (1.6)	6.0 (2.4)	**<0.001**$^{\Sigma}$
Pain score (min:0; max:10)	2.1 (2.3)	3.1 (2.5)	6.0 (2.7)	**<0.001**$^{\Sigma}$
Modified Falls Efficacy Scale	9.7 (0.8)	9.2 (1.2)	7.8 (1.9)	**<0.001**$^{\Sigma}$
CESD-8 scale	1.1 (1.5)	2.0 (1.9)	3.8 (2.5)	**<0.001**$^{\Sigma}$
HADS (anxiety subscale)	4.4 (2.9)	5.8 (3.9)	8.4 (4.4)	**<0.001**$^{\Sigma}$
Perceived social support (LSNS-18)	50.3 (12.3)	45.9 (12.6)	38.9 (15.0)	**<0.001**$^{\Sigma}$
Perceived Stress Scale	7.8 (5.7)	10.4 (7.0)	11.6 (6.9)	**<0.001**$^{\Sigma}$
Social loneliness (De Jong-Gierveld-6)	0.4 (0.7)	0.5 (0.8)	0.6 (0.9)	0.136$^{\Sigma}$
Emotional loneliness (De Jong-Gierveld-6)	0.6 (0.8)	0.9 (1.0)	1.1 (1.0)	**<0.001**$^{\Sigma}$
Pittsburgh Sleep Quality Index	6.0 (3.8)	7.2 (4.0)	7.7 (4.1)	**0.001**$^{\Sigma}$

$^{\Sigma}$ Spearman's rank correlation coefficient; $^{\chi t}$ Chi-squared test for trend; significant *P* values (< 0.01) are highlighted in bold; statistical trends ($P < 0.05$) are indicated in italics. HbA1c: glycated haemoglobin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PTH: parathyroid hormone; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-B Natriuretic Peptide; MMSE: Mini-Mental State Examination; TMT: trail making test; EPI: Eysenck Personality Inventory; CESD: Center for Epidemiological Studies Depression scale; HADS: Hospital Anxiety and Depression scale; LSNS: Lubben Social Network Scale.

As Tables 8.3a and 8.3b show, there were statistically significant linear trends across frailty subgroups in all the domains considered, consistent with the hypothesis that the construct underlying the modified Fried's definition was of *biopsychosocial* nature. The classification of the sample in three increasing frailty phenotypes revealed significant gradients (in the expected directions) in age, education, deprivation, comorbidities, nutritional status, medication burden, falls, disability, mobility and balance (i.e. time to get up and go, Berg balance score), inflammatory markers (i.e. CRP, ESR), cognition, and psychological/psychosocial markers. There was not a significant gender gradient across frailty subgroups.

In keeping with the remarks made in Chapter 4 on sample recruitment, self-referred participants were over-represented in the non-frail and pre-frail groups, and under-represented in the frail group ($P < 0.001$). This effect was expected and suggests that, despite the non-representativity of the sample, having two different recruitment sources helped to widen the spectrum of frailty in the sample.

An interesting phenomenon involves the correlation of frailty with serum Vitamin D (Table 8.3b). Considering all subjects, no significant gradient in serum Vitamin D was demonstrated (non-frail: 49.5 nmol/L, pre-frail: 50.5 nmol/L, frail: 42.1 nmol/L, *P* for trend = 0.392); however, when the analysis was repeated excluding those who were on Vitamin D supplements, a significant gradient in serum Vitamin D was demonstrated (non-frail: 45.5 nmol/L, pre-frail: 39.9 nmol/L, frail: 27.9 nmol/L, *P* for trend = 0.002). There was a trend towards increasing use of Vitamin D supplements across frailty

categories (non-frail: 30.3%, pre-frail: 39.9%, frail: 45.2%, *P* for trend = 0.023). This supports the previously stated hypothesis by the candidate (493) that vitamin D supplementation may be a *confounder* of the emerging association between frailty and serum Vitamin D in epidemiological studies (312, 315); indeed, Vitamin D supplementation could be a marker of frailty, perhaps in relation to the higher number of healthcare episodes involving frailer people and the associated increased odds of being prescribed Vitamin D supplements (493).

In summary, the modified Fried's definition had sufficient internal validity (as assessed by SEM) and concurrent validity (as assessed by the correlations of the frailty groups with age, overall health, functional assessments, and cognitive and psychological markers). The modified frailty definition had the expected associations with falls (4) and relevant *biological* and *psychosocial* parameters, in keeping with frailty being a holistic, multidimensional construct (210, 494, 495).

TRIL Frailty Index (Rockwood's approach)

As an alternative definition of frailty for the purpose of subsequent correlations with orthostatic hypotension, a Frailty Index (TRIL-FI) was created based on Rockwood *et al*.'s *standard procedure* (286). Even though the TRIL Clinic research protocol did not measure the exact same deficits as described in Rockwood's standard procedure and related publications (234, 282-285), reproducibility of the findings in relation to the FI is, as Rockwood *et al*. themselves argue, 'of low concern because none of the samples in which the FI has been operationalised considered the same deficits, and results were all consistent' (286). The construction of a FI allows flexibility in criteria selection.

Selection of candidate deficits and construction of TRIL-FI

To select candidate deficits for the construction of a FI, Rockwood *et al*. recommended the following criteria (286): (1) the variables must be deficits associated with health status; (2) a deficit's prevalence must generally increase with age; (3) the deficits must not saturate too early (e.g. presbyopia is nearly universal by age 55, so it saturates too early to be considered as a deficit); (4) the deficits must cover a range of systems, and (5) there should be at least 30 – 40 total deficits.

With the above criteria in mind, 38 deficit variables were selected from the TRIL Clinic database; they are presented in Table 8.4. The deficits include individual items of the Charlson Comorbidity Index (CCI), the modified Fried's criteria themselves, and other variables as defined in the previous subsection. Cut-off points for continuous variables were established on the basis of published literature, or the lowest 20th percentile rule.

Table 8.4. Health variables and cut-points for the TRIL-FI (38 deficits).

Variable and source	Cut point	Cut point source
Comorbidities		
Ischaemic heart disease (from CCI)	0 = No; 1 = Yes	
Chronic ischaemia on 12-lead ECG	0 = No; 1 = Yes	
Congestive heart failure (from CCI)	0 = No; 1 = Yes	
Atrial fibrillation	0 = No; 1 = Yes	
Peripheral vascular disease (from CCI)	0 = No; 1 = Yes	
CVD/TIA (from CCI)	0 = No; 1 = Yes	
Stroke (from CCI)	0 = No; 1 = Yes	
Hypertension	0 = No; 1 = Yes	
Cockcroft-Gault eGFR < 60 mL/min	0 = No; 1 = Yes	
Asthma/COPD (from CCI)	0 = No; 1 = Yes	
Connective tissue disease (from CCI)	0 = No; 1 = Yes	
Peptic ulcer disease (from CCI)	0 = No; 1 = Yes	
Chronic liver disease (from CCI)	0 = No; 1 = Yes	
History of cancer (from CCI)	0 = No; 1 = Yes	
Abnormal Mini Nutritional Assessment (MNA®)	0 = No; 1 = Yes	
Weight loss (modified Fried's criterion)	0 = No; 1 = Yes	
Anaemia (Haemoglobin, g/dL)	Men: < 13 = Yes Women: < 12 = Yes	(496)
Medication burden		
Polypharmacy (on ≥ 4 regular medications)	0 = No; 1 = Yes	
On ≥ 2 antihypertensive medications	0 = No; 1 = Yes	
On ≥ 2 psychotropic medications	0 = No; 1 = Yes	
On regular benzodiazepines	0 = No; 1 = Yes	
Falls, disability and dependency		
≥ 1 fall in the last 6 months	0 = No; 1 = Yes	
≥ 1 fall related fracture (last 5 years)	0 = No; 1 = Yes	
ADL disability	< 21 = Yes	20th percentile
IADL disability	< 25 = Yes	20th percentile
Needs walking aid	0 = No; 1 = Yes	
Low activity (modified Fried's criterion)	0 = No; 1 = Yes	
Receives home help (domestic and/or personal)	0 = No; 1 = Yes	
Receives meals on wheels	0 = No; 1 = Yes	
Functional assessments		
Visual impairment (binocular logMAR)	logMAR ≤ 0.3 = 0 logMAR 0.4–0.9 = 0.5 logMAR ≥ 1.0 = 1	(497)
Hearing impairment (pure tone audiogram)	Acceptable hearing = 0 Mild hearing impairment = 0.5 Poor hearing = 1	
Poor mobility (time to get up and go)	Age 60-69: > 9 seconds = 1 Age 70-79: > 10.2 seconds = 1 Age 80-99: > 12.7 seconds = 1	(498)
Poor balance (Berg balance score)	< 45 = 1	(479)
Weakness (modified Fried's criterion)	0 = No; 1 = Yes	
Slowness (modified Fried's criterion)	0 = No; 1 = Yes	
Psychological (health-related)		
Fear of falling (Modified Falls Efficacy Scale)	< 8.9 = 1	20th percentile
Exhaustion (modified Fried's criterion)	0 = No; 1 = Yes	
Emotional loneliness (De Jong Gierveld-6)	≥ 2 = Yes	

CCI: Charlson Comorbidity Index; CVD/TIA: cerebrovascular disease/transient ischaemic attack; eGFR: Cockcroft-Gault estimated glomerular filtration rate; COPD: chronic obstructive pulmonary disease; (I)ADL: (independent) activities of daily living.

Results of the TRIL-FI classification

As per standard FI procedure, missing data were replaced with the mean for each series. For each subject, the total number of deficits (as per Table 8.4 codes) was counted and then divided by the number of deficits considered (i.e. 38). For the division of the sample into three increasing frailty categories, previously used FI cut-offs were applied (234): FI < 0.08: *non-frail*; 0.08 ≤ FI < 0.25: *pre-frail*; FI ≥ 0.25: *frail*. Figure 8.2 shows the TRIL-FI distribution (of gamma type as expected) and cut-off points for the frailty classification. Of the total sample (N = 442), TRIL-FI classified 155 (35.1%) subjects as non-frail, 201 (45.5%) as pre-frail, and 86 (19.5%) as frail.

Figure 8.2. Distribution of the TRIL-FI based on 38 deficits.

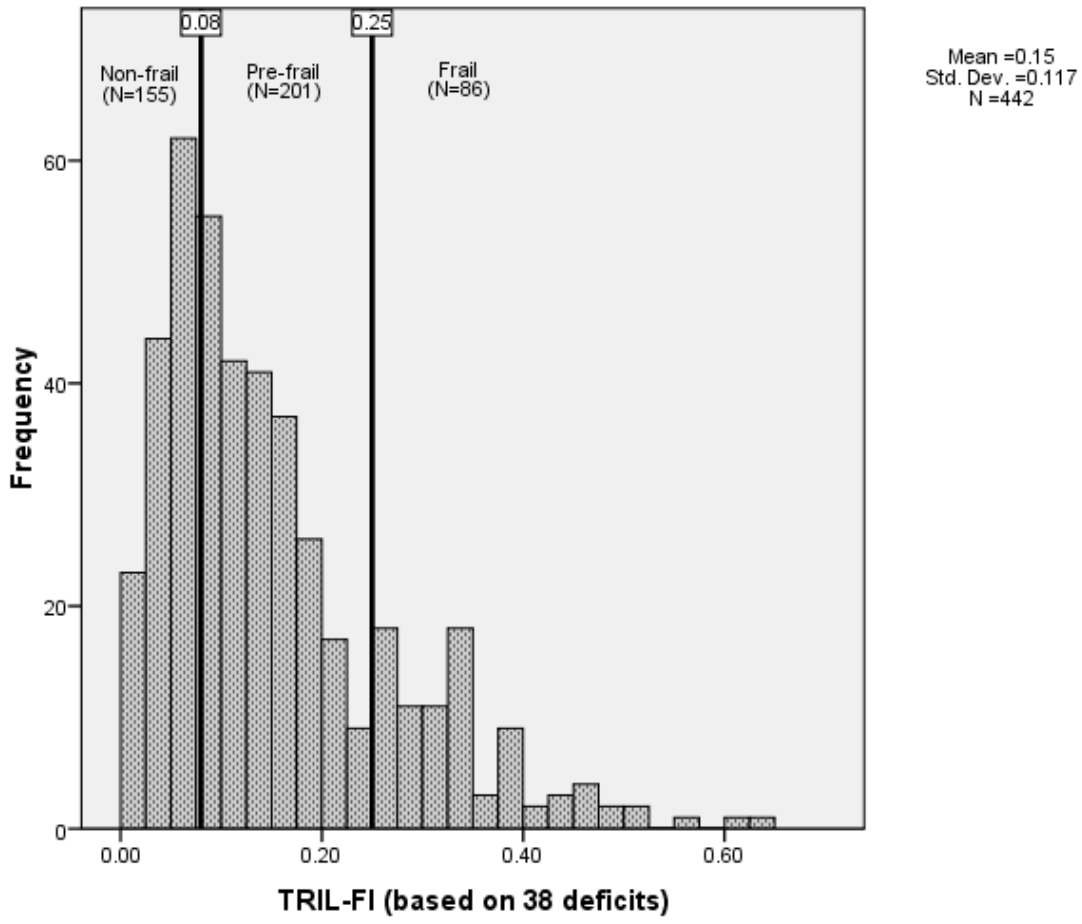


Figure 8.3 shows the correlation between TRIL-FI and the participants' age in the total sample (N = 442). As expected, simple linear regression between these two variables was significant: $F(1, 438) = 145.90$, $P < 0.001$, adjusted $R^2 = 0.25$. The unstandardised regression coefficient (B = 0.01) would indicate a 1% deficit accumulation per year.

Figure 8.3. Correlation of TRIL-FI with age (N = 442).
The regression line is shown with 95% confidence intervals for the mean.

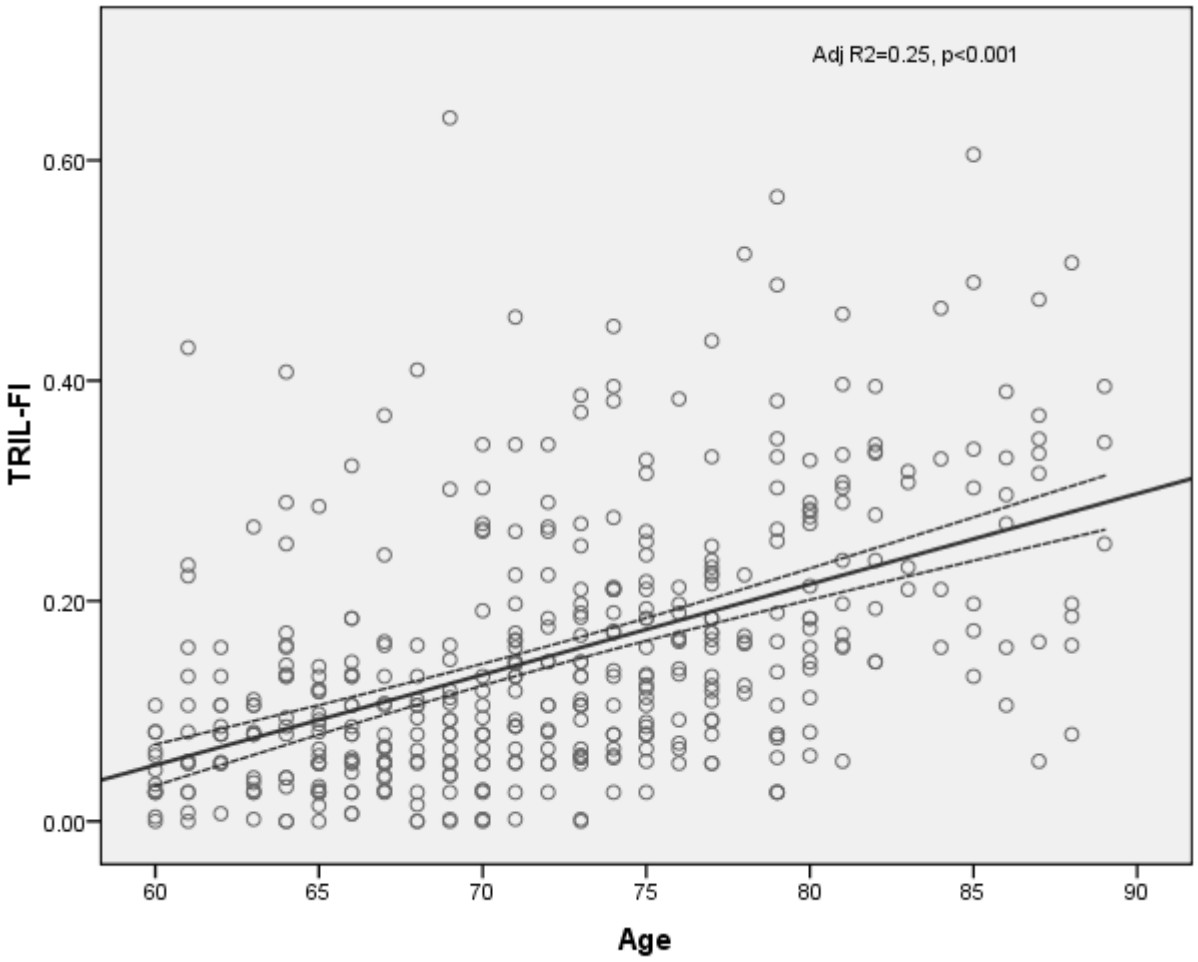


Table 8.5 shows the correlations between the TRIL-FI categories and the health deficit variables used to create TRIL-FI.

Table 8.5. Correlations between the TRIL-FI categories and the 38 variables used to create TRIL-FI.

	Non-frail *N* = 155	Pre-frail *N* = 201	Frail *N* = 86	*P* value (linear trend)
Comorbidities				
Ischaemic heart disease (%)	1.3	15.4	37.2	**<0.001**$^{\chi t}$
Chronic ischaemia on ECG (%)	6.5	18.4	31.4	**<0.001**$^{\chi t}$
Congestive heart failure (%)	8.4	29.4	64.0	**<0.001**$^{\chi t}$
Atrial fibrillation (%)	0.0	4.5	10.5	**<0.001**$^{\chi t}$
Peripheral vascular disease (%)	0.0	3.5	18.6	**<0.001**$^{\chi t}$
CVD/TIA (%)	1.3	9.0	32.6	**<0.001**$^{\chi t}$
Stroke (%)	0.0	2.0	11.6	**<0.001**$^{\chi t}$
Hypertension (%)	14.8	52.2	68.6	**<0.001**$^{\chi t}$
Cockcroft-Gault eGFR < 60 mL/min (%)	7.7	30.3	57.0	**<0.001**$^{\chi t}$
Asthma/COPD (%)	4.5	10.9	24.4	**<0.001**$^{\chi t}$
Connective tissue disease (%)	3.9	5.0	7.0	0.299$^{\chi t}$
Peptic ulcer disease (%)	3.9	9.5	15.1	**0.002**$^{\chi t}$
Chronic liver disease (%)	1.3	3.5	12.8	**<0.001**$^{\chi t}$
History of cancer (%)	2.6	4.0	9.3	*0.024*$^{\chi t}$
Abnormal MNA® (%)	0.0	5.2	23.5	**<0.001**$^{\chi t}$
Weight loss (modified Fried) (%)	7.1	16.1	28.2	**<0.001**$^{\chi t}$
Haemoglobin (g/dL)	13.8 (1.2)	13.6 (1.2)	12.7 (1.6)	**<0.001**$^{\Sigma}$
Medication burden				
Polypharmacy (%)	9.0	49.3	81.4	**<0.001**$^{\chi t}$
On ≥ 2 antihypertensives (%)	0.6	30.3	54.7	**<0.001**$^{\chi t}$
On ≥ 2 psychotropics (%)	0.0	3.5	19.8	**<0.001**$^{\chi t}$
On regular benzodiazepines (%)	2.6	16.4	34.9	**<0.001**$^{\chi t}$
Falls, disability and dependency				
≥ 1 fall in the last 6 months (%)	2.6	13.9	30.2	**<0.001**$^{\chi t}$
≥ 1 fall related fracture (last 5 years)	5.9	15.7	31.0	**<0.001**$^{\chi t}$
ADL score	23.2 (1.4)	22.9 (1.5)	21.7 (1.9)	**<0.001**$^{\Sigma}$
IADL score	26.7 (0.6)	26.2 (1.4)	23.8 (2.8)	**<0.001**$^{\Sigma}$
Walking aid (%)	0.8	4.2	26.9	**<0.001**$^{\chi t}$
Low activity (modified Fried) (%)	9.7	13.9	38.4	**<0.001**$^{\chi t}$
Receives home help (%)	6.5	8.5	30.2	**<0.001**$^{\chi t}$
Receives meals on wheels (%)	0.6	0.5	3.5	0.083$^{\chi t}$
Functional assessments				
Vision (Binocular LogMAR)	0.09 (0.12)	0.12 (0.15)	0.16 (0.20)	**0.008**$^{\Sigma}$
Poor hearing (PTA) (%)	5.6	15.9	23.2	**<0.001**$^{\chi t}$
TUG (s)	7.5 (1.5)	9.0 (2.3)	14.4 (6.0)	**<0.001**$^{\Sigma}$
Berg balance score	55.0 (2.2)	53.2 (3.0)	45.1 (8.0)	**<0.001**$^{\Sigma}$
Weakness (modified Fried) (%)	10.3	19.9	31.4	**<0.001**$^{\chi t}$
Slowness (modified Fried) (%)	2.0	13.9	65.3	**<0.001**$^{\chi t}$
Psychological (health-related)				
MFES score	9.9 (0.3)	9.4 (1.1)	8.1 (1.7)	**<0.001**$^{\Sigma}$
Exhaustion (modified Fried) (%)	5.9	17.1	53.2	**<0.001**$^{\chi t}$
Emotional loneliness (De Jong-Gierveld-6)	0.5 (0.7)	0.8 (0.9)	1.2 (1.1)	**<0.001**$^{\Sigma}$

$^{\Sigma}$ Spearman's rank correlation coefficient; $^{\chi t}$ Chi-squared test for trend; significant *P* values (< 0.01) are highlighted in bold; statistical trends (*P* < 0.05) are indicated in italics. CVD/TIA: cerebrovascular disease/transient ischaemic attack; eGFR: estimated glomerular filtration rate; COPD: chronic obstructive pulmonary disease; MNA®: Mini-Nutritional Assessment; (I)ADL: (independent) activities of daily living; PTA: pure tone audiogram; TUG: time to get up and go.

Concurrent validity of TRIL-FI

As previously done for the modified Fried's categories, the three TRIL-FI categories were correlated against a biopsychosocial range of variables in order to assess the concurrent validity of the classification. Results are shown in Tables 8.6a and 8.6b.

Table 8.6a. Correlations between the frailty categories (TRIL-FI) and a bio-psychosocial range of variables from the comprehensive geriatric assessment.

	Non-frail *N* = 155	Pre-frail *N* = 201	Frail *N* = 86	*P* value (linear trend)
Socio-demographics				
Age (years)	68.4 (5.7)	72.6 (6.6)	77.4 (7.0)	**<0.001**$^{\Sigma}$
Female gender (%)	65.8	76.1	72.1	0.166$^{\chi t}$
Manual social class (%)	30.0	32.8	51.8	**0.002**$^{\chi t}$
Education level	2.6 (1.2)	2.4 (1.2)	1.9 (1.0)	**<0.001**$^{\Sigma}$
National Deprivation Score 2006	-0.27 (1.70)	0.35 (2.18)	1.33 (2.32)	**<0.001**$^{\Sigma}$
Referral source				
Self-referral rate (%)	90.3	76.1	33.7	**<0.001**$^{\chi t}$
Comorbidities				
CCI: median (IQR)	0 (1)	1 (1)	3.5 (3)	**<0.001**$^{\Sigma}$
Functional markers				
Grip strength (Kg): median (IQR)	25.7 (13.2)	20.9 (10.1)	16.5 (7.4)	**<0.001**$^{\Sigma}$
Height-normalised gait speed (LL/s)	1.4 (0.2)	1.2 (0.3)	0.9 (0.3)	**<0.001**$^{\Sigma}$
Outdoor walking (hours/week)	4.7 (2.4)	4.2 (2.2)	2.5 (1.9)	**<0.001**$^{\Sigma}$
Inflammatory markers				
HbA1c (%)	5.6 (0.3)	5.7 (0.6)	5.7 (0.4)	**0.003**$^{\Sigma}$
Fibrinogen (g/L)	3.1 (0.5)	3.4 (0.6)	3.4 (0.6)	**0.001**$^{\Sigma}$
CRP (mg/L)	3.0 (4.9)	3.2 (3.9)	4.1 (4.4)	**<0.001**$^{\Sigma}$
ESR (mm/h)	13.9 (10.3)	15.2 (10.8)	23.4 (16.4)	**<0.001**$^{\Sigma}$
Other biomarkers				
Vitamin D (nmol/L)	47.4 (19.1)	51.0 (24.1)	49.3 (29.4)	0.817$^{\Sigma}$
On Vitamin D supplements (%)	30.3	36.3	45.3	*0.021*$^{\chi t}$
Vitamin D (nmol/L) (not on supplements)	44.9 (19.4) (*N* = 95)	43.2 (21.0) (*N* = 116)	32.3 (18.9) (*N* = 41)	**0.003**$^{\Sigma}$
PTH (pg/mL)	42.2 (16.1)	45.6 (16.2)	53.1 (21.9)	**<0.001**$^{\Sigma}$
Albumin (g/L)	42.2 (2.7)	41.7 (2.8)	40.6 (3.1)	**<0.001**$^{\Sigma}$
Cockcroft-Gault eGFR (mL/min)	82.2 (18.9)	74.0 (23.3)	61.7 (21.5)	**<0.001**$^{\Sigma}$
NT-proBNP (pg/mL)	94.9 (88.2)	217.8 (347.5)	669.3 (801.1)	**<0.001**$^{\Sigma}$
Serum osmolality (mOsm/Kg)	296.1 (5.7)	295.5 (5.9)	294.0 (8.8)	0.092$^{\Sigma}$

$^{\Sigma}$ Spearman's rank correlation coefficient; $^{\chi t}$ Chi-squared test for trend; significant *P* values (< 0.01) are highlighted in bold; statistical trends (*P* < 0.05) are indicated in italics. CCI: Charlson comorbidity index; IQR: interquartile range; LL/s: leg lengths per second; HbA1c: glycated haemoglobin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PTH: parathyroid hormone; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-Brain Natriuretic peptide.

Table 8.6b. Correlations between the frailty categories (TRIL-FI) and a bio-psychosocial range of variables from the comprehensive geriatric assessment.

	Non-frail *N* = 155	Pre-frail *N* = 201	Frail *N* = 86	*P* value (linear trend)
Cognitive				
MMSE	28.3 (1.5)	27.9 (1.8)	26.7 (2.0)	**<0.001**$^{\Sigma}$
Delayed word recall	4.3 (1.8)	3.9 (2.0)	3.0 (2.0)	**<0.001**$^{\Sigma}$
Animal naming	18.3 (5.6)	17.1 (4.6)	15.9 (6.0)	**0.005**$^{\Sigma}$
TMT B-A	60.8 (42.1)	74.0 (53.8)	112.9 (64.2)	**<0.001**$^{\Sigma}$
Psychological				
EPI-Extraversion	11.2 (3.8)	10.9 (4.2)	10.0 (3.8)	*0.027*$^{\Sigma}$
EPI-Neuroticism	7.8 (4.5)	9.6 (4.4)	11.0 (4.3)	**<0.001**$^{\Sigma}$
EPI-Lie	4.5 (1.9)	4.4 (1.9)	4.8 (1.9)	0.231$^{\Sigma}$
Self-rated health	8.3 (1.2)	7.8 (1.3)	6.3 (2.1)	**<0.001**$^{\Sigma}$
Pain score (min:0; max:10)	1.9 (2.1)	2.9 (2.4)	4.7 (2.7)	**<0.001**$^{\Sigma}$
CESD-8 scale	1.0 (1.5)	1.7 (1.9)	3.0 (2.2)	**<0.001**$^{\Sigma}$
HADS (anxiety subscale)	4.6 (2.9)	5.2 (3.5)	7.1 (4.5)	**<0.001**$^{\Sigma}$
Perceived social support (LSNS-18)	51.2 (12.8)	47.3 (11.5)	40.8 (14.0)	**<0.001**$^{\Sigma}$
Perceived Stress Scale	7.6 (6.0)	9.4 (6.1)	12.2 (7.6)	**<0.001**$^{\Sigma}$
Social loneliness (De Jong-Gierveld-6)	0.4 (0.7)	0.5 (0.8)	0.7 (0.9)	0.075$^{\Sigma}$
Pittsburgh Sleep Quality Index	5.7 (3.5)	7.0 (4.1)	8.0 (4.1)	**<0.001**$^{\Sigma}$

$^{\Sigma}$ Spearman's rank correlation coefficient; $^{\chi t}$ Chi-squared test for trend; significant *P* values (< 0.01) are highlighted in bold; statistical trends (*P* < 0.05) are indicated in italics. MMSE: Mini-Mental State Examination; TMT: trail making test; EPI: Eysenck Personality Inventory; CESD: Center for Epidemiological Studies Depression scale; HADS: Hospital Anxiety and Depression Scale; LSNS: Lubben Social Network Scale.

As shown for the modified Fried's definition, the characterisation of TRIL-FI showed significant gradients (in the expected directions) in age, education, deprivation, comorbidities, functional markers, inflammatory markers, cognition and psychological markers, consistent with TRIL-FI being a *biopsychosocial* construct. Classification of the sample by TRIL-FI resulted in statistically significant associations with social class, glycated haemoglobin, fibrinogen, parathyroid hormone, albumin, and animal naming, which had not been significant with the modified Fried's classification. Among all the variables studied, extraversion score was the only one significantly associated with the modified Fried's classification but not with TRIL-FI.

Correlation between the modified Fried's classification and TRIL-FI

The sample prevalence of frailty was higher by TRIL-FI (19.5%) than by the modified Fried's classification (7.0%), in keeping with differences in the literature referred to in Chapter 2.

The agreement between the modified Fried and the TRIL-FI classifications was high, as shown by the Spearman's rank correlation coefficient between these two (ordinal) variables: r_s (440) = 0.51, $P < 0.001$. Table 8.7 shows their cross-tabulation. Of 31 subjects classified as frail by the modified Fried's classification, 28 were also classified as frail by TRIL-FI; most of the remaining 58 subjects that were frail by TRIL-FI were classified as pre-frail by the modified Fried's classification, suggesting that, on average, those who were frail by the modified Fried's classification were somewhat frailer than those who were frail by TRIL-FI.

Table 8.7. Cross-tabulation between the modified Fried's classification and TRIL-FI.

		TRIL-FI			
		Non-frail (N=155)	**Pre-frail (N=201)**	**Frail (N=86)**	**Total**
Modified Fried's classification	**Non-frail (N=198)**	107	87	4	198 (44.8%)
	Pre-frail (N=213)	48	111	54	213 (48.2%)
	Frail (N=31)	0	3	28	31 (7.0%)
	Total	155 (35.1%)	201 (45.5%)	86 (19.5%)	442

Chapter 9

The orthostatic hemodynamics of frailty

In this chapter, the two frailty classifications (i.e. modified Fried's and TRIL Frailty Index) are characterised according to their orthostatic hemodynamic profiles for systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR), using the hemodynamic variables described in Chapter 6. The frailty categories are also characterised in terms of their prevalences of orthostatic hypotension as per *consensus*, *Fedorowski-modified*, *initial*, *morphological* and *orthostatic intolerance* definitions.

Modified Fried's frailty categories: orthostatic hemodynamic profiles and prevalence of orthostatic hypotension

Table 9.1 summarises the orthostatic hemodynamic profiles and the OH prevalences of the modified Fried's frailty categories and Figures 9.1a-c show their 5-second-averaged hemodynamic profiles for SBP, DBP and HR, respectively.

Table 9.1. Orthostatic hemodynamic profiles and orthostatic hypotension prevalences of the modified Fried's frailty phenotypes.

	Non-frail $N = 198$	Pre-frail $N = 213$	Frail $N = 31$	P value (overall difference)	P value (linear trend)
Systolic blood pressure (SBP)					
Baseline SBP (mmHg)	158.3 (23.1)	162.3 (25.6)	160.1 (23.0)	$0.249^{\S}$	0.155^{Σ}
Delta SBP (mmHg)	34.1 (17.3)	37.2 (18.8)	37.0 (23.8)	$0.871^{\#}$	0.113^{Σ}
Recovery 1: mean SBP (mmHg) (SE)	152.5 (2.0)	151.6 (1.9)	144.4 (5.0)	0.318^{∞}	0.578^{Σ}
Recovery 2: mean SBP (mmHg) (SE)	154.5 (2.0)	154.4 (1.9)	148.0 (4.9)	0.447^{∞}	0.711^{Σ}
Recovery 3: mean SBP (mmHg) (SE)	156.2 (2.0)	157.8 (1.9)	155.0 (4.9)	0.778^{∞}	0.590^{Σ}
Recovery 4: mean SBP (mmHg) (SE)	155.8 (2.0)	157.4 (1.9)	153.7 (5.0)	0.732^{∞}	0.668^{Σ}
Diastolic blood pressure (DBP)					
Baseline DBP (mmHg)	78.4 (10.5)	78.9 (12.3)	76.6 (10.7)	$0.550^{\S}$	0.859^{Σ}
Delta DBP (mmHg)	23.0 (11.4)	24.7 (12.0)	22.8 (14.0)	$0.277^{\S}$	0.387^{Σ}
Recovery 1: mean DBP (mmHg) (SE)	72.5 (1.0)	70.8 (1.0)	66.7 (2.6)	0.096^{∞}	0.209^{Σ}
Recovery 2: mean DBP (mmHg) (SE)	76.1 (0.9)	74.5 (0.9)	70.0 (2.4)	0.050^{∞}	0.194^{Σ}
Recovery 3: mean DBP (mmHg) (SE)	76.7 (0.9)	75.6 (0.9)	72.1 (2.4)	0.186^{∞}	0.447^{Σ}
Recovery 4: mean DBP (mmHg) (SE)	76.4 (0.9)	75.3 (0.9)	71.9 (2.3)	0.195^{∞}	0.513^{Σ}
Heart rate (HR)					
Baseline HR (bpm)	67.7 (10.7)	68.8 (10.6)	73.0 (9.2)	$\mathit{0.033}^{\S}$	$\mathbf{0.008}^{\Sigma}$
Delta HR (bpm)	15.5 (6.2)	13.7 (10.5)	13.3 (7.1)	$0.927^{\#}$	$\mathbf{<0.001}^{\Sigma}$
Recovery 1: mean HR (mmHg) (SE)	75.7 (0.9)	76.0 (0.8)	80.6 (2.2)	0.115^{∞}	0.111^{Σ}
Recovery 2: mean HR (mmHg) (SE)	75.9 (0.9)	76.6 (0.9)	81.8 (2.2)	$\mathit{0.048}^{\infty}$	0.081^{Σ}
Recovery 3: mean HR(mmHg) (SE)	75.1 (0.9)	75.7 (0.9)	80.5 (2.2)	0.078^{∞}	0.118^{Σ}
Recovery 4: mean HR (mmHg) (SE)	74.3 (0.9)	75.1 (0.8)	80.3 (2.2)	$\mathit{0.039}^{\infty}$	0.056^{Σ}
OH diagnoses					
OI symptoms (%)	19.8	32.1	61.3	$\mathbf{<0.001}^{\chi}$	$\mathbf{<0.001}^{\chi t}$
COH (%)	92.4	96.2	90.3	0.168^{χ}	$0.473^{\chi t}$
FOH (%)	92.4	94.8	87.1	0.233^{χ}	$0.918^{\chi t}$
IOH (%)	12.7	22.6	38.7	$\mathbf{0.001}^{\chi}$	$\mathbf{<0.001}^{\chi t}$
MOH – overshoot (%)	28.8	22.5	22.6	0.324^{χ}	$0.171^{\chi t}$
MOH – slow recovery (%)	53.0	54.9	51.6	0.898^{χ}	$0.886^{\chi t}$
MOH – non-recovery (%)	18.2	22.5	25.8	0.431^{χ}	$0.197^{\chi t}$

§ One way ANOVA test; $^{\#}$ Kruskal-Wallis test; $^{\infty}$ Repeated measures ANOVA; $^{\Sigma}$ Spearman's rank correlation coefficient; $^{\chi}$ Chi-squared test; $^{\chi t}$ Chi-squared test for trend. Significant P values ($P < 0.01$) are highlighted in bold, and statistical trends ($P < 0.05$) are indicated in italics. SE: standard error; OI: orthostatic intolerance; COH: consensus orthostatic hypotension (OH); FOH: Fedorowski's OH; IOH: initial OH; MOH: morphological OH.

Figure 9.1a. Orthostatic systolic blood pressure (SBP) profiles of the modified Fried's frailty phenotypes.

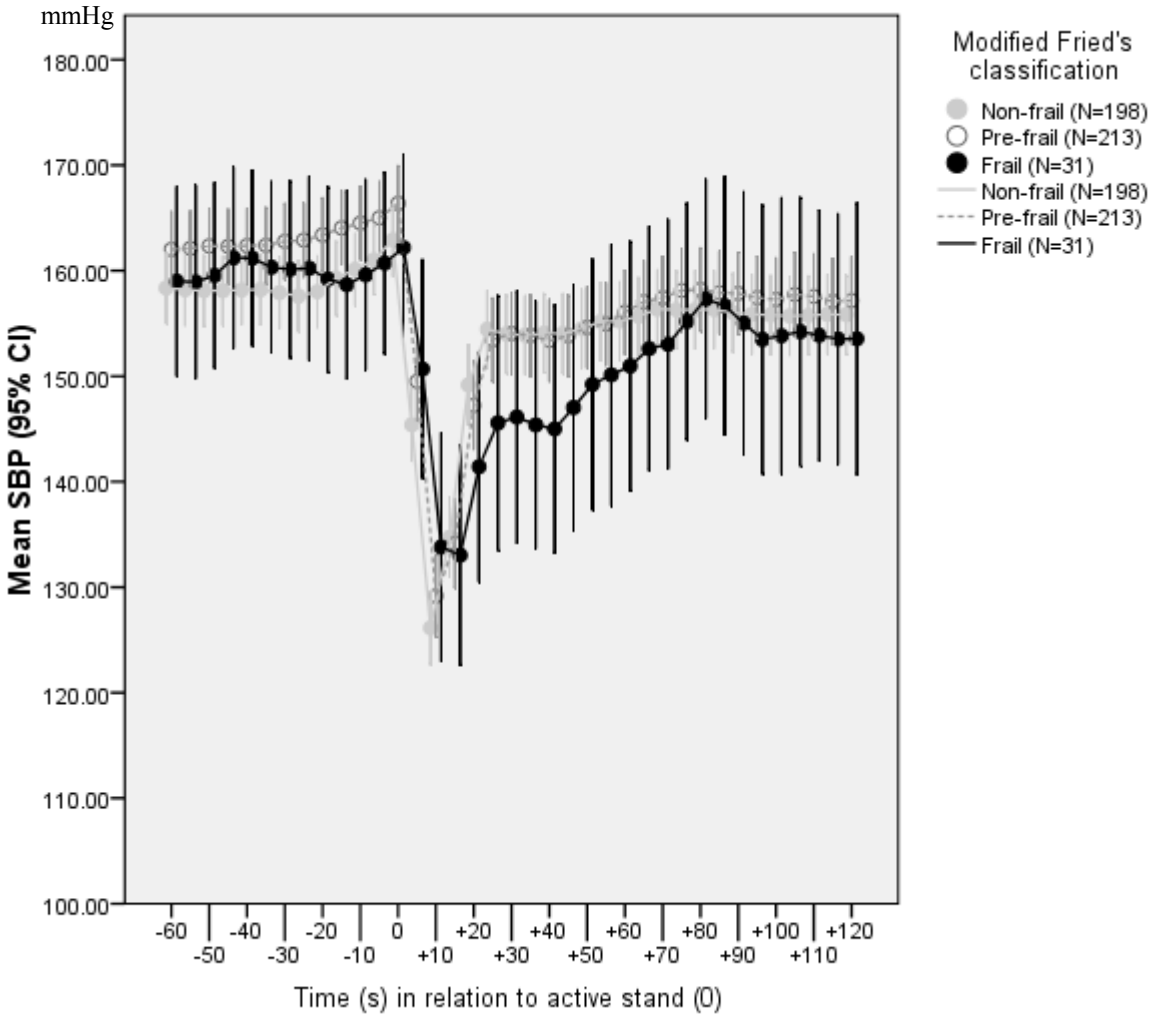


Figure 9.1b. Orthostatic diastolic blood pressure (DBP) profiles of the modified Fried's frailty phenotypes.

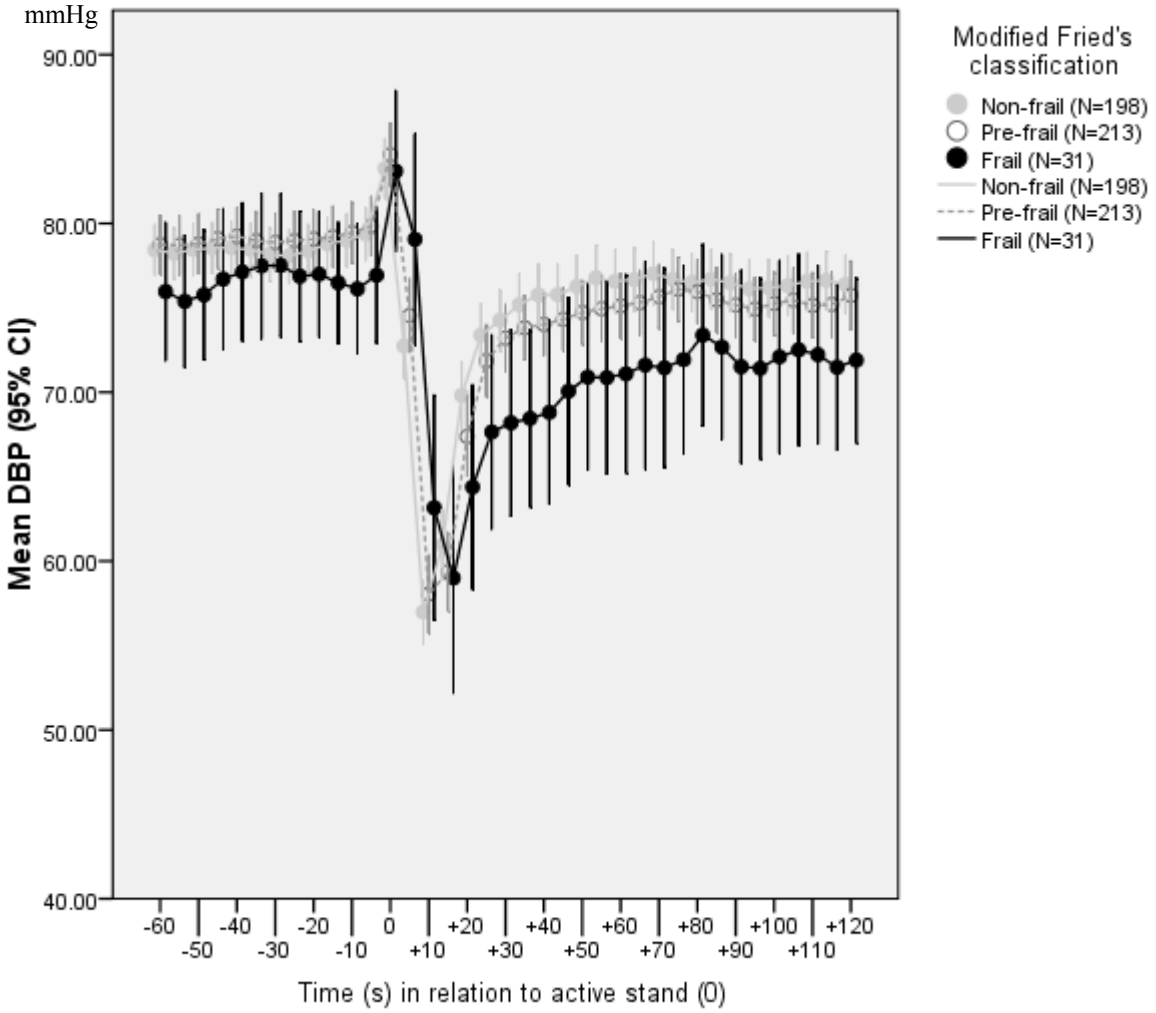
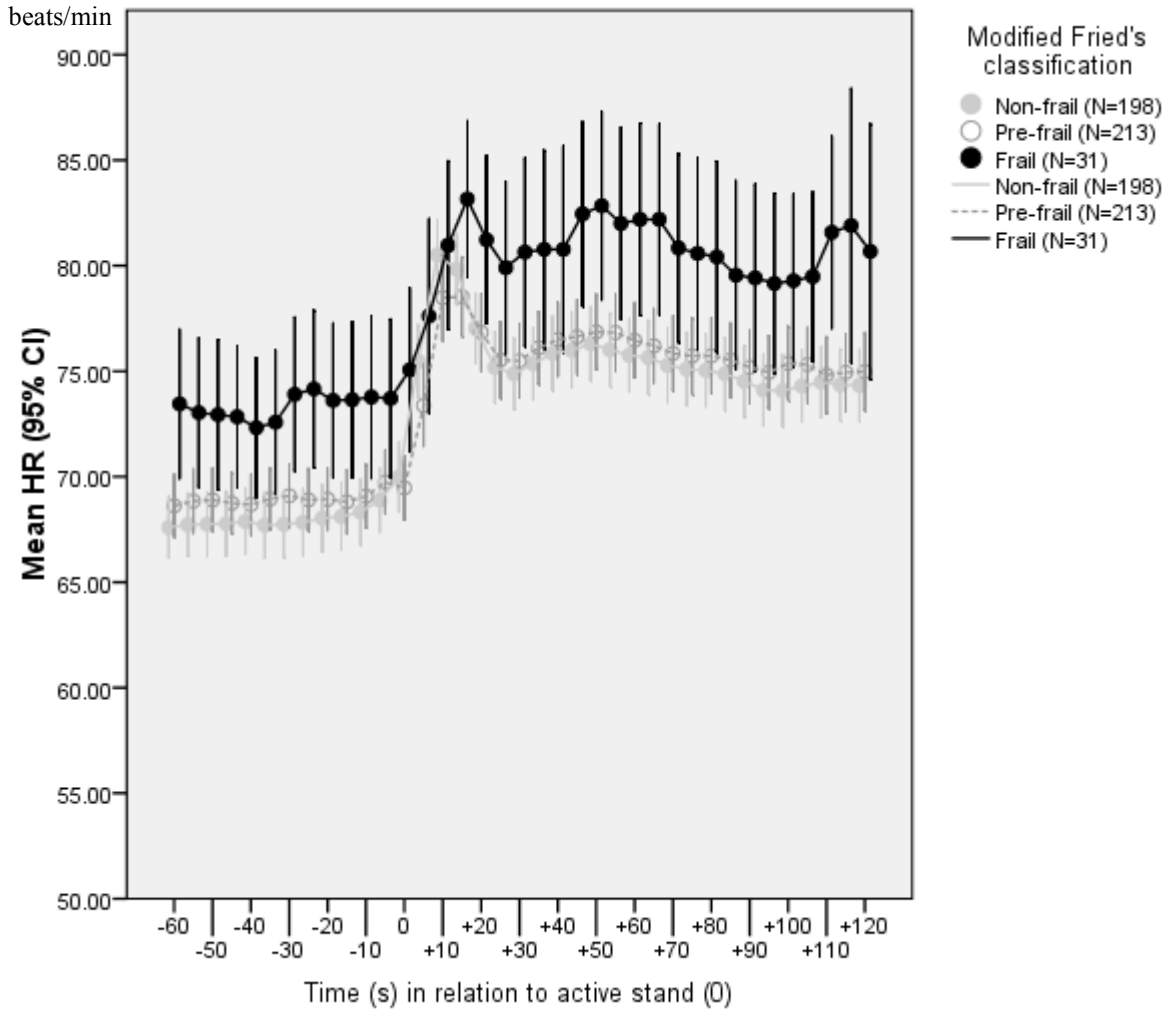


Figure 9.1c. Orthostatic heart rate (HR) profiles
of the modified Fried's frailty phenotypes.



Systolic blood pressure (SBP) profiles

No significant overall differences or linear trends were detected (Table 9.1); this is consistent with the generalised overlap of 95% confidence intervals (CIs) shown in Figure 9.1a.

Diastolic blood pressure (DBP) profiles

No significant overall differences or linear trends were detected (Table 9.1). However, there seemed to be close-to-trend overall differences in mean DBP in recovery phase 1 ($P = 0.096$) and phase 2 ($P = 0.050$). In Figure 9.1b, this is suggested as a lesser degree of overlap between 95% CIs of non-frail and frail subgroups, with the latter appearing to have lower absolute DBP values in recovery phases 1 and 2.

Heart rate (HR) profiles

There was a significant *increasing gradient in mean baseline HR* across frailty groups (non-frail: 67.7 bpm; pre-frail: 68.8 bpm; frail: 73.0 bpm; $P = 0.008$), with a trend towards an overall between-groups difference ($P = 0.033$) at the expense of the trend between non-frail and frail (Bonferroni-adjusted $P = 0.029$) (Figure 9.1c). A significant *decreasing gradient in mean delta HR* across frailty groups was also detected (non-frail: 15.5 bpm; pre-frail: 13.7 bpm; frail: 13.3 bpm; $P < 0.001$), although the between-group differences did not reach significance. However, there seemed to be close-to-trend overall differences in mean HR in recovery phase 2 ($P = 0.048$), phase 3 ($P = 0.078$) and phase 4 ($P = 0.039$). In Figure 9.1c, this is suggested as a lesser degree of overlap between 95% CIs of non-frail and frail subgroups, with the latter appearing to have higher absolute HR values in recovery phases 2, 3 and 4.

Orthostatic hypotension (OH) diagnoses

In terms of OH diagnoses, the only significant correlations of the modified Fried's classification were with *orthostatic intolerance* (OI) and *initial OH* (IOH) ($P < 0.001$, both for gradients and overall differences). 19.8% of the non-frail had OI during active stand (the subgroup prevalence of IOH was 12.7%); 32.1% of the pre-frail had OI (22.6% prevalence of IOH); and 61.3% of the frail had OI (38.7% prevalence of IOH) (Table 9.1).

TRIL Frailty Index (TRIL-FI) categories: orthostatic hemodynamic profiles and prevalence of orthostatic hypotension

Table 9.2 summarises the orthostatic hemodynamic profiles and OH prevalences for the TRIL-FI categories and Figures 9.2a-c show their 5-second-averaged hemodynamic profiles for SBP, DBP and HR, respectively.

Table 9.2. Orthostatic hemodynamic profiles and orthostatic hypotension prevalences of the TRIL-FI categories.

	Non-frail $N = 155$	Pre-frail $N = 201$	Frail $N = 86$	P value (overall difference)	P value (linear trend)
Systolic blood pressure (SBP)					
Baseline SBP (mmHg)	157.7 (20.6)	160.0 (24.2)	166.2 (29.8)	*0.034*§	*0.046*$^{\Sigma}$
Delta SBP (mmHg)	35.7 (17.1)	34.3 (17.6)	39.5 (22.6)	0.195$^{\#}$	0.499$^{\Sigma}$
Recovery 1: mean SBP (mmHg) (SE)	150.8 (2.2)	153.6 (2.0)	147.8 (3.0)	0.258$^{\infty}$	0.831$^{\Sigma}$
Recovery 2: mean SBP (mmHg) (SE)	153.2 (2.2)	155.0 (1.9)	153.2 (3.0)	0.795$^{\infty}$	0.912$^{\Sigma}$
Recovery 3: mean SBP (mmHg) (SE)	153.7 (2.2)	157.6 (1.9)	160.9 (3.0)	0.135$^{\infty}$	0.056$^{\Sigma}$
Recovery 4: mean SBP (mmHg) (SE)	153.4 (2.2)	156.1 (2.0)	162.6 (3.0)	0.051$^{\infty}$	*0.035*$^{\Sigma}$
Diastolic blood pressure (DBP)					
Baseline DBP (mmHg)	78.9 (10.4)	78.5 (11.5)	78.0 (12.7)	0.839§	0.465$^{\Sigma}$
Delta DBP (mmHg)	24.3 (11.6)	22.7 (11.4)	25.5 (13.3)	0.153§	0.880$^{\Sigma}$
Recovery 1: mean DBP (mmHg) (SE)	72.5 (1.1)	72.2 (1.0)	66.9 (1.5)	**0.006**$^{\infty}$	*0.034*$^{\Sigma}$
Recovery 2: mean DBP (mmHg) (SE)	76.6 (1.0)	75.2 (0.9)	71.0 (1.4)	**0.005**$^{\infty}$	*0.010*$^{\Sigma}$
Recovery 3: mean DBP (mmHg) (SE)	76.7 (1.1)	76.0 (0.9)	73.9 (1.4)	0.266$^{\infty}$	0.225$^{\Sigma}$
Recovery 4: mean DBP (mmHg) (SE)	76.4 (1.0)	75.4 (0.9)	74.3 (1.4)	0.455$^{\infty}$	0.365$^{\Sigma}$
Heart rate (HR)					
Baseline HR (bpm)	68.2 (9.4)	68.5 (11.5)	69.7 (10.3)	0.573§	0.143$^{\Sigma}$
Delta HR (bpm)	15.8 (6.2)	14.8 (10.4)	11.4 (7.4)	**<0.001**$^{\#}$	**<0.001**$^{\Sigma}$
Recovery 1: mean HR (mmHg) (SE)	76.5 (1.0)	76.1 (0.9)	75.8 (1.3)	0.906$^{\infty}$	0.727$^{\Sigma}$
Recovery 2: mean HR (mmHg) (SE)	76.8 (1.0)	76.2 (0.9)	77.3 (1.4)	0.799$^{\infty}$	0.543$^{\Sigma}$
Recovery 3: mean HR(mmHg) (SE)	76.1 (1.0)	75.2 (0.9)	76.5 (1.3)	0.663$^{\infty}$	0.868$^{\Sigma}$
Recovery 4: mean HR (mmHg) (SE)	75.6 (1.0)	74.3 (0.9)	75.9 (1.3)	0.502$^{\infty}$	0.911$^{\Sigma}$
OI and OH diagnoses					
OI symptoms (%)	15.0	34.3	39.5	**<0.001**$^{\chi}$	**<0.001**$^{\chi t}$
COH (%)	92.9	94.5	95.3	0.701$^{\chi}$	0.411$^{\chi t}$
FOH (%)	92.3	94.0	93.0	0.802$^{\chi}$	0.730$^{\chi t}$
IOH (%)	11.1	22.4	26.7	**0.004**$^{\chi}$	**0.002**$^{\chi t}$
MOH – overshoot (%)	25.2	26.4	23.3	0.855$^{\chi}$	0.819$^{\chi t}$
MOH – slow recovery (%)	57.4	54.2	46.5	0.263$^{\chi}$	0.118$^{\chi t}$
MOH – non-recovery (%)	17.4	19.4	30.2	0.051$^{\chi}$	*0.030*$^{\chi t}$

§ One way ANOVA test; $^{\#}$ Kruskal-Wallis test; $^{\infty}$ Repeated measures ANOVA; $^{\Sigma}$ Spearman's rank correlation coefficient; $^{\chi}$ Chi-squared test; $^{\chi t}$ Chi-squared test for trend. Significant P values ($P < 0.01$) are highlighted in bold, and statistical trends ($P < 0.05$) are indicated in italics. SE: standard error; OI: orthostatic intolerance; COH: consensus orthostatic hypotension (OH); FOH: Fedorowski's OH; IOH: initial OH; MOH: morphological OH.

Figure 9.2a. Orthostatic systolic blood pressure (SBP) profiles of the TRIL-FI categories.

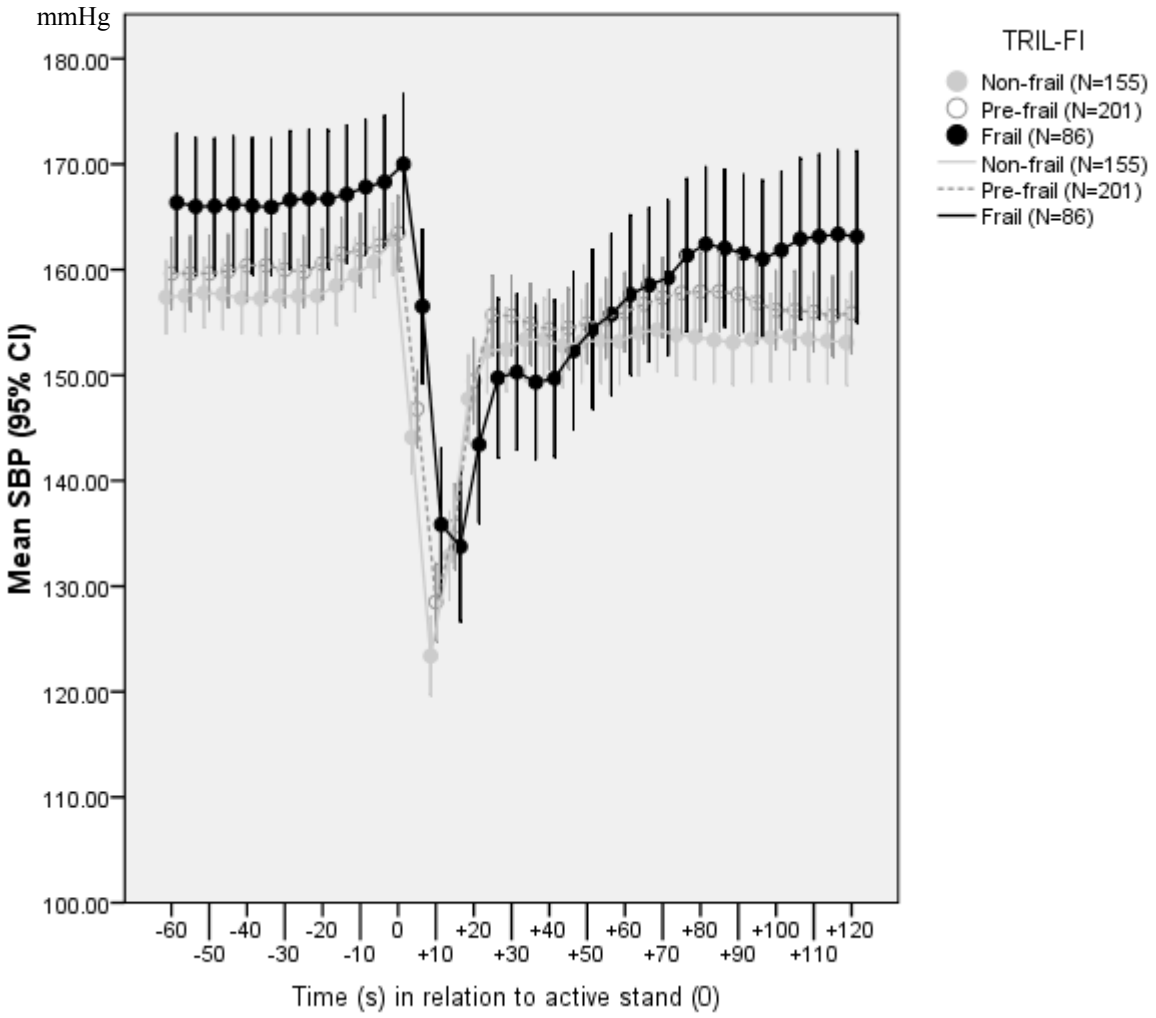


Figure 9.2b. Orthostatic diastolic blood pressure (DBP) profiles of the TRIL-FI categories.

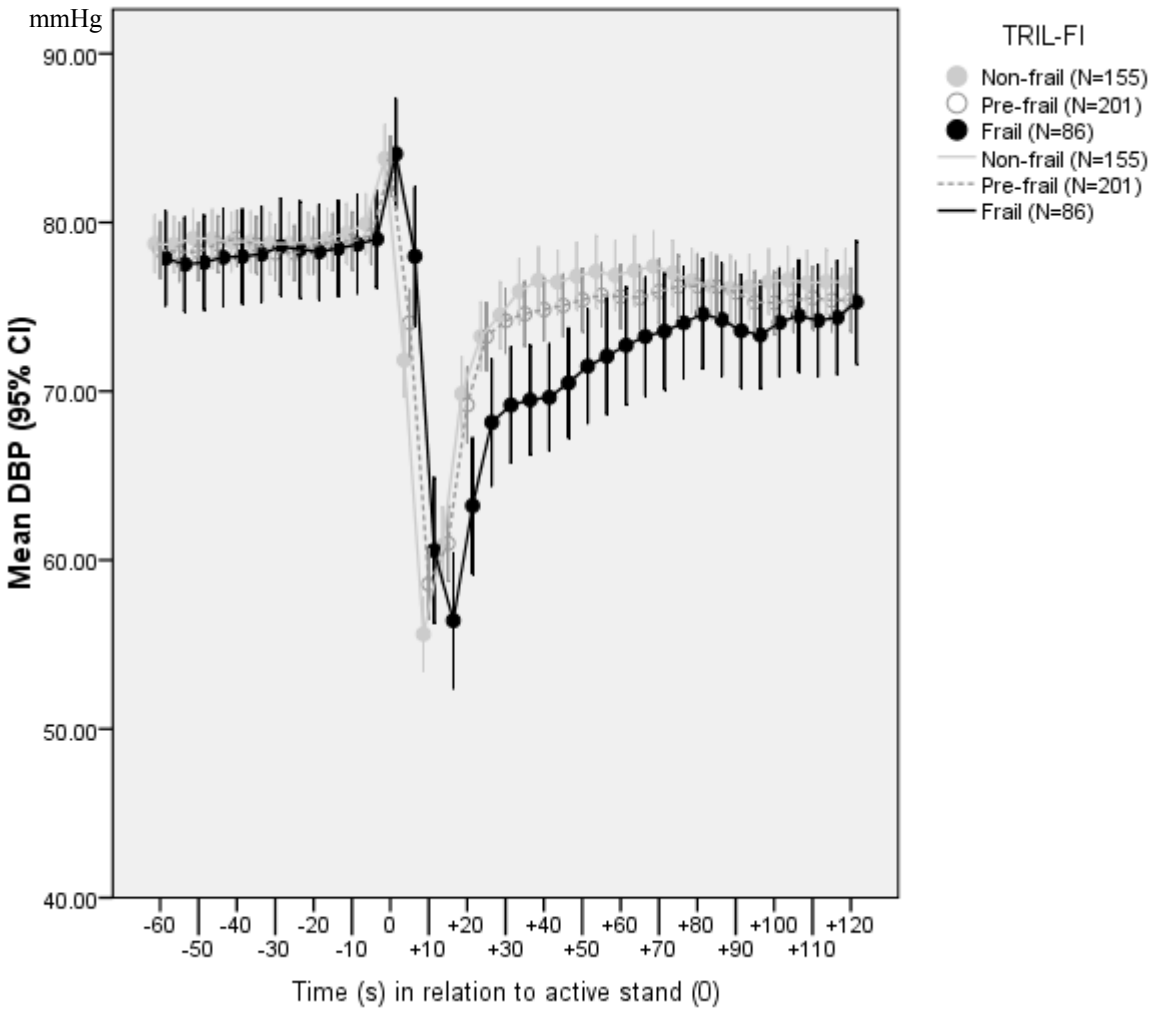
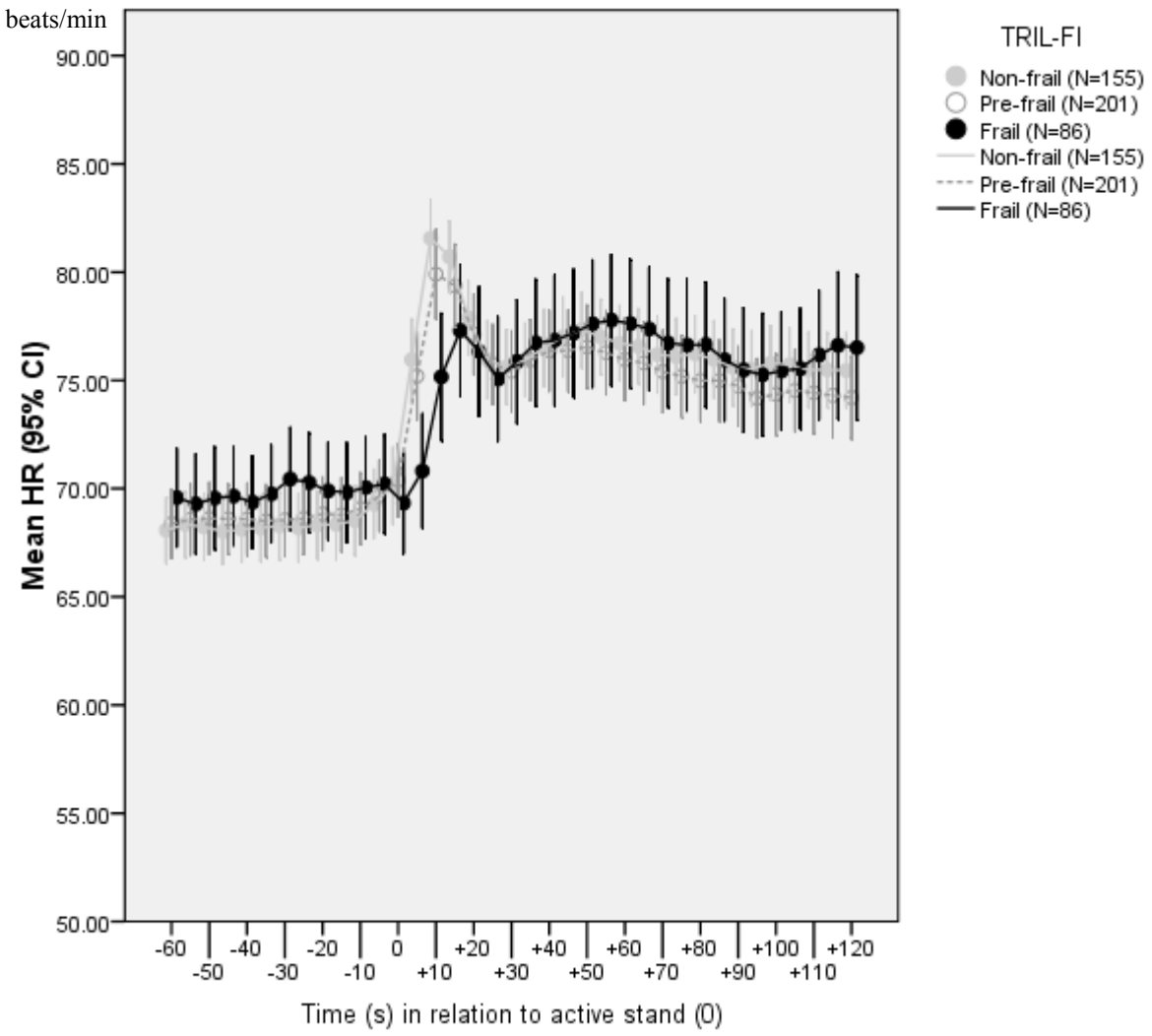


Figure 9.2c. Orthostatic heart rate (HR) profiles of the TRIL-FI categories.



Systolic blood pressure (SBP) profiles

The TRIL-FI classification revealed a statistical trend towards an *increasing gradient in mean baseline SBP* across frailty subgroups (non-frail: 157.7 mmHg; pre-frail: 160.0 mmHg; frail: 166.2 mmHg; $P = 0.046$). Pairwise comparisons suggested that the overall trend towards difference between subgroups ($P = 0.034$) was at the expense of a trend towards difference between the frail and non-frail (Tamhane-adjusted $P = 0.061$). There was also a trend towards an increasing gradient of SBP at recovery phase 4 ($P = 0.035$), consistent with the trend found at baseline (Figure 9.2a).

Diastolic blood pressure (DBP) profiles

There were significant overall differences in mean DBP at recovery phase 1 ($P = 0.006$) and phase 2 ($P = 0.005$), with trends towards *decreasing gradients of mean DBP* across subgroups in the first two recovery phases ($P = 0.034$ and $P = 0.010$, respectively). In recovery phase 1, the pairwise comparisons suggested trends towards differences between frail and pre-frail (Tamhane-adjusted $P = 0.033$), and between frail and non-frail (Tamhane-adjusted $P = 0.021$). In recovery phase 2, there was a trend towards a difference between frail and non-frail (Tamhane-adjusted $P = 0.010$). In Figure 9.2b, these differences are suggested by the lack of overlap between 95% CIs in recovery phases 1 and 2, with frail having lower mean DBP values than pre-frail and non-frail.

Heart rate (HR) profiles

There was a significant *decreasing gradient in mean delta HR* across frailty subgroups (non-frail: 15.8 bpm; pre-frail: 14.8 bpm; frail: 11.4 bpm; $P < 0.001$), with significant between-group differences ($P < 0.001$). The pairwise comparisons indicated significant

differences between frail and non-frail (Bonferroni-adjusted $P = 0.001$), and between frail and pre-frail (Bonferroni-adjusted $P = 0.006$). There were no baseline or recovery differences in HR with the TRIL-FI classification (Figure 9.2c).

Orthostatic hypotension (OH) diagnoses

TRIL-FI had significant correlations with *orthostatic intolerance* (OI) ($P < 0.001$, both for gradient and overall difference) and *initial OH* (IOH) ($P = 0.002$ for gradient and $P = 0.004$ for overall difference). 15.0% of the non-frail had OI during active stand (the subgroup prevalence of IOH was 11.1%); 34.3% of the pre-frail had OI (22.4% prevalence of IOH); and 39.5% of the frail had OI (26.7% prevalence of IOH) (Table 9.2).

TRIL-FI also revealed a trend for an *increasing gradient of prevalence in non-recovery pattern* according to the morphological OH (MOH) classification ($P = 0.030$), with a close-to-trend overall difference ($P = 0.051$). The prevalences of MOH non-recovery pattern were 17.4% in the non-frail, 19.4% in the pre-frail and 30.2% in the frail (Table 9.2).

Summary: the orthostatic hallmarks of frailty

In this chapter, the aim was to classify a sample of community-dwelling older people into three increasing frailty categories according to two frailty classification methods (i.e. modified Fried and TRIL-FI) and compare their orthostatic hemodynamic profiles and prevalences of OH, looking for the presence of gradients (i.e. linear trends).

Statistically significant bivariate correlations with both classifications were: (1) the association of *decreasing orthostatic HR response* (i.e. delta HR) with increasing frailty; and (2) the *increasing prevalence of OI and IOH* with increasing frailty. In addition, the modified Fried's classification showed that *increasing baseline HR* is associated with increasing frailty. TRIL-FI also suggested (1): that *increasing baseline SBP* is associated with increasing frailty; (2) that lower DBP during early recovery (phases 1, 2) is associated with increasing frailty; and (3) that the non-recovery pattern in SBP (MOH Cluster 3) is increasingly prevalent in frailty.

Regarding the differences in orthostatic HR response across frailty subgroups, results are consistent with previous studies showing a tendency towards attenuation of the orthostatic HR response with *age* (36, 37, 499-504). A decreasing orthostatic HR response with *frailty* was consistently found in the present study (Tables 8.3a and 8.6a), mirroring that the frailty categories represent *increasing ageing stages within old age*.

Regarding the baseline HR finding, the recent *Treating New Targets* trial showed that a resting HR $\geq$ 70 beats/min (NB: as in the frail subgroup according to the modified Fried's classification) was associated with a 40% increased risk of all-cause mortality

(505), in keeping with previous evidence that elevated resting HR is an independent risk factor for cardiovascular disease (506) and death (507). Frailty is also a powerful predictor of mortality (289, 373) and, interestingly, Fried *et al*. have suggested that HR dynamics might be useful for the screening and monitoring of clinical vulnerability in older adults (508), and that cardiac autonomic control is impaired in frailty (9). In 1983, Wieling *et al*. had already reported that an abrupt and large HR increase after actively standing excludes cardiac parasympathetic neuropathy (509).

The suggestion that increasing baseline SBP may be associated with increasing frailty could be seen together with the well-known increasing prevalence of isolated systolic hypertension with age (47), which has deleterious, frailty-like consequences (510-517). The other suggestion that impaired orthostatic blood pressure recoverability may be associated with frailty (i.e. DBP and MOH trends) is also supported by studies that focused on ageing; for example, a study showed that ageing is associated with slower corrections of MAP following standing (518), and another study showed that the increase of the DBP on standing was reduced in elderly individuals (503).

Chapter 10

Is orthostatic hypotension a marker of frailty?

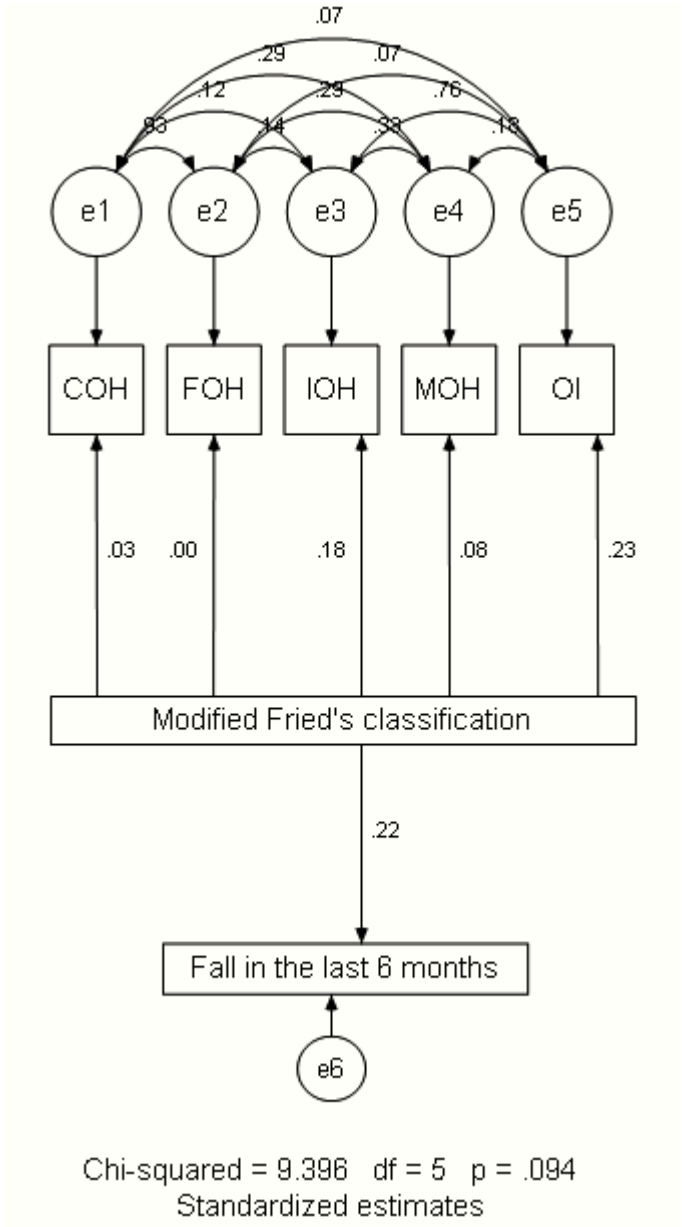
In this chapter, structural equation models are employed to answer the question whether any of the orthostatic hypotension (OH) definitions (*consensus*, *Fedorowski-modified*, *initial*, *morphological*, and *orthostatic intolerance* classifications) are markers of frailty (by the *modified Fried*'s classification or the TRIL *Frailty Index*). SEM models are also used to assess the independent association of OH with falls in the face of frailty, and to assess the potential confounding effect of polypharmacy on the association between OH and frailty. A final pathophysiological SEM model of interrelationships between frailty, orthostatic hemodynamics, orthostatic intolerance and previous falls is tested, and the findings are discussed in the light of previous literature.

Using structural equation modelling to test the orthostatic hypotension classifications as indicators of frailty and predictors of falls

Figure 10.1a shows a structural equation model (SEM) with the OH classifications as indicators of frailty (modified Fried's frailty classification), and Figure 10.1b shows the same model with the significant frailty indicators in Figure 10.1a being postulated as independent risk factors for falls. In both models, frailty is postulated as a risk factor for falls, and the errors of all the OH definitions are drawn as inter-correlated, because their measurement errors are not independent (i.e. for each case the five definitions are based on the same active stand) (519). In Figure 10.1a, the significant regression coefficients were Frailty → IOH ($\beta = 0.18$, $P < 0.001$), Frailty → OI ($\beta = 0.23$, $P < 0.001$) and Frailty → Faller ($\beta = 0.22$, $P < 0.001$). All error covariances were significant ($P < 0.01$), except for e1 ⇔ e3 ($\beta = 0.12$, $P = 0.014$), e1 ⇔ e5 ($\beta = 0.07$, $P = 0.159$) and e2 ⇔ e5 ($\beta = 0.07$, $P = 0.120$). Overall, the model had good fit: Chi-squared = 9.396, df = 5, $P = 0.094$; other fit indices are shown in Table 10.1a. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

In Figure 10.1b, the significant regression coefficients were Frailty → IOH ($\beta = 0.18$, $P < 0.001$), Frailty → OI ($\beta = 0.23$, $P < 0.001$) and Frailty → Faller ($\beta = 0.19$, $P < 0.001$). The postulated regressions IOH → Faller ($\beta = 0.12$, $P = 0.113$) and OI → Faller ($\beta = 0.02$, $P = 0.766$) were not statistically significant. All error covariances were significant ($P < 0.01$), except for e1 ⇔ e3 ($\beta = 0.12$, $P = 0.014$), e1 ⇔ e5 ($\beta = 0.07$, $P = 0.159$) and e2 ⇔ e5 ($\beta = 0.07$, $P = 0.120$). Overall, the model had a good fit: Chi-squared = 1.478, df = 3, $P = 0.687$; other fit indices are shown in Table 10.1b. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 10.1a. SEM with the OH classifications as indicators of frailty (modified Fried's classification).

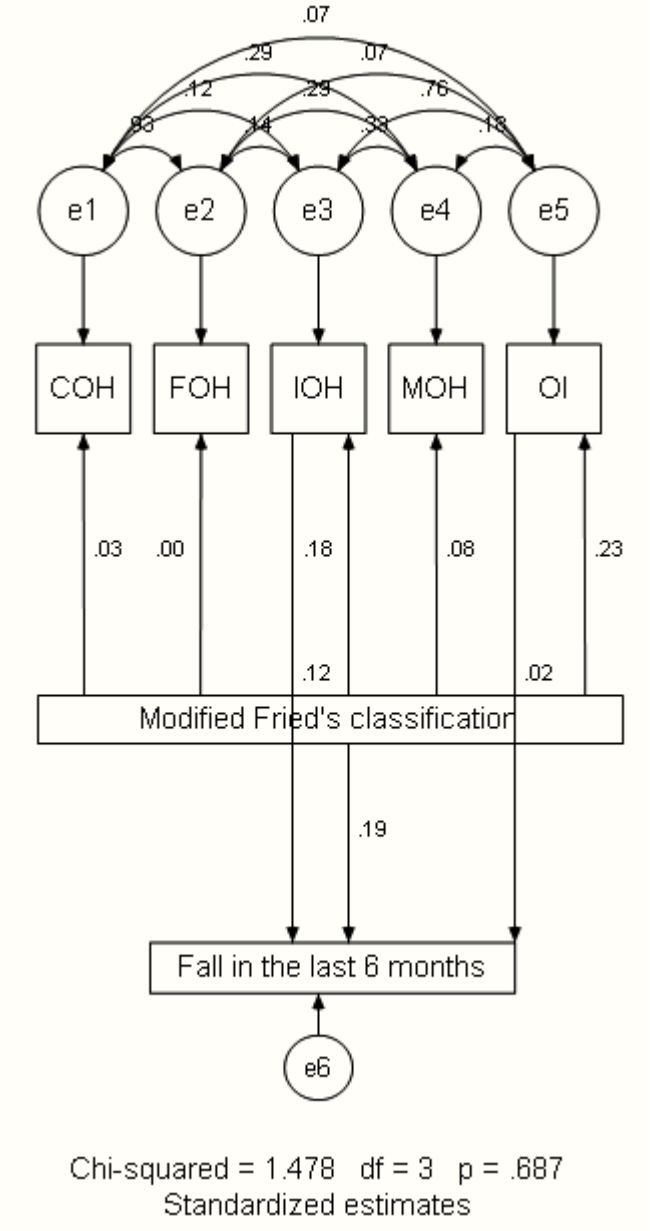


Significant regression coefficients: Frailty → IOH (β = 0.18, $P < 0.001$), Frailty → OI (β = 0.23, $P < 0.001$); Frailty → Faller (β = 0.22, $P < 0.001$).

Table 10.1a. Fit indices for the SEM in Figure 10.1a.

Fit index	Values
NFI (normalized fit index)	0.99
RFI (relative fit index)	0.96
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	0.98
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.05 (0.00 – 0.09, $P = 0.516$)

Figure 10.1b. SEM with the OH classifications as indicators of frailty (modified Fried's classification). The significant indicators were postulated as independent risk factor for falls.



Significant regression coefficients: Frailty → IOH (β = 0.18, $P < 0.001$), Frailty → OI (β = 0.23, $P < 0.001$), Frailty → Faller (β = 0.19, $P < 0.001$).

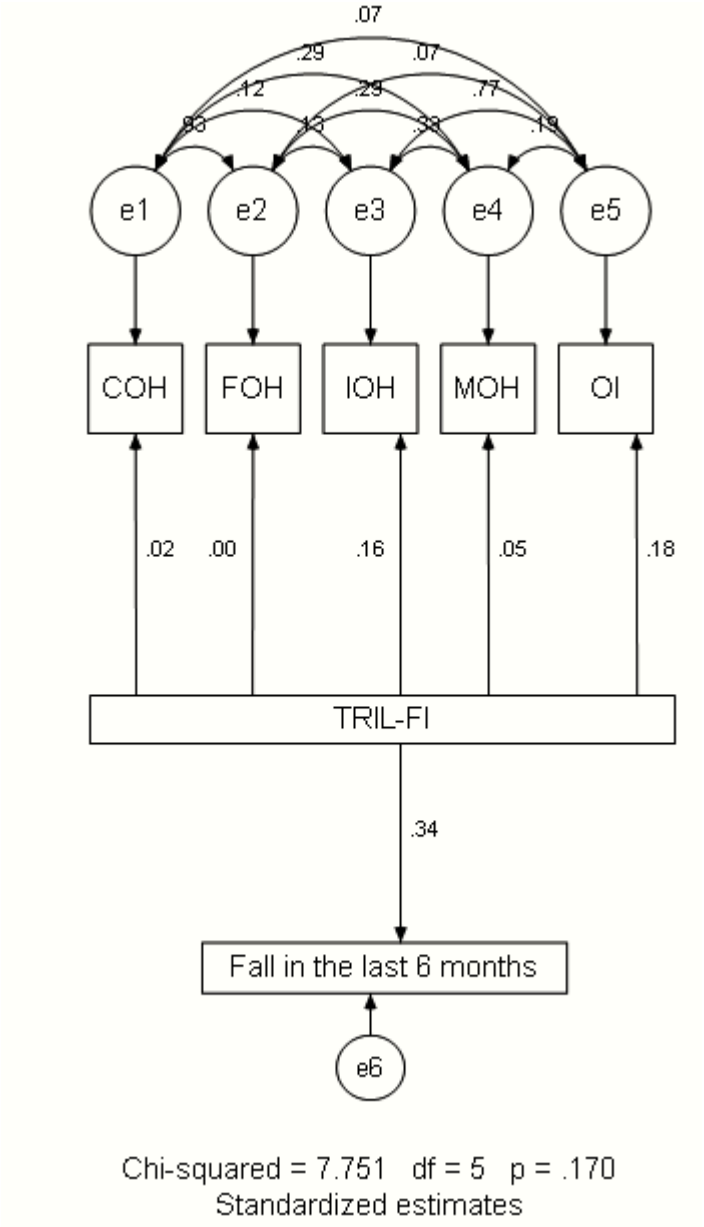
Table 10.1b. Fit indices for the SEM in Figure 10.1b.

Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	0.99
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.06, $P = 0.909$)

Figures 10.2a and 10.2b show the same two models above using TRIL-FI instead of the modified Fried's classification. Results were the same. In Figure 10.2a, the significant regression coefficients were Frailty → IOH (β = 0.16, $P < 0.001$), Frailty → OI (β = 0.18, $P < 0.001$) and Frailty → Faller (β = 0.34, $P < 0.001$). All error covariances were significant ($P < 0.01$), except for e1 ⇔ e3 (β = 0.12, $P = 0.012$), e1 ⇔ e5 (β = 0.07, $P = 0.137$) and e2 ⇔ e5 (β = 0.07, $P = 0.135$). Overall, the model had a good fit: Chi-squared = 7.751, df = 5, $P = 0.170$; other fit indices are shown in Table 10.2a. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

In Figure 10.2b, the significant regression coefficients were Frailty → IOH (β = 0.16, $P < 0.001$), Frailty → OI (β = 0.18, $P < 0.001$) and Frailty → Faller (β = 0.32, $P < 0.001$). The postulated regressions IOH → Faller (β = 0.10, $P = 0.168$) and OI → Faller (β = 0.02, $P = 0.754$) were not significant. All error covariances were significant ($P < 0.01$), except for e1 ⇔ e3 (β = 0.12, $P = 0.012$), e1 ⇔ e5 (β = 0.07, $P = 0.137$) and e2 ⇔ e5 (β = 0.07, $P = 0.135$). Overall, the model had a good fit: Chi-squared = 1.333, df = 3, $P = 0.721$; other fit indices are shown in Table 10.2b. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 10.2a. SEM with the OH classifications as indicators of frailty (TRIL-FI).

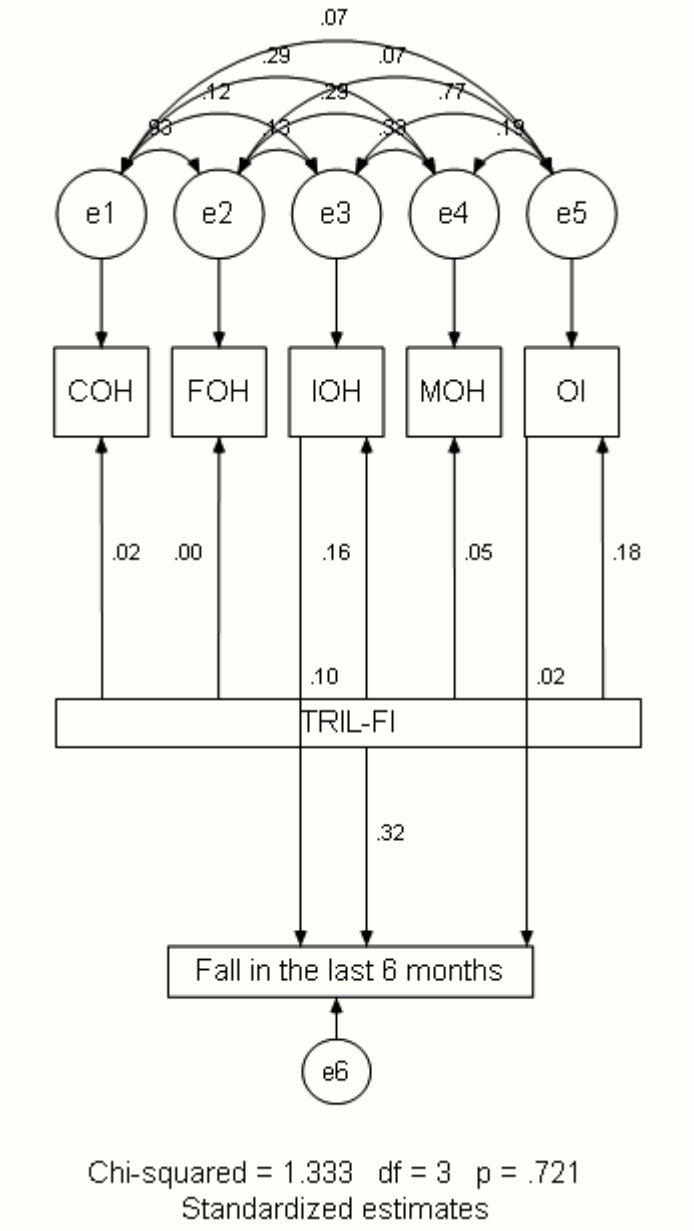


Significant regression coefficients: Frailty → IOH (β = 0.16, $P < 0.001$), Frailty → OI (β = 0.18, $P < 0.001$), Frailty → Faller (β = 0.34, $P < 0.001$).

Table 10.2a. Fit indices for the SEM in Figure 10.2a.

Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	0.97
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	0.99
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.04 (0.00 – 0.08, $P = 0.641$)

Figure 10.2b. SEM with the OH classifications as indicators of frailty (TRIL-FI).
The significant indicators were postulated as independent risk factor for falls.



Significant regression coefficients: Frailty → IOH (β = 0.16, $P < 0.001$),
Frailty → OI (β = 0.18, $P < 0.001$), Frailty → Faller (β = 0.32, $P < 0.001$).

Table 10.2b. Fit indices for the SEM in Figure 10.2b.

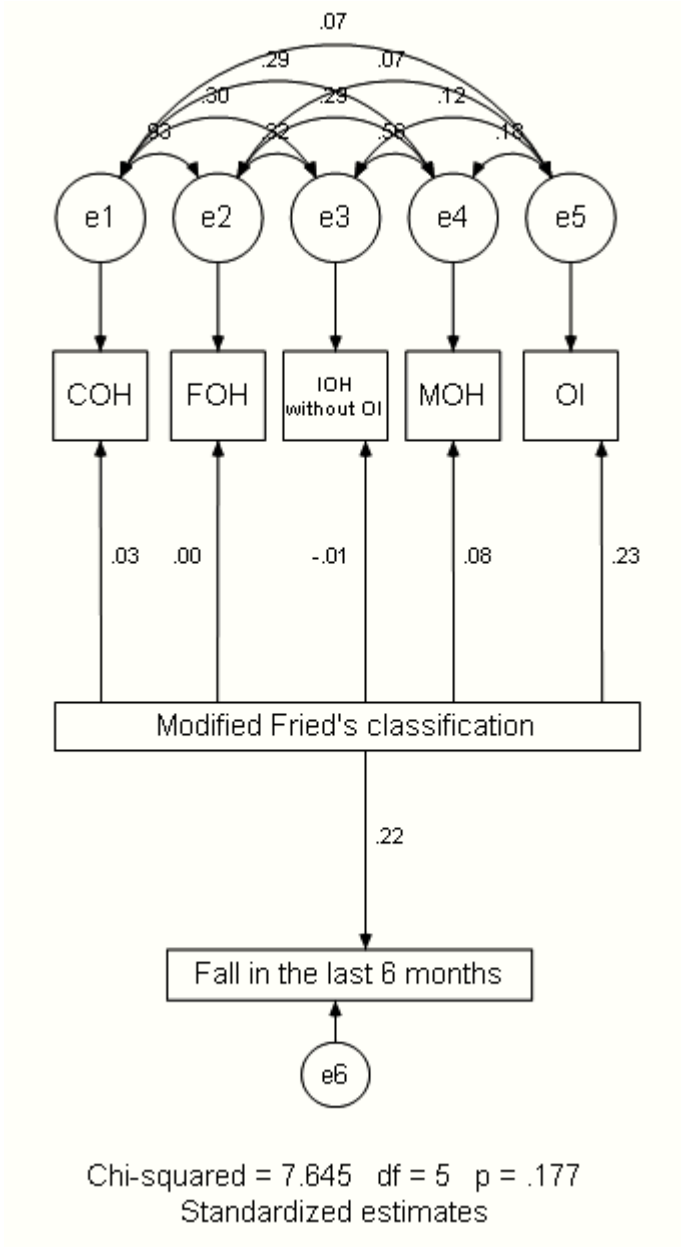
Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	0.99
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.06, $P = 0.921$)

In the above models, both IOH and OI were significant indicators of frailty. However, *since OI is included in the IOH definition*, it is possible that the correlation of IOH with frailty could be at the expense of its *OI component*. To explore the extent to which *the hemodynamic component* of IOH was independently correlated with frailty, the above four SEM models were repeated using a modified version of the IOH definition (i.e. basing it on the initial SBP and DBP drop criteria only, and not taking OI into account).

In Figure 10.3a, the significant regression coefficients were Frailty → OI ($\beta = 0.23$, $P < 0.001$) and Frailty → Faller ($\beta = 0.22$, $P < 0.001$). All error covariances were significant ($P < 0.01$), except for e3 ⇔ e5 ($\beta = 0.12$, $P = 0.016$), e1 ⇔ e5 ($\beta = 0.07$, $P = 0.159$) and e2 ⇔ e5 ($\beta = 0.07$, $P = 0.120$). Overall, the model had a good fit: Chi-squared = 7.645, df = 5, $P = 0.177$; other fit indices are shown in Table 10.3a. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

In Figure 10.3b, the significant regression coefficients were Frailty → OI ($\beta = 0.23$, $P < 0.001$) and Frailty → Faller ($\beta = 0.19$, $P < 0.001$). The postulated regression OI → Faller ($\beta = 0.11$, $P = 0.020$) had a *trend towards significance*. All error covariances were significant ($P < 0.01$), except for e3 ⇔ e5 ($\beta = 0.12$, $P = 0.016$), e1 ⇔ e5 ($\beta = 0.07$, $P = 0.159$) and e2 ⇔ e5 ($\beta = 0.07$, $P = 0.120$). Overall, the model had a good fit: Chi-squared = 2.238, df = 4, $P = 0.692$; other fit indices are shown in Table 10.3b. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 10.3a. SEM with the OH classifications (IOH modified) as indicators of frailty (modified Fried's classification).

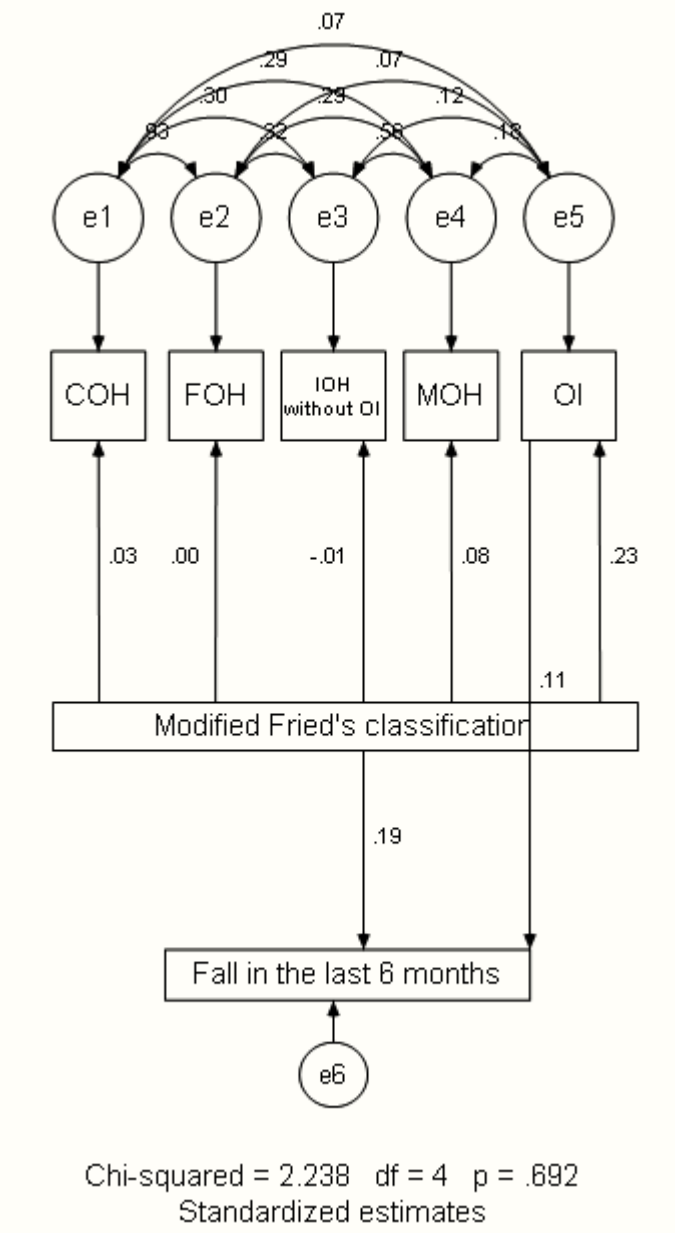


Significant regression coefficients:
Frailty → OI (β = 0.23, $P < 0.001$), Frailty → Faller (β = 0.22, $P < 0.001$).

Table 10.3a. Fit indices for the SEM in Figure 10.3a.

Fit index	Values
NFI (normalized fit index)	0.99
RFI (relative fit index)	0.96
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.04 (0.00 – 0.08, $P = 0.649$)

Figure 10.3b. SEM with the OH classifications (IOH modified) as indicators of frailty (modified Fried's classification). The significant indicators were postulated as independent risk factor for falls.



Significant regression coefficients: Frailty → OI (β = 0.23, $P < 0.001$),
Frailty → Faller (β = 0.19, $P < 0.001$). Trend: OI → Faller (β = 0.11, $P = 0.020$).

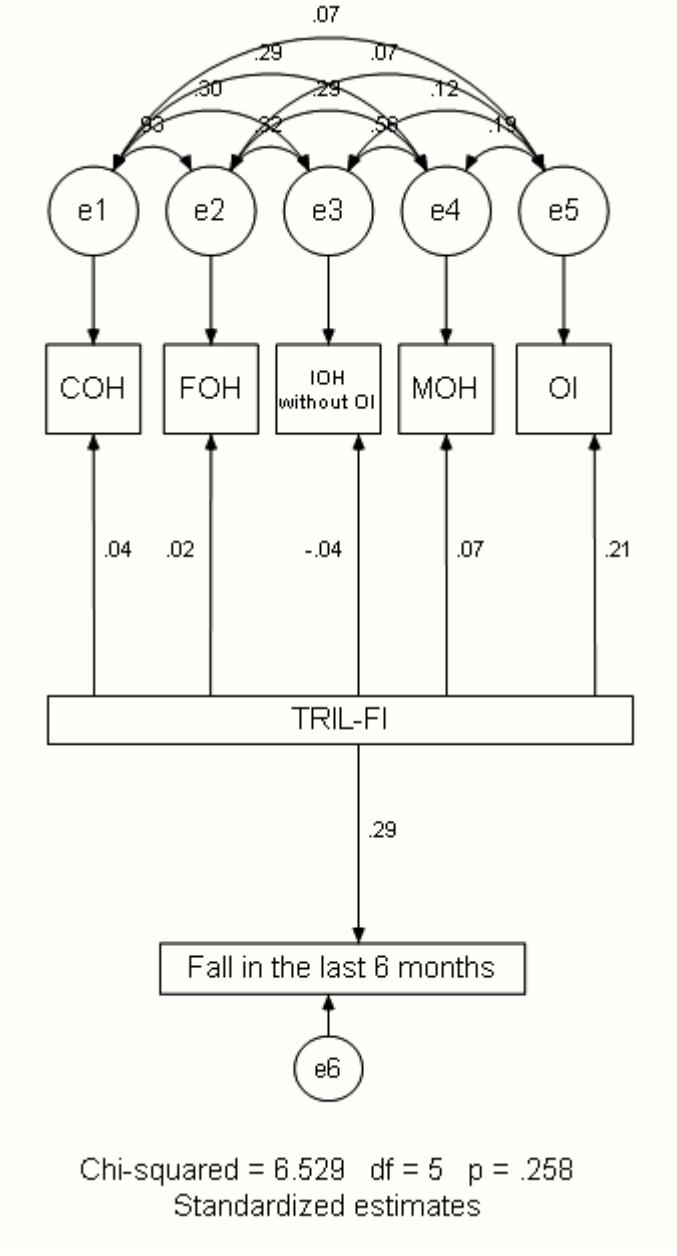
Table 10.3b. Fit indices for the SEM in Figure 10.3b.

Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	1.00
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.06, $P = 0.932$)

Figures 10.4a and 10.4b show the two models above repeated with TRIL-FI. In Figure 10.4a, the significant regression coefficients were Frailty → OI (β = 0.21, $P < 0.001$) and Frailty → Faller (β = 0.29, $P < 0.001$). All error covariances were significant ($P < 0.01$), except for e3 ⇔ e5 (β = 0.12, $P = 0.012$), e1 ⇔ e5 (β = 0.07, $P = 0.165$) and e2 ⇔ e5 (β = 0.07, $P = 0.147$). Overall, the model had a good fit: Chi-squared = 6.529, df = 5, $P = 0.258$; other fit indices are shown in Table 10.4a. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

In Figure 10.4b, the significant regression coefficients were Frailty → OI (β = 0.21, $P < 0.001$) and Frailty → Faller (β = 0.27, $P < 0.001$). The postulated regression OI → Faller (β = 0.10, $P = 0.035$) had a *trend towards significance*. All error covariances were significant ($P < 0.01$), except for e3 ⇔ e5 (β = 0.12, $P = 0.012$), e1 ⇔ e5 (β = 0.07, $P = 0.165$) and e2 ⇔ e5 (β = 0.07, $P = 0.147$). Overall, the model had a good fit: Chi-squared = 2.086, df = 4, $P = 0.720$; other fit indices are shown in Table 10.4b. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 10.4a. SEM with the OH classifications (IOH modified) as indicators of frailty (TRIL-FI).

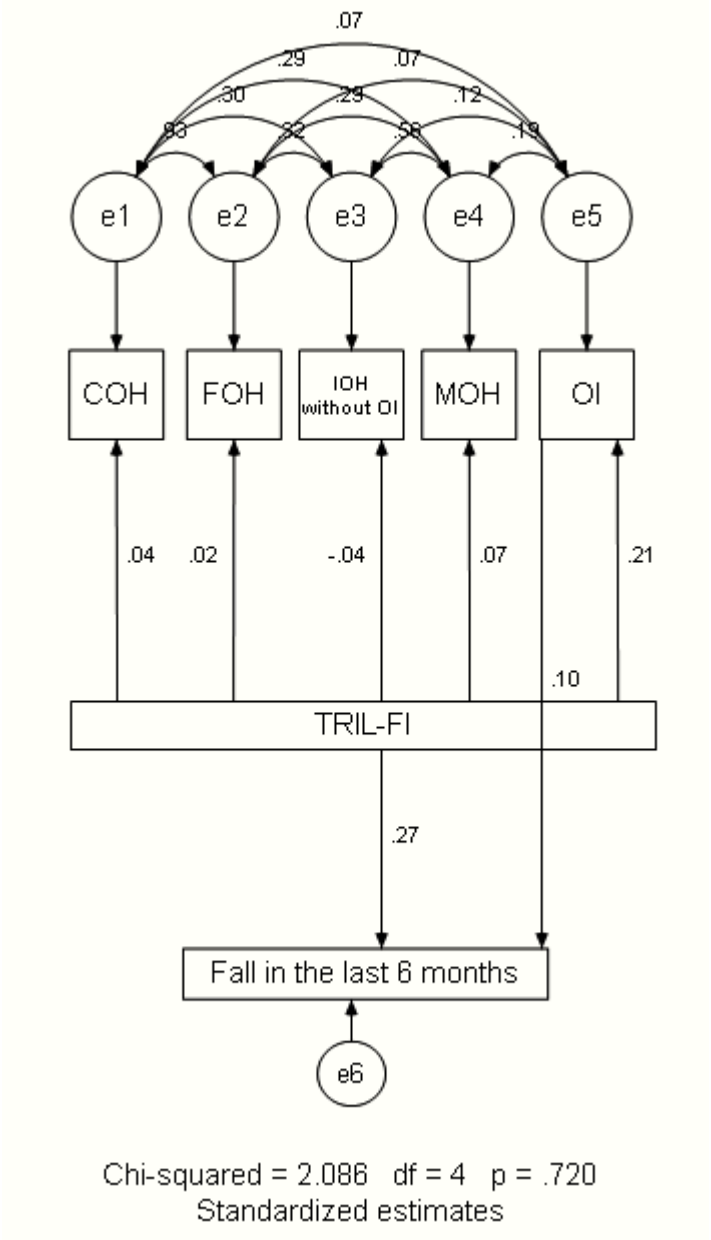


Significant regression coefficients:
Frailty → OI (β = 0.21, $P < 0.001$), Frailty → Faller (β = 0.29, $P < 0.001$).

Table 10.4a. Fit indices for the SEM in Figure 10.4a.

Fit index	Values
NFI (normalized fit index)	0.99
RFI (relative fit index)	0.97
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	0.99
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.03 (0.00 – 0.08, $P = 0.735$)

Figure 10.4b. SEM with the OH classifications (IOH modified) as indicators of frailty (TRIL-FI). The significant indicators were postulated as independent risk factor for falls.



Significant regression coefficients: Frailty → OI (β = 0.21, $P < 0.001$)
and Frailty → Faller (β = 0.27, $P < 0.001$). Trend: OI → Faller (β = 0.10, $P = 0.035$).

Table 10.4b. Fit indices for the SEM in Figure 10.4b.

Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	0.99
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.05, $P = 0.941$)

The above models suggest that (1) of the various OH definitions considered, *OI was the only one that significantly indicated frailty*; and (2) *the apparent correlation between IOH and frailty may have been at the expense of OI being included in its definition*. The models also suggest that neither IOH nor OI were significant independent predictors of falls in the face of frailty, but OI could have a weak ($P < 0.05$) independent effect.

Orthostatic intolerance (OI) and frailty: is medication burden a confounder?

In this section, the candidate explores whether the association between OI and frailty (and OI and previous falls) could have been confounded by the burden of medications. Whilst frailty is strongly linked with polypharmacy (Tables 8.3a and 8.5), OI has been linked with vasoactive drugs that interfere with sympathetic tone (520, 521); therefore, it is theoretically possible that the association between OI and frailty could have been due to medication burden *alone*.

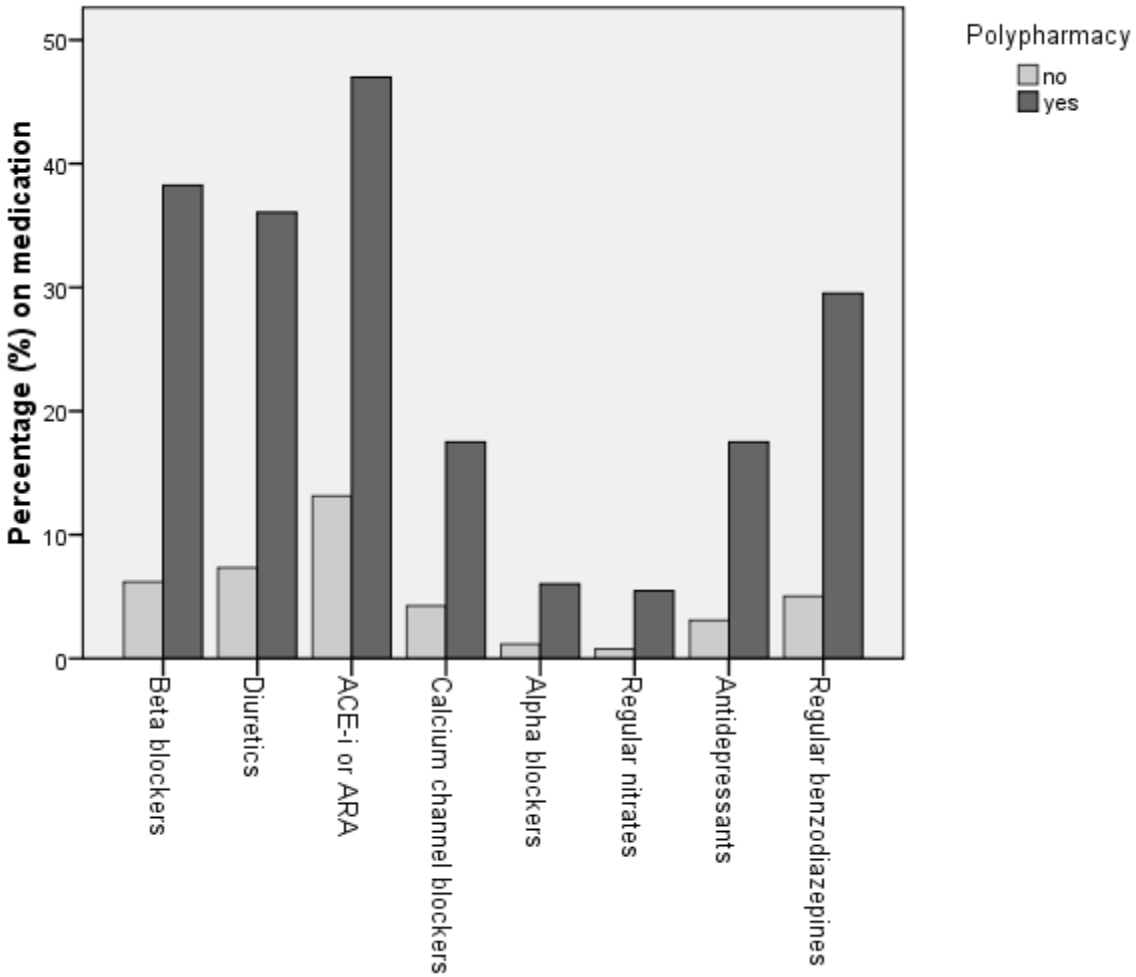
Polypharmacy was defined as the regular use of ≥ 4 prescription medications. Of the total sample of $N = 442$, 183 participants (41.4%) were on polypharmacy, the same as 67.7% of the frail by the modified Fried's classification and 81.4% of the frail by TRIL-FI. Table 10.5 and Figure 10.5 compare the two polypharmacy groups (i.e. absent *vs*. present) in terms of the relative burden of individual medication types. As expected, antihypertensives and psychotropics were more prevalent in the 'polypharmacy present' group.

Table 10.5. Burden of individual medication types by polypharmacy status.

Medication type	Polypharmacy absent (*N* = 259)	Polypharmacy present (*N* = 183)	Significance of the difference (*P*)
Beta-blockers (%)	6.2	38.3	**<0.001**$^{\chi}$
Diuretics (%)	7.3	36.1	**<0.001**$^{\chi}$
ACE-i or ARA (%)	13.1	47.0	**<0.001**$^{\chi}$
Calcium channel blockers (%)	4.2	17.5	**<0.001**$^{\chi}$
Alpha blockers (%)	1.2	6.0	**0.004**$^{\chi}$
Regular nitrate (%)	0.8	5.5	**0.005**$^{\int}$
Antidepressant (%)	3.1	17.5	**<0.001**$^{\chi}$
Regular benzodiazepine (%)	5.0	29.5	**<0.001**$^{\chi}$

$^{\chi}$ Chi-squared test; $^{\int}$ Fisher's exact test (2-sided).
ACE-i: angiotensin converting enzyme inhibitor; **ARA**: angiotensin receptor antagonist.

Figure 10.5. Burden of individual medication types by polypharmacy status.



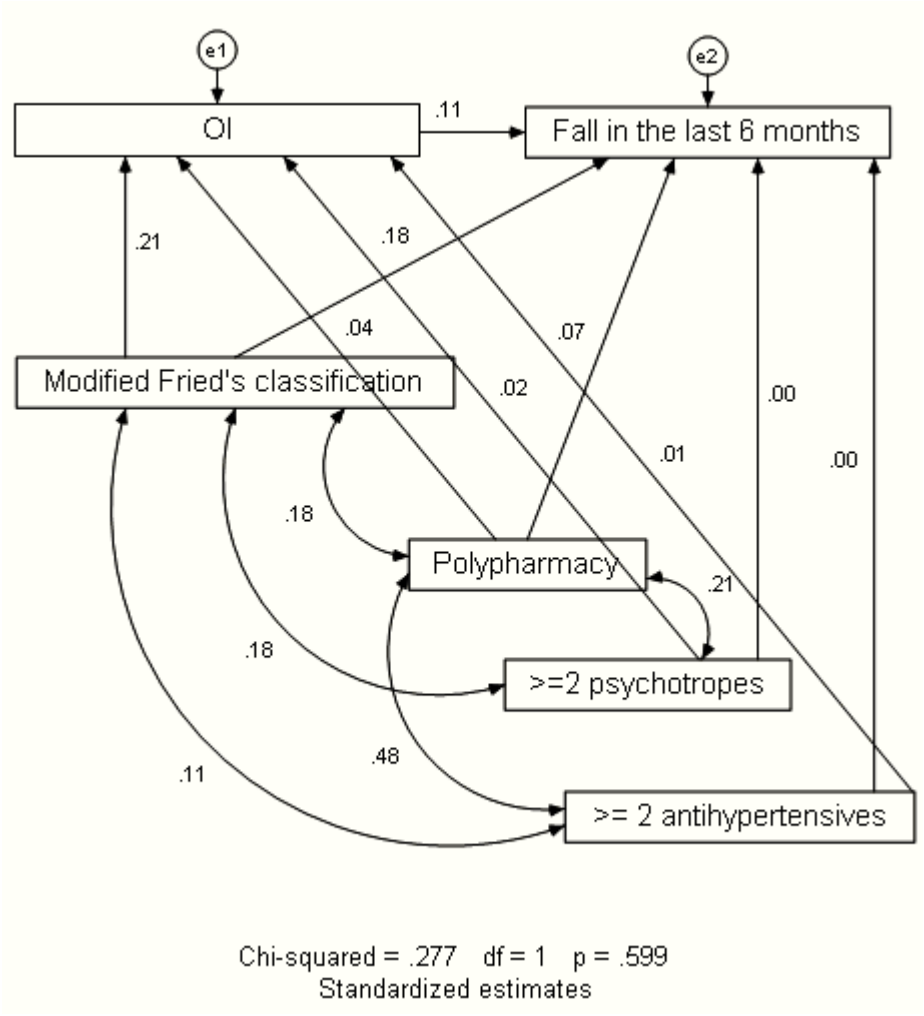
To clarify the issue whether the association between OI and frailty could have been confounded by the burden of medications, the structural equation model in Figures 10.6a (modified Fried's classification) and 10.6b (TRIL-FI) was used.

In the model, OI is postulated as an indicator of frailty and as a cause of previous falls. Frailty is postulated as a cause of falls and as a correlate of polypharmacy (i.e. ≥ 4 regular medications), burden of psychotropic medications (i.e. ≥ 2 antidepressants or benzodiazepines), and burden of antihypertensive medications (i.e. ≥ 2 items from the following list: beta blockers, diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, calcium channel blockers, alpha blockers and regular nitrates). Polypharmacy is correlated with the burden of psychotropes and antihypertensives, and the three latter variables are postulated as causes of OI and falls.

In Figure 10.6a, the significant regression coefficients were Frailty → OI ($\beta = 0.21$, $P < 0.001$) and Frailty → Faller ($\beta = 0.18$, $P < 0.001$). The postulated regression OI → Faller ($\beta = 0.11$, $P = 0.024$) had a *trend towards significance*. None of the medication variables had a significant effect on OI or falls. All covariances were significant ($P < 0.01$) except for frailty ⇔ ≥ 2 antihypertensives, which tended towards significance ($\beta = 0.11$, $P = 0.021$). Overall, the model had a good fit: Chi-squared = 0.277, df = 1, $P = 0.599$; other fit indices are shown in Table 10.6a. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

In Figure 10.6b, the significant regression coefficients were Frailty → OI (β = 0.24, $P < 0.001$) and Frailty → Faller (β = 0.33, $P < 0.001$). The postulated regression OI → Faller (β = 0.09, $P = 0.042$) had a *trend towards significance*. None of the medication variables had a significant effect on OI or falls. All covariances were significant ($P < 0.01$). Overall, the model had a good fit: Chi-squared = 0.277, df = 1, $P = 0.599$; other fit indices are shown in Table 10.6b. The MCMC estimation method yielded similar results, with good model fit (Appendix 7).

Figure 10.6a. SEM with medication burden being postulated as a confounder of the association between frailty (modified Fried's classification) and orthostatic intolerance (OI).

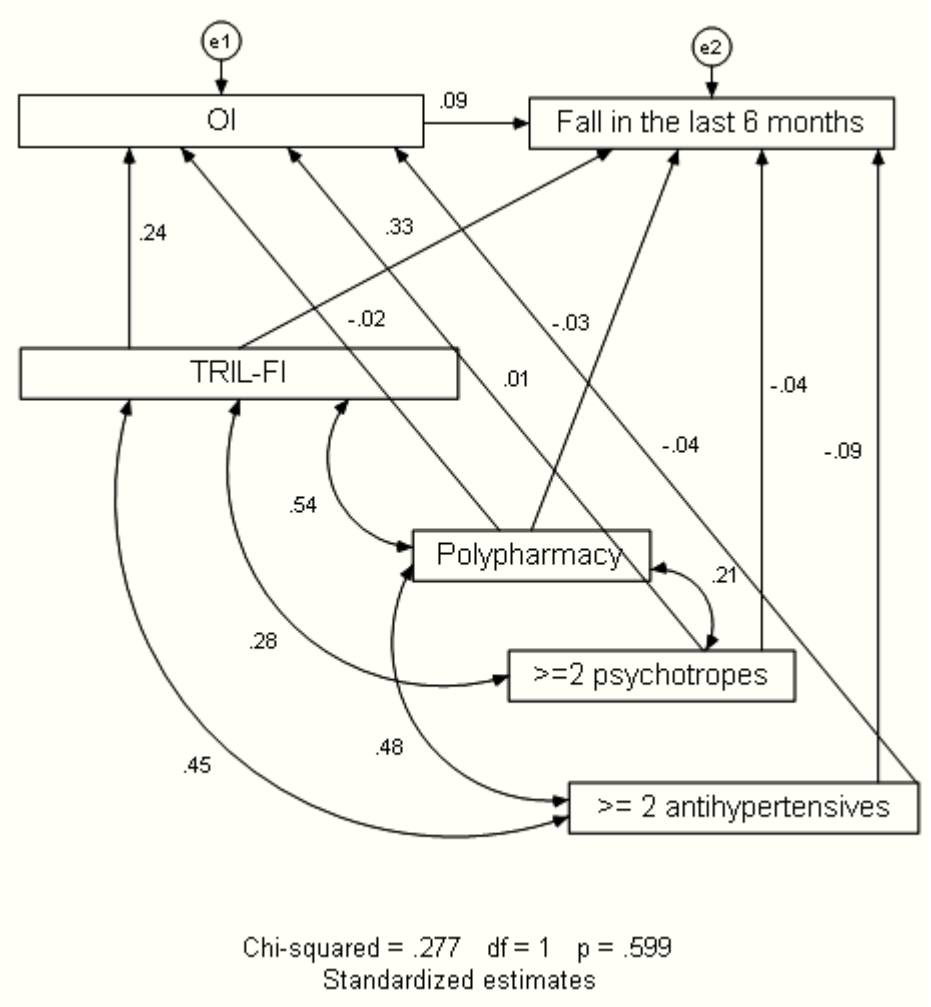


Significant regression coefficients: Frailty → OI (β = 0.21, $P < 0.001$), Frailty → Faller (β = 0.18, $P < 0.001$). Trend: OI → Faller (β = 0.11, $P = 0.024$).

Table 10.6a. Fit indices for the SEM in Figure 10.6a.

Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	0.97
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.10, $P = 0.757$)

Figure 10.6b. SEM with medication burden being postulated as a confounder of the association between frailty (TRIL-FI) and orthostatic intolerance (OI).



Significant regression coefficients: Frailty → OI (β = 0.24, *P* < 0.001), Frailty → Faller (β = 0.33, *P* < 0.001). Trend: OI → Faller (β = 0.09, *P* = 0.042).

Table 10.6b. Fit indices for the SEM in Figure 10.6b.

Fit index	Values
NFI (normalized fit index)	1.00
RFI (relative fit index)	0.99
IFI (incremental fit index)	1.00
TLI (Tucker-Lewis index)	1.00
CFI (comparative fit index)	1.00
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.00 (0.00 – 0.10, *P* = 0.757)

Overall, results from the above two SEMs suggest that, despite frailty having a strong association with medication burden, the association between frailty and OI did *not* seem to be explained by the burden of medications alone. A more detailed subanalysis with individual medication types (Table 10.7) supported the lack of statistically significant differences ($P < 0.01$), but revealed some interesting statistical *trends* ($P < 0.05$) with *calcium channel blockers*, *alpha blockers* and *benzodiazepines*:

Table 10.7. Burden of individual medication types by orthostatic intolerance (OI) status.

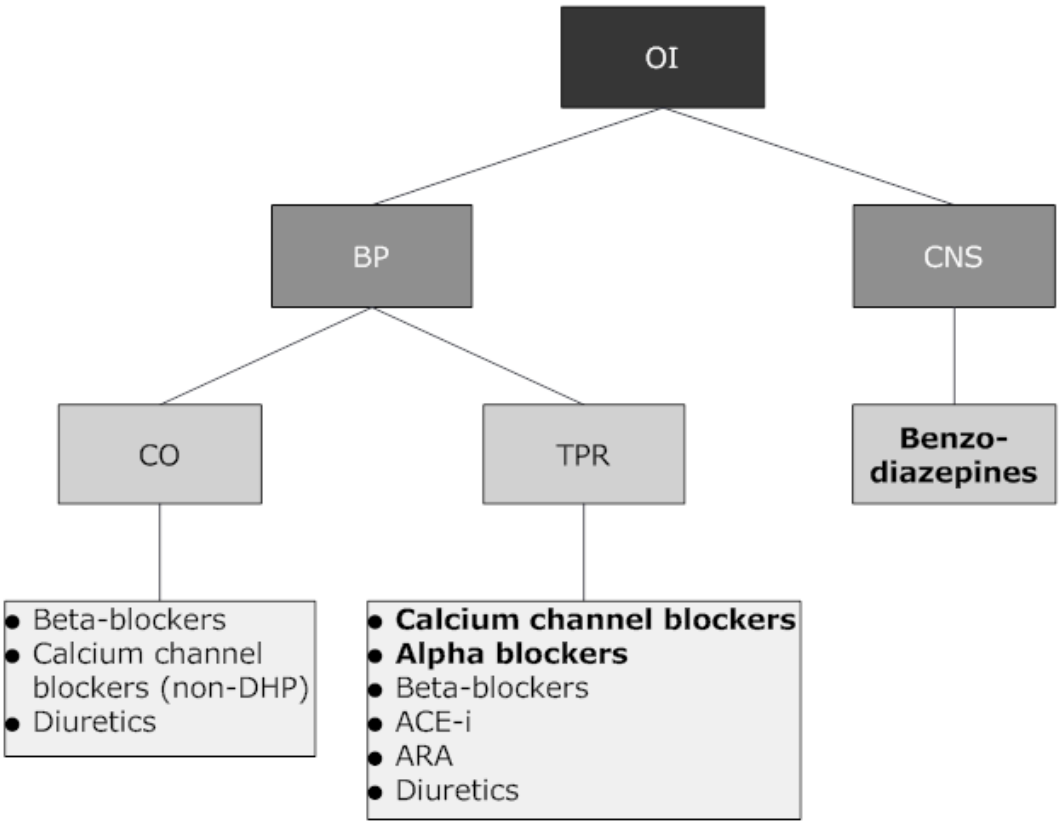
Medication type	OI absent ($N = 316$)	OI present ($N = 126$)	Significance of the difference (P)
Beta-blockers (%)	19.4	19.8	0.921[χ]
Diuretics (%)	17.2	24.6	0.075[χ]
ACE-i or ARA (%)	26.8	28.6	0.698[χ]
Calcium channel blockers (%)	7.6	15.1	*0.018*[χ]
Alpha blockers (%)	1.9	6.3	*0.030*[∫]
Antidepressant (%)	8.3	11.1	0.350[χ]
Regular benzodiazepine (%)	13.1	20.6	*0.046*[χ]

[χ] Chi-squared test; [∫] Fisher's exact test (2-sided).
ACE-i: angiotensin converting enzyme inhibitor; **ARA**: angiotensin receptor antagonist.

Interestingly, Wieling *et al*. previously reported that 'patients prone to *initial OH* include those taking medication *interfering with vasoconstrictor mechanisms*, such as *alpha blockers* or *sympathetic outflow blocking* agents, and *psychiatric* medication' (31), which are the same medications as the ones found here in mild association with OI. Although there is still controversy as to whether antihypertensives may worsen OH or not, the present findings are consistent with a report regarding polypharmacy (17), and coincide with those of a review by Hajjis *et al*. that peripheral vasodilators, specifically alpha blockers and non-dihydropyridine calcium channel blockers can exacerbate postural blood pressure changes and lead to OH (522). Benzodiazepines could possibly lead to OI via *central nervous system* mechanisms (523, 524).

Figure 10.7 proposes a potentially useful system for the classification of medications according to the predominant mechanism through which they may produce OI. On the one hand, OI may be caused by hemodynamic (e.g. blood pressure) mechanisms, or be caused by central nervous system mechanisms. It is known that drugs influencing blood pressure may do so via reductions of cardiac output, total peripheral resistance, or both (525). The trends found in Table 10.7 suggest that drugs affecting TPR and CNS may have increased risk of OI in older people.

Figure 10.7. A proposed classification system for medications according to the mechanism through which they may produce OI in older people.



OI: orthostatic intolerance; **BP**: blood pressure; **CNS**: central nervous system; **CO**: cardiac output; **TPR**: total peripheral resistance; **DHP**: dihydropyridine; **ACE-i**: angiotensin convertor enzyme inhibitors; **ARA**: angiotensin receptor antagonists. The list of CO and TPR medications was adapted from http://www.hypertensiononline.org (525).

Postulating interplays between frailty, orthostatic hemodynamics, OI and falls

Based on the results of the cross-sectional analyses reported so far in this investigation, the candidate presents a final SEM exploring various inter-associations between frailty, OI, orthostatic hemodynamics and falls. The model in Figure 10.8a uses the modified Fried's classification; figure 10.8b is the same model using TRIL-FI.

The SEM postulates that frailty may determine the prevalences of OI during active stand and previous falls, and also influence the following hemodynamic parameters: baseline SBP (Table 9.2), baseline HR (Table 9.1), and delta HR (Tables 9.1, 9.2); in addition, it is postulated that frailty may determine the degree of initial SBP drop (i.e. entered in the model as the systolic IOH criterion, without the diastolic criterion or OI), and increase the prevalence of non-recovery SBP pattern (i.e. MOH Cluster 3) (Table 9.2). Consistent with Figure 7.8 findings, baseline SBP influences the degree of initial SBP drop; the latter causes impaired SBP recoverability (i.e. increases the prevalence of MOH Cluster 3), and influences delta HR, OI and falls. Baseline SBP and baseline HR are postulated as influences on delta HR, and the latter is postulated as influencing the pattern of SBP recoverability (i.e. Cluster 3) and the prevalence of OI. Lack of SBP recoverability is postulated as a cause of OI (Figure 7.8), and both MOH Cluster 3 and OI are postulated as cause of falls.

Figure 10.8a. Postulating interplays between frailty (modified Fried's definition), orthostatic hemodynamics, orthostatic intolerance and falls.

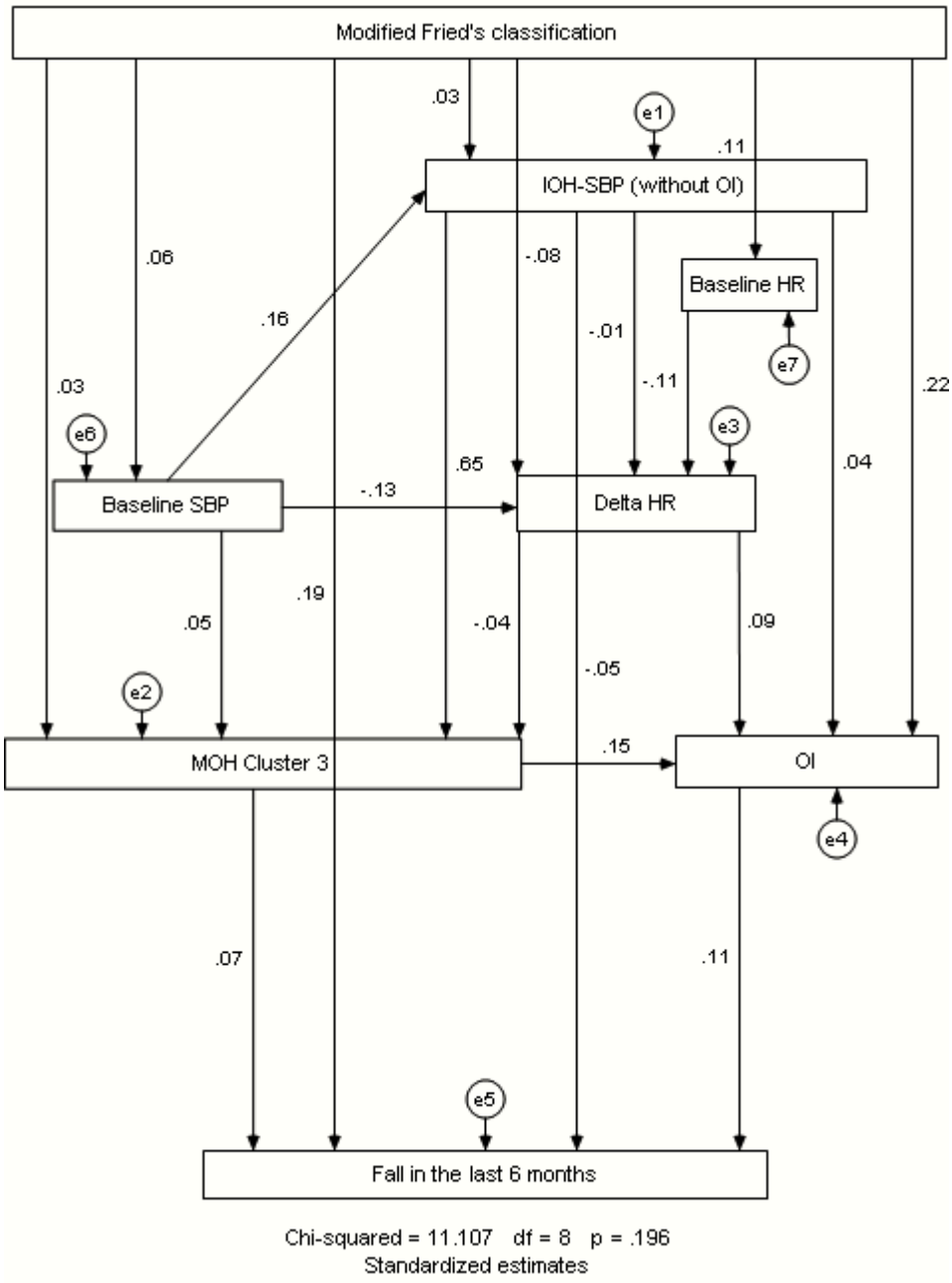


Table 10.8a. Fit indices for the SEM in Figure 10.8a.

Fit index	Values
NFI (normalized fit index)	0.97
RFI (relative fit index)	0.87
IFI (incremental fit index)	0.99
TLI (Tucker-Lewis index)	0.96
CFI (comparative fit index)	0.99
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.03 (0.00 – 0.07, *P* = 0.776)

In Figure 10.8a, the significant ($P < 0.01$) regression coefficients were the following:

- Initial SBP drop → MOH Cluster 3 ($\beta = 0.65$, $P < 0.001$).
- Frailty → OI ($\beta = 0.22$, $P < 0.001$).
- Frailty → Faller ($\beta = 0.19$, $P < 0.001$).
- Baseline SBP → Initial SBP drop ($\beta = 0.16$, $P < 0.001$).
- Baseline SBP → delta HR ($\beta = -0.13$, $P = 0.005$).

In addition, the following postulated relationships had a trend towards significance ($P < 0.05$):

- MOH Cluster 3 → OI ($\beta = 0.15$, $P = 0.014$).
- OI → Faller ($\beta = 0.11$, $P = 0.027$).
- Frailty → Baseline HR ($\beta = 0.11$, $P = 0.021$).
- Baseline HR → Delta HR ($\beta = -0.11$, $P = 0.014$).
- Delta HR → OI ($\beta = 0.09$, $P = 0.044$).

Overall, the model had a good fit: Chi-squared = 11.107, df = 8, $P = 0.196$; other fit indices are shown in Table 10.8a. The MCMC estimation method yielded similar results with an acceptable model fit (Appendix 7).

Figure 10.8b. Postulating interplays between frailty (TRIL-FI), orthostatic hemodynamics, orthostatic intolerance and falls.

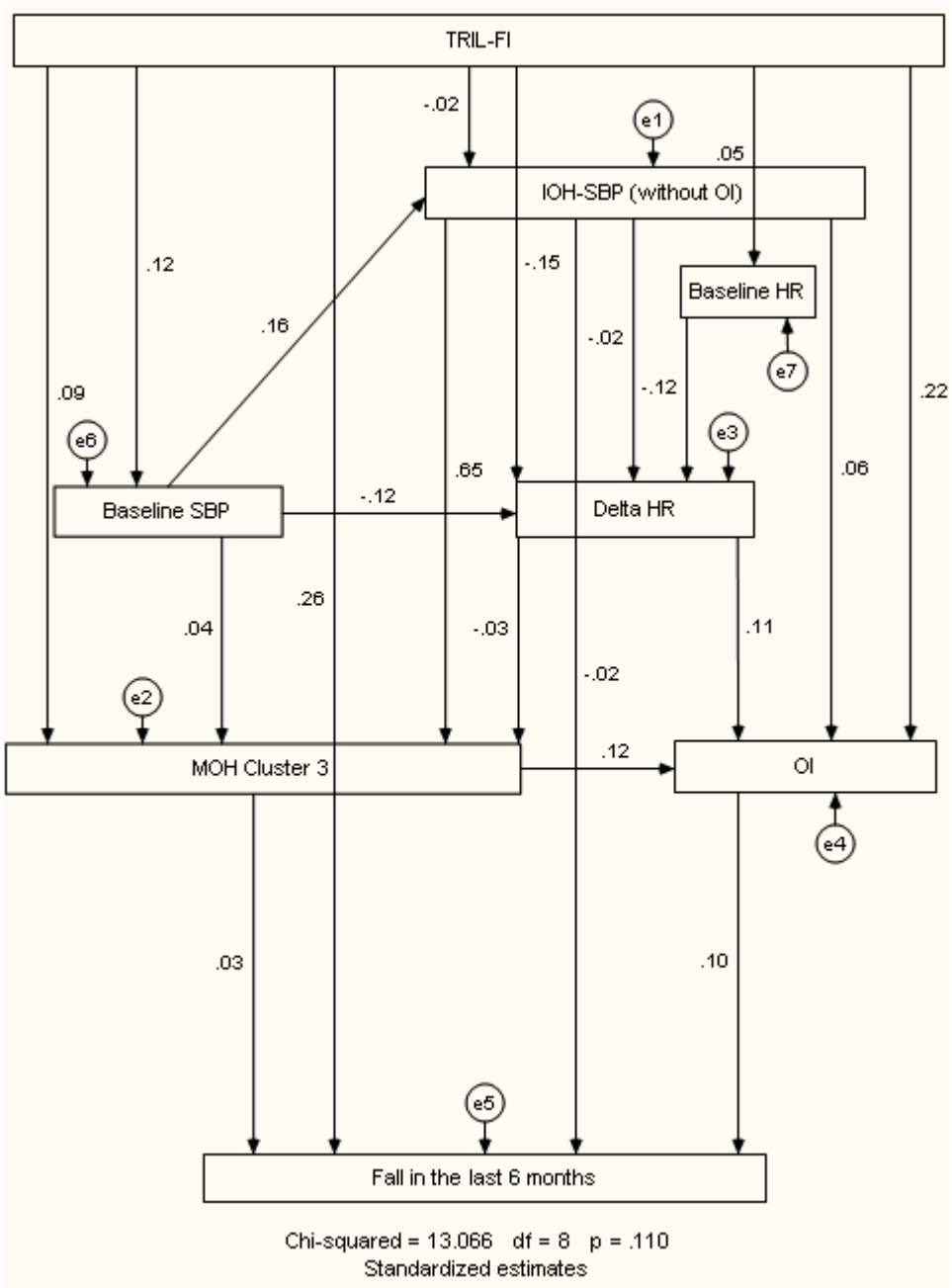


Table 10.8b. Fit indices for the SEM in Figure 10.8b.

Fit index	Values
NFI (normalized fit index)	0.97
RFI (relative fit index)	0.85
IFI (incremental fit index)	0.99
TLI (Tucker-Lewis index)	0.94
CFI (comparative fit index)	0.99
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.04 (0.00 – 0.07, *P* = 0.667)

In Figure 10.8b, the significant ($P < 0.01$) regression coefficients were the following:

- Initial SBP drop → MOH Cluster 3 ($\beta = 0.65$, $P < 0.001$).
- Frailty → Faller ($\beta = 0.26$, $P < 0.001$).
- Frailty → OI ($\beta = 0.22$, $P < 0.001$).
- Baseline SBP → Initial SBP drop ($\beta = 0.16$, $P < 0.001$).
- Frailty → Delta HR ($\beta = -0.15$, $P = 0.002$).
- Frailty → MOH Cluster 3 ($\beta = 0.09$, $P = 0.009$).

In addition, the following relationships had a trend towards significance ($P < 0.05$):

- Frailty → Baseline SBP ($\beta = 0.12$, $P = 0.013$).
- Baseline HR → Delta HR ($\beta = -0.12$, $P = 0.012$).
- Baseline SBP → delta HR ($\beta = -0.12$, $P = 0.011$).
- MOH Cluster 3 → OI ($\beta = 0.12$, $P = 0.045$).
- Delta HR → OI ($\beta = 0.11$, $P = 0.024$).
- OI → Faller ($\beta = 0.10$, $P = 0.043$).

Overall, the model had a good fit: Chi-squared = 13.066, df = 8, $P = 0.110$; other fit indices are shown in Table 10.8b. The MCMC estimation method yielded similar results with an acceptable model fit (Appendix 7).

To assess the potential confounding effect of polypharmacy, the two models above were repeated postulating polypharmacy as a consequence of frailty and as having potential influences on all the other parameters in the model (Figures 10.9a and 10.9b).

Figure 10.9a. Postulating interplays between frailty (modified Fried's definition), orthostatic hemodynamics, orthostatic intolerance and falls, in the presence of polypharmacy.

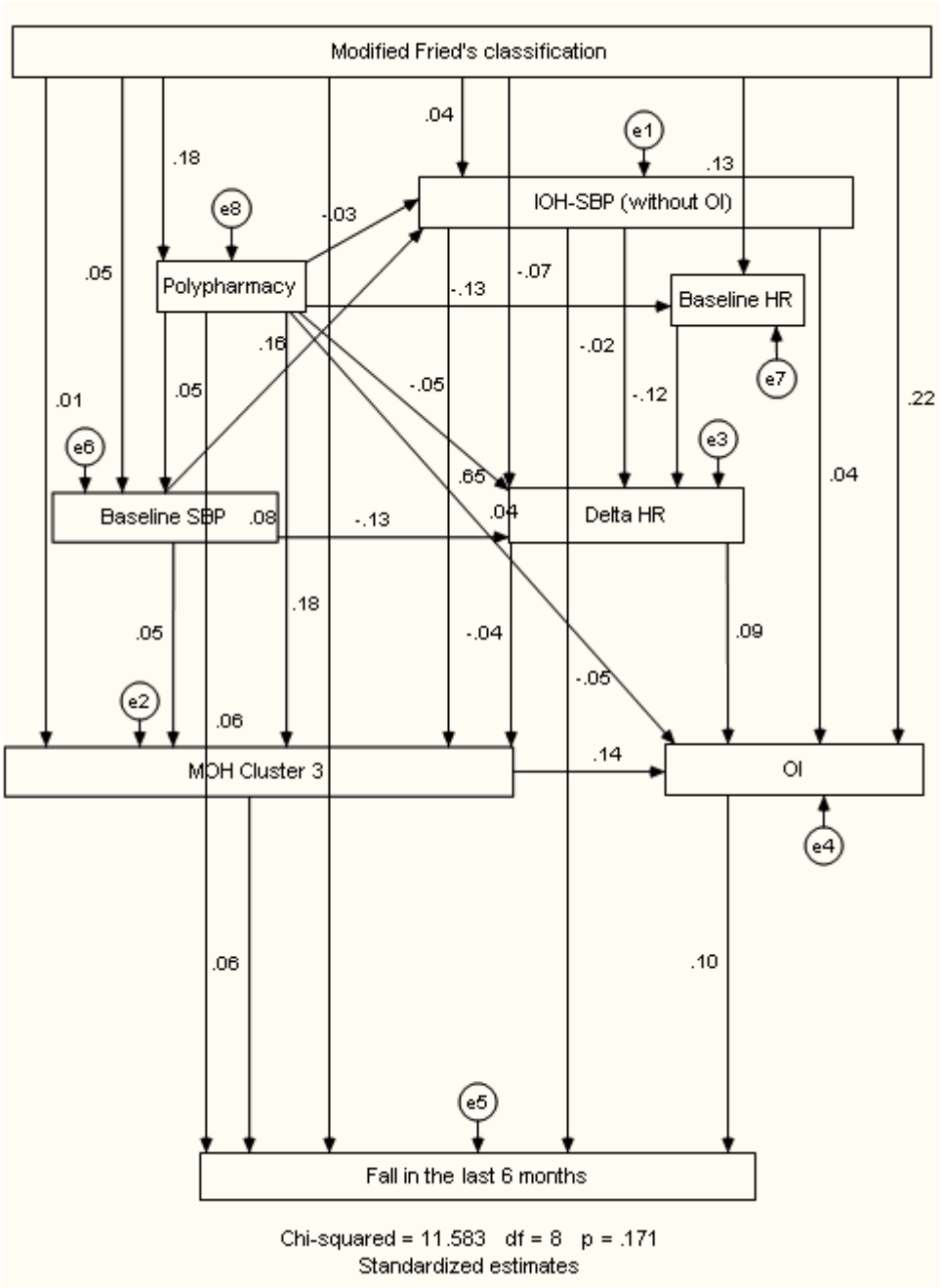


Table 10.9a. Fit indices for the SEM in Figure 10.9a.

Fit index	Values
NFI (normalized fit index)	0.97
RFI (relative fit index)	0.84
IFI (incremental fit index)	0.99
TLI (Tucker-Lewis index)	0.94
CFI (comparative fit index)	0.99
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.03 (0.00 – 0.07, *P* = 0.751)

In Figure 10.9a, the significant ($P < 0.01$) regression coefficients were the following:

- Initial SBP drop → MOH Cluster 3 ($\beta = 0.65$, $P < 0.001$).
- Frailty → OI ($\beta = 0.22$, $P < 0.001$).
- Frailty → Faller ($\beta = 0.18$, $P < 0.001$).
- Frailty → Polypharmacy ($\beta = 0.18$, $P < 0.001$).
- Baseline SBP → Initial SBP drop ($\beta = 0.16$, $P < 0.001$).
- Frailty → Baseline HR ($\beta = 0.13$, $P = 0.006$).
- Polypharmacy → Baseline HR ($\beta = -0.13$, $P = 0.008$).
- Baseline SBP → delta HR ($\beta = -0.13$, $P = 0.006$).

In addition, the following postulated relationships had a trend towards significance ($P < 0.05$):

- MOH Cluster 3 → OI ($\beta = 0.14$, $P = 0.019$).
- Baseline HR → Delta HR ($\beta = -0.12$, $P = 0.011$).
- OI → Faller ($\beta = 0.10$, $P = 0.031$).
- Delta HR → OI ($\beta = 0.09$, $P = 0.041$).
- Polypharmacy → MOH Cluster 3 ($\beta = 0.08$, $P = 0.033$).

Overall, the model had a good fit: Chi-squared = 11.583, df = 8, $P = 0.171$; other fit indices are shown in Table 10.9a. The MCMC estimation method yielded similar results with an acceptable model fit (Appendix 7).

Figure 10.9b. Postulating interplays between frailty (TRIL-FI), orthostatic hemodynamics, orthostatic intolerance and falls, in the presence of polypharmacy.

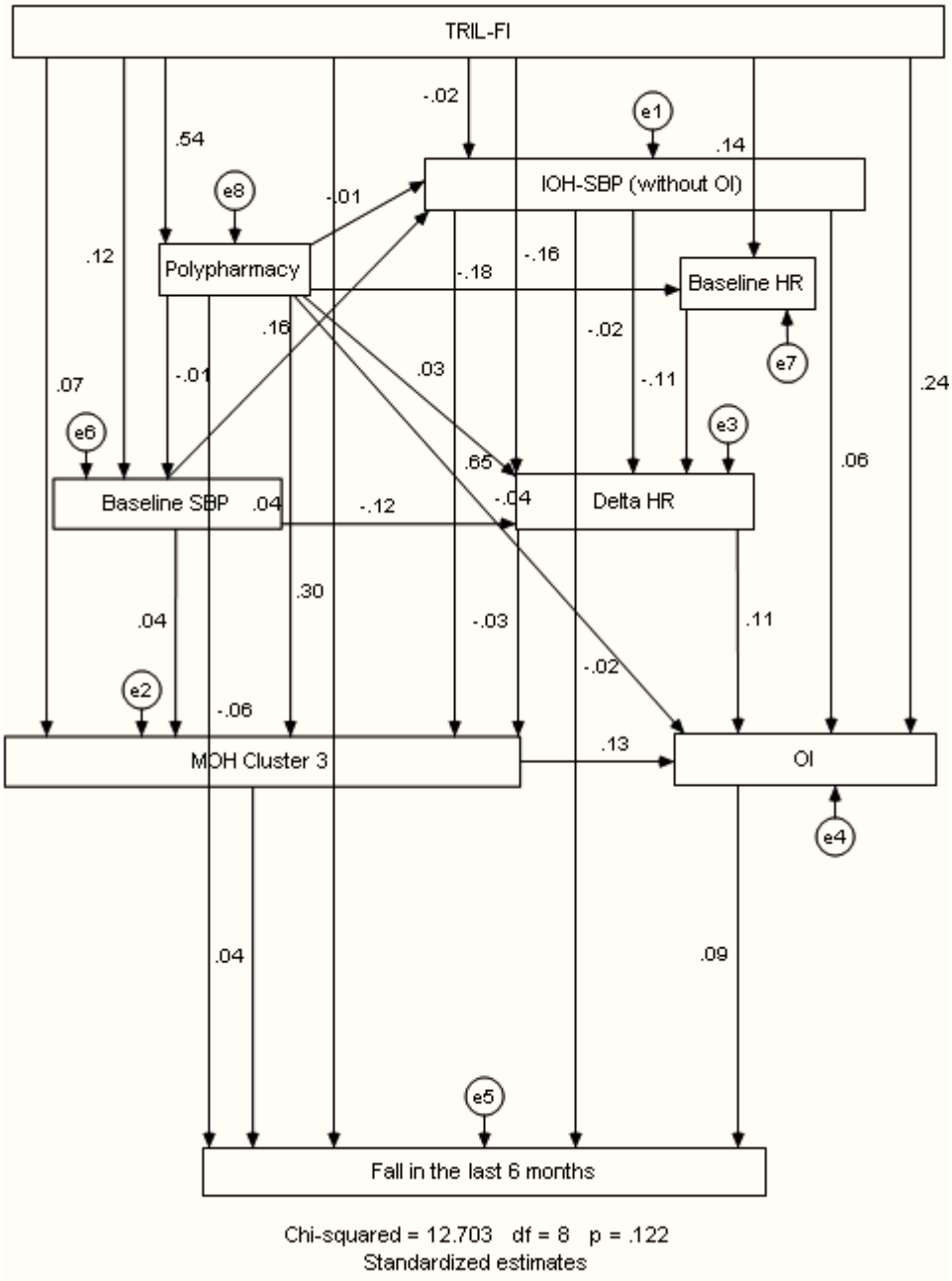


Table 10.9b. Fit indices for the SEM in Figure 10.9b.

Fit index	Values
NFI (normalized fit index)	0.98
RFI (relative fit index)	0.87
IFI (incremental fit index)	0.99
TLI (Tucker-Lewis index)	0.95
CFI (comparative fit index)	0.99
RMSEA (Root mean square error of approximation) (90% CI, *P*)	0.04 (0.00 – 0.07, *P* = 0.688)

In Figure 10.9b, the significant ($P < 0.01$) regression coefficients were the following:

- Initial SBP drop → MOH Cluster 3 ($\beta = 0.65$, $P < 0.001$).
- Frailty → Polypharmacy ($\beta = 0.54$, $P < 0.001$).
- Frailty → Faller ($\beta = 0.30$, $P < 0.001$).
- Frailty → OI ($\beta = 0.24$, $P < 0.001$).
- Polypharmacy → Baseline HR ($\beta = -0.18$, $P = 0.001$).
- Baseline SBP → Initial SBP drop ($\beta = 0.16$, $P < 0.001$).
- Frailty → delta HR ($\beta = -0.16$, $P = 0.003$).

In addition, the following postulated relationships had a trend towards significance ($P < 0.05$):

- Frailty → Baseline HR ($\beta = 0.14$, $P = 0.010$).
- MOH Cluster 3 → OI ($\beta = 0.13$, $P = 0.041$).
- Frailty → Baseline SBP ($\beta = 0.12$, $P = 0.032$).
- Baseline SBP → delta HR ($\beta = -0.12$, $P = 0.011$).
- Delta HR → OI ($\beta = 0.11$, $P = 0.022$).
- Baseline HR → Delta HR ($\beta = -0.11$, $P = 0.016$).
- OI → Faller ($\beta = 0.09$, $P = 0.047$).

Overall, the model had a good fit: Chi-squared = 12.703, df = 8, $P = 0.122$; other fit indices are shown in Table 10.9b. The MCMC estimation method yielded similar results with an acceptable model fit (Appendix 7).

In the two SEMs above, polypharmacy had a significant association with frailty, but the addition of polypharmacy did not blur the independent associations of Frailty with falls, and frailty with OI. However, polypharmacy appeared significantly associated with baseline HR, and the previously significant association between Frailty and Delta HR disappeared in the model using the modified Fried's classification (but not in the one using TRIL-FI). The latter suggests that polypharmacy (which includes beta blocker burden) may have been a confounder of the association between frailty and Delta HR.

Discussion of the main findings

From the SEMs in Figures 10.8a-b and 10.9a-b, the most consistent significant ($P < 0.01$) associations were:

- Baseline SBP → Initial SBP drop (mild effect size: $\beta = 0.16$).
- Initial SBP drop → MOH Cluster 3 (strong effect size: $\beta = 0.65$).
- Frailty → Polypharmacy (mild effect size with modified Fried's classification: $\beta = 0.18$; medium effect size with TRIL-FI: $\beta = 0.54$).
- Frailty → Faller (mild-medium effect size: β between 0.18 and 0.30).
- Frailty → OI (mild effect size: β between 0.22 and 0.24).

Consistent statistical trends ($P < 0.05$) in the models were:

- MOH Cluster 3 → OI (mild effect size: β between 0.12 and 0.15).
- OI → Faller (mild effect size: β between 0.09 and 0.11).

Baseline SBP → Initial SBP drop

This association is consistent with previous studies reporting a significant correlation between baseline blood pressure and orthostatic blood pressure drop (35, 454, 455). The suggestion in the SEMs that the degree of initial SBP drop *per se* (i.e. without taking into account the correlated pattern of SBP recoverability) is not significantly correlated with OI or falls may have implications for the understanding and treatment of the *syndrome of supine hypertension–orthostatic hypotension* (105-108), especially with respect to the practice of stopping antihypertensives in the management of this syndrome. Based on the SEM results, the candidate agrees with the recent letter by Choulerton *et al*. that, in older people, postural symptoms (i.e. OI) correlate much more strongly with falls than does OH (i.e. measured as BP drop) (526).

Initial SBP drop → MOH cluster 3

The degree of systolic blood pressure (SBP) drop within the first 15 seconds post-stand and the pattern of non-recoverability of SBP from the MOH classification were directly correlated with the standardised regression coefficient in all four models, indicating a strong relationship between these two variables ($\beta = 0.65$). This is consistent with the SEM in Figure 7.8, supporting that delta SBP was a strong ($\beta = -0.71$) determinant of the percentage of baseline SBP recovered by 30 seconds. This finding is externally valid in the face of previous studies by Wieling *et al*. on the morphological patterns of orthostatic blood pressure recovery (30, 36, 37, 449), and makes clinical hemodynamic sense.

MOH Cluster 3 → OI

In all four models, there was a suggestion ($P < 0.05$) that the presence of a non-SBP recovery pattern (i.e. MOH Cluster 3) is associated with a higher proportion of subjects reporting OI during active stand. In a previous published paper (49), the candidate quoted that, in situations of intolerance to initial orthostasis, patients typically complain of OI symptoms 5–10 seconds after rising, usually after prolonged recumbence (e.g. patients have often walked some steps before fainting or near fainting occurs). It is thought that such an interval between the moment of rising and the onset of symptoms corresponds to the latency time between the onset of cerebral hypoperfusion and symptoms, which has been estimated at 6 seconds (31). In view of this, it was postulated that between nadir and 30 seconds post-stand, a quick recovery of SBP could be the most crucial aspect in providing protection against initial OI symptoms, because a speedy recovery would be able to restore cerebral blood flow before that critical latency period expires (49).

In the present sample ($N = 442$), 24 out of 45 (53.3%) subjects not recovering at least 80% of their baseline SBP by 30 seconds after stand reported OI; among those who recovered at least 80% of their SBP baseline by 30 seconds ($N = 395$), a significantly lower proportion ($N = 102$, 25.8%) reported OI (Chi-squared = 14.96, df = 1, $P < 0.001$). While this association supports the above hypothesis, the lack of orthostatic cerebral blood flow data is a limitation and should be incorporated in future research.

Frailty → OI

All four SEMs were consistent in that *OI was a significant indicator of frailty*, with the correlation having mild effect size. To the candidate's knowledge, a pathophysiological explanation for this association has not been explicitly offered in the literature, and it merits to be addressed in further longitudinal research. Although the OI of frailty could be due to non-cardiovascular (e.g. central nervous system) causes, OI was, in the context of frailty, found in association with specific hemodynamic abnormalities (i.e. *orthostatic HR response blunting* and *reduced early SBP recoverability*), and various possible cardiovascular mechanisms for the latter abnormalities are discussed below:

- (1) Frailty may be comparable to a state of *cardiovascular deconditioning*. It is known that humans subjected to prolonged periods of bed rest or microgravity undergo *deconditioning* of the cardiovascular system, characterised by *resting tachycardia*, *reduced exercise capability* and *predisposition to OI* (527), all of which were found to be associated with frailty. Those alterations may be due to changes in control of body fluid balance, cardiac alterations, vascular (arterial or venous) alterations, blunted baroreflex-mediated sympathoexcitation and/or reduced activation of cardiovascular hormones (527), all of which may be present in frailty.

- (2) OI may be related to the *exhaustion* complex present in frailty. Frailty may have overlap with the *chronic fatigue syndrome* (CFS), and both share OI as a common clinical manifestation. For example, Costigan *et al*. showed that OI predicts functional capacity (in a 'frailty-like' fashion) in CFS (528); in CFS, reduced cardiac stroke volume and cardiac output have been shown, which may clinically present as OI. Cardiovascular and autonomic dysfunctions have been suggested to

underlie the OI of CFS, with potential underlying mechanisms including increased and/or maladaptive peripheral vasomotor tone, cerebral hypoperfusion, cerebral vasoconstriction and/or inadequate central autonomic activation (529-533). Interestingly, Sutcliffe *et al*. recently showed that home orthostatic training in CFS is related to reductions in OI (534).

The possibility of overlap between the OI of frailty and the chronic OI of the *postural orthostatic tachycardia syndrome* (POTS) is less plausible than the overlap between OI-frailty and OI-CFS. Firstly, POTS is a condition of the young; and secondly, POTS is characterised by symptomatic marked HR increases (> 30 bpm or to > 120 bpm) and blood pressure instability during tilt table testing (27). The lack of *cardiovascular reserve* in frailty may help understand why POTS remain as a condition of the (non-frail) young (i.e. who have enough cardiovascular reserve to mount such HR responses).

- (3) Another possibility is that the OI of frailty may be the clinical manifestation of a *concomitant impairment of the cerebral autoregulation*. Although there is evidence that *healthy* older adults can autoregulate cerebral blood flow (CBF) as well as younger subjects (57), and that IOH is *unrelated* to orthostatic tolerance in *healthy young* subjects (535), the CBF *reserve* in patients with cerebrovascular disease (in a frailty context) may be impaired (536). In addition, recent evidence has shown that impaired CBF regulation is associated with slow gait speed and may lead to the development of falls in elderly people (537). To shed light on this issue, cerebral blood flow (CBF) data is needed and non-availability is one of the limitations of this study.

- (4) A postulated defence against OH and OI is the *skeletal muscle pump*, in which contractions of leg and gluteal muscles during active standing help propel venous blood back to the heart (335). Decreased skeletal muscle pump activity has been found in patients with OI syndromes (538-540) and delayed OH (33). On the other hand, it has been argued that in patients with Marfan's syndrome, the smaller skeletal muscle mass, and therefore, the less adequate skeletal muscle pump, could impair venous return and contribute to their tendency to OI (541, 542). Since frailty overlaps with sarcopenia (329, 330, 334), the loss of muscle pump in frailty could potentially explain the association found in this investigation between OI and frailty. Unfortunately, the research protocol did not include any measures of muscle mass, so further research should correlate muscle mass with OI in frail patients.

- (5) In Figure 10.7 it was suggested that the cardiovascular (and/or central) effects of certain *medications* (the burden of which is higher in frail patients) may also have a contribution towards the OI of frailty.

Finally, another possibility is that a *self-report bias* may have occurred whereby frail participants tended to report OI (in response to *being asked* by the attending physician and/or nurse) more than non-frail subjects, as a means to attract healthcare attention (i.e. in a context where a considerable proportion of participants attended for a 'free health check'). Table 6.6 showed no age or gender differences between those reporting and not reporting OI. Furthermore, as measured by the Lie scale of the *Eysenck Personality Inventory* (485) (which measures dissimulation and social desirability), there were no statistically significant differences between those reporting (mean L: 4.3, SD 1.9) and not reporting OI (mean L: 4.5, SD 1.8) (Mann-Whitney *U* test, $P = 0.674$).

Another potential self-report bias may have involved the possibility of subjects who reported OI having more *depressive symptoms* than those not reporting OI, as this was previously found to be the case (172). In the present sample, the mean (SD) *Center for Epidemiological Studies Depression scale* (CESD-8) score in those who did not report OI was 1.6 (SD 1.9), as compared to a mean CESD-8 of 2.0 (SD 2.1) in those who reported OI symptoms. However, the Mann-Whitney *U* test did not reach statistical significance: $P = 0.224$.

Despite the above negative results, a learning point for future studies is that to minimise possible self-report bias in OI, the direct retrospective questioning should be replaced by a more 'prospective' self-triggered mechanism (e.g. button that the subject presses *as in when* OI symptoms arise), which would provide additional valuable temporal OI information.

OI → Falls

In all four models (Figures 10.8a-b and 10.9a-b), there was a suggestion ($P < 0.05$) that, even in the face of frailty, OI on active stand may have been an independent predictor of the presence of falls in the previous six months. The effect size of the correlation was small.

Chapter 11

Are the orthostatic hypotension definitions good screening tools for frailty?

In this chapter, the five orthostatic hypotension definitions (i.e. *consensus*, *Fedorowski-modified*, *initial*, *morphological* and *orthostatic intolerance*) are tested as screening tools for frailty, in terms of their sensitivity, specificity and predictive values for the screening of an abnormal group composed by pre-frail and frail individuals. A potential frailty screening tool based on *present orthostatic intolerance* and *previous history of falls* is presented, with an emphasis on its potential usefulness in primary care settings.

Orthostatic hypotension definitions as diagnostic tools for frailty

This chapter explores the diagnostic properties of the five OH definitions as screening tools for frailty. Tables 11.1a and 11.1b summarise those properties for the screening of an 'abnormal' group composed by pre-frail and frail individuals, based on the modified Fried's classification and TRIL-FI, respectively. Tables 11.2a and 11.2b refer to the screening of an abnormal group composed by frail individuals only.

Sensitivity refers to the percentage of frail people who are correctly identified by the OH definition as being frail; *specificity* refers to the percentage of non-frail people who are correctly identified as such; the *positive predictive value* (PPV) is the proportion of subjects with a positive test for OH who are correctly diagnosed as frail; the *negative predictive value* (NPV) is the proportion of subjects with negative OH test result who are correctly diagnosed as non-frail (543).

According to the modified Fried's classification, the combined sample prevalence of pre-frailty and frailty was 55.2%. As Table 11.1a shows, and as expected, the OH definitions with the highest PPV for this combined diagnosis were IOH (70.6%) and OI (69.0%). That means that in the sample, about 70% of the subjects with OI (considered alone or as an IOH diagnosis) were either pre-frail or frail. As a comparator, a positive history of at least one fall in the last six months had a PPV of 77.6%, only marginally higher than OI. The combination of the falls criterion *plus* OI on standing increased the PPV to almost 90%. In other words, 90% of the subjects in the sample who reported OI on standing *and* at least one fall in the past six months were either pre-frail or frail.

Table 11.1a. Diagnostic properties of the OH definitions and previous history of falls as frailty screening tools. The sample prevalence of pre-frailty + frailty (modified Fried's definition) was 55.2%.

OH definition	Sensitivity	Specificity	PPV	NPV
COH	95.5%	7.6%	56.0%	57.7%
FOH	93.9%	7.6%	55.6%	50.0%
IOH	24.7%	87.3%	70.6%	48.5%
IOH without OI	59.8%	41.9%	55.9%	45.9%
MOH-Cluster 1	22.5%	71.2%	49.1%	42.7%
MOH-Cluster 2	54.5%	47.0%	55.9%	45.6%
MOH-Cluster 3	23.0%	81.8%	60.9%	46.3%
OI	35.8%	80.2%	69.0%	50.3%
Faller	18.4%	93.4%	77.6%	48.2%
OI and Faller	9.8%	98.5%	88.9%	47.0%

PPV: positive predictive value; NPV: negative predictive value.

According to TRIL-FI, the combined sample prevalence of pre-frailty and frailty was 64.9%. As Table 11.1b shows, similarly to results in Table 11.1a, the OH definitions with the highest PPV for this combined diagnosis were OI (81.7%) and IOH (80.0%). A positive history of at least one fall in the last six months had a PPV of 93.1%, and the addition of OI to the falls criterion increased the PPV to 96.3%. The performance of OI and previous falls to diagnose pre-frailty/frailty was therefore slightly better with TRIL-FI than with the modified Fried's classification.

Table 11.1b. Diagnostic properties of the OH definitions and previous history of falls as frailty screening tools. The sample prevalence of pre-frailty + frailty (TRIL-FI) was 64.9%.

OH definition	Sensitivity	Specificity	PPV	NPV
COH	94.8%	7.1%	65.4%	42.3%
FOH	93.7%	7.7%	65.3%	40.0%
IOH	23.7%	88.9%	80.0%	38.3%
IOH without OI	56.8%	36.8%	62.5%	31.5%
MOH-Cluster 1	25.4%	74.8%	65.2%	35.2%
MOH-Cluster 2	51.9%	42.6%	62.6%	32.4%
MOH-Cluster 3	22.6%	82.6%	70.7%	36.6%
OI	35.9%	85.0%	81.7%	41.4%
Faller	18.8%	97.4%	93.1%	39.3%
OI and Faller	9.1%	99.4%	96.3%	37.1%

PPV: positive predictive value; NPV: negative predictive value.

According to the modified Fried's definition, the sample prevalence of frailty alone was 7.0%. As Table 11.2a shows, the OH definitions with the highest PPV for this diagnosis remained being OI (15.1%) and IOH (14.1%), but with their absolute PPV values being too low to be useful in the prediction of frailty. Instead, the usefulness of OI and IOH was related to them having the highest NPVs (96.2% and 94.6%, respectively); in other words, 96% of subjects *not* reporting OI on standing were non-frail. Interestingly, the NPV of OI was slightly higher than that of previous falls (94.8%), and the NPV of the combined criterion OI/falls (94.0%) was not better than that of OI alone.

Table 11.2a. Diagnostic properties of the OH definitions and previous history of falls as frailty screening tools. The sample prevalence of frailty (modified Fried's classification) was 7.0%.

OH definition	Sensitivity	Specificity	PPV	NPV
COH	90.3%	5.6%	6.7%	88.5%
FOH	87.1%	6.3%	6.6%	86.7%
IOH	38.7%	82.2%	14.1%	94.6%
IOH without OI	48.4%	40.1%	5.7%	91.2%
MOH-Cluster 1	22.6%	74.5%	6.3%	92.7%
MOH-Cluster 2	51.6%	46%	6.7%	92.6%
MOH-Cluster 3	25.8%	79.6%	8.7%	93.4%
OI	61.3%	73.8%	15.1%	96.2%
Faller	35.5%	88.6%	19.0%	94.8%
OI and Faller	19.4%	94.9%	22.2%	94.0%

PPV: positive predictive value; NPV: negative predictive value.

According to TRIL-FI, the prevalence of frailty alone was 19.5%. As Table 11.2b shows, all OH definitions had too low absolute PPV values for them to be useful frailty predictors (interestingly, MOH Cluster 3 had a slightly higher PPV than OI or IOH). With TRIL-FI, the NPV of OI was lower than with the modified Fried's classification, with only 83.4% of subjects who did *not* report OI on standing being non-frail. The NPV of the combined criterion OI/falls (82.2%) was not superior to that of OI alone.

Table 11.2b. Diagnostic properties of the OH definitions and previous history of falls as frailty screening tools. The sample prevalence of frailty (TRIL-FI) was 19.5%.

OH definition	Sensitivity	Specificity	PPV	NPV
COH	95.3%	6.2%	19.7%	84.6%
FOH	93.0%	6.7%	19.4%	80.0%
IOH	26.7%	82.5%	27.1%	82.3%
IOH without OI	59.3%	41.0%	19.5%	80.7%
MOH-Cluster 1	23.3%	74.2%	17.9%	80.0%
MOH-Cluster 2	46.5%	44.4%	16.8%	77.5%
MOH-Cluster 3	30.2%	81.5%	28.3%	82.9%
OI	39.5%	74.0%	27.0%	83.4%
Faller	30.2%	91.0%	44.8%	84.4%
OI and Faller	14.0%	95.8%	44.4%	82.2%

PPV: positive predictive value; NPV: negative predictive value.

A frailty tool for primary care?

With the ageing of the population in Western societies and the rising costs of health and social care, many countries are refocusing health policy on health promotion and disability prevention among older people. It has been argued that efforts aimed at identifying at-risk groups of older people in order to provide early intervention and/or multidisciplinary case management should be done *at the level of general practice* via adoption of a clinical paradigm based on the concept of frailty, which fits well with the biopsychosocial model of primary care (544). However, this ideal has exposed the lack of frailty metrics that are appropriate for primary care. Indeed, family physicians and community practitioners are in need of easy instruments for frailty screening (545). A simple diagnostic tool (for the presence of pre-frailty or frailty) based on the self-report of OI on standing *and* at least one fall in the past six months could be useful in primary care, and would complement a recently developed instrument by the candidate (274). Further research to externally validate the OI/falls tool for frailty screening is needed.

Chapter 12

Limitations, conclusions and future research

Limitations of the investigation

Lack of universally accepted definitions on orthostatic hypotension and frailty

The main question of this investigation was whether *OH* (generically conceptualised) could be a marker of *frailty* in community-dwelling older people.

Traditionally, OH and frailty have been two ill-defined concepts in Geriatric Medicine. Although a consensus definition of OH was established in 1996, the introduction of continuous non-invasive measurement of finger arterial blood pressure (i.e. as used in this investigation) left many clinicians and researchers unsatisfied with the consensus definition. On the other hand, the definition of frailty has also been elusive, and even though clear operationalisations have been proposed over the last decade, a universal consensus definition of frailty does not exist either. A first challenge was therefore to review the concepts and definitions of OH and frailty, and that was addressed in Chapters 1 and 2, respectively. A departing premise for this investigation was that the correlation of two complex concepts without universally accepted definitions would require the use of various alternative definitions for each of them, in order to maximise the chances of clinically meaningful findings.

In Chapter 1, five definitions of OH were presented: *consensus* (COH), *Fedorowski et al*.'s modification of the consensus (FOH), *initial* (IOH), *morphological* (MOH), and *orthostatic intolerance* (OI). Together, these five definitions not only covered the degree of orthostatic blood pressure drop (i.e. COH, FOH, IOH, MOH), but also the morphology of the blood pressure recovery (i.e. MOH, defined by the candidate using cluster analysis) and the presence of orthostatic intolerance symptoms (i.e. OI, IOH).

In Chapter 2, a review of frailty definitions was presented with a special focus on two particularly popular ones at present: Fried's *phenotypic* approach and Rockwood's *frailty index* approach. From the point of view of the frailty definition, this investigation adopted an eclectic approach and employed both operationalisations for the purpose of the correlations with OH, in order to assess the degree of agreement between them. The premise was that consistent findings with both frailty definitions could help increase the internal validity of the findings. In addition, the use of two frailty operationalisations was an opportunity to learn and practise the methodology for their construction.

Exploratory nature of the investigation

Departing from various definitions for each concept and conducting cross-correlations between them is a reflection of the *exploratory* nature of this investigation. Exploratory research is 'a type of research conducted because a problem has not been clearly defined', it 'provides insights into and comprehension of an issue or situation', and its results 'are not usually useful for decision-making by themselves, but they can provide significant insight into a given situation' (546); the findings of this investigation should be seen in that precise light.

Limitations of the research setting

For the purpose of this doctoral investigation, the main advantage of the TRIL Clinic research setting was that it offered a highly *multidisciplinary* environment and allowed sufficient time for each participant to be fully characterised according to the principles of *comprehensive geriatric assessment*, without which a study on frailty would not have been possible.

However, as explained in Chapter 4, the research design also imposed limitations on the study. *Firstly*, the data were *cross-sectional*, which precludes the inference of causality relationships; and even though *structural equation modelling* (SEM) was employed as a statistical technique to assess the extent to which *postulated* causal relationships were *supported* by the data, significant SEM findings only indicate *plausibility* and *need for further confirmatory testing* in more appropriate (i.e. longitudinal and/or experimental) settings. *Secondly*, the TRIL Clinic recruitment strategy resulted in a *non-random, convenience* sample, which does not guarantee the *external* validity of the findings until they are replicated independently.

Limitations imposed by the research protocol

Regarding blood pressure measurements, a limitation imposed by the research protocol was that the orthostatic blood pressure measurements were performed only once and at different times of the day (547), seasons (548), and without standardisation for meals (549, 550), medications and lifestyle habits such as smoking and drinking coffee or alcohol (551-554). In older people, the variability of orthostatic blood pressure responses (and to a lesser-known degree, of OI) can be considerable, leading to poor reproducibility (549, 555-561). Although not all studies have found the reproducibility issue a cause for concern (562, 563), it is possible that repeated evaluations of orthostatism could yield different results and patterns of orthostatism within the same subject, so further research should examine the extent to which a single orthostatic assessment is representative of the person's 'orthostatic status' for the purpose of correlations with frailty.

Regarding orthostatic intolerance (OI), a proxy for the above 'orthostatic status' could have been obtained through the use of a chronic orthostatic intolerance questionnaire such as the *chronic OI subscale* of the *Autonomic Symptom Profile* questionnaire, which captures the frequency and severity of OI symptoms over the preceding year (564). A limitation of the TRIL Clinic research protocol is the lack of availability of such an instrument, which would have been useful to assess the extent to which chronic OI symptoms correlate with OI symptoms during the 'one-off' active stand. A high degree of correlation between 'chronic OI' and 'active stand OI' would have enhanced the internal validity of the association found between frailty and 'active stand OI'.

Another protocol-driven limitation in the area of blood pressure measurement was the inability to measure orthostatic hemodynamic responses beyond three minutes post-stand (i.e. the inability to examine *delayed* OH as a potential correlate of frailty). In general, the limitations identified in the protocol would be easy to address in future, purpose-designed studies.

Main conclusions

With the above caveats in mind, this investigation reached the following conclusions:

- The application of the COH or FOH definitions to beat-to-beat orthostatic blood pressure data resulted in labelling as pathological over 90% of the sample, which suggests their lack of specificity for the diagnosis of OH. This investigation supports previously stated concerns that the application of the COH definition to the analysis of beat-to-beat data is *unlikely to be clinically meaningful*.

- Whilst all the OH definitions considered (COH, FOH, IOH, MOH and OI) resulted in significant orthostatic hemodynamic differences between their respective OH – and OH + subgroups, COH and FOH had no significant clinical correlates in terms of OI and previous falls; IOH (which includes OI in its definition) and OI correlated with previous falls; MOH (based on the SBP recovery pattern and not including OI in its definition) correlated with OI.

- IOH, MOH and OI had a similarity in that they established subgroup differences in SBP recoverability *beyond* phase 1 of the recovery period (i.e. > 30 seconds post-stand); a structural equation model supported the previously published finding by the candidate that impaired SBP recoverability is the main *hemodynamic* predictor of OI in this sample. The degree of SBP drop (i.e. delta) is the main predictor of SBP recoverability, but delta SBP itself had no independent correlation with OI or previous falls.

- In general, the structural equation models supported the hypothesis that OI may be a *mediator* between orthostatic hemodynamic changes and falls, but did not support orthostatic hemodynamic variables having an independent association with falls.

- Amongst the various orthostatic hemodynamic parameters, the most consistently associated with frailty was delta HR, in the direction of a decreasing orthostatic HR response with increasing frailty. However, the possible effect of medications on this relationship should be clarified in further research.

- Amongst the five OH definitions considered, *OI was the only significant marker of frailty*. IOH was also associated with frailty, but further reanalyses (e.g. using a modified IOH definition not including OI) suggested that this may have been due to the inclusion of OI in the IOH definition. The link of OI with frailty found in this study supports previous claims that 'dizziness might be better considered a *geriatric syndrome* that results from impairment or disease in *multiple systems*' (565).

- Interestingly, OI (which was consistently associated with *frailty*) was not associated with *age* alone, suggesting that OI may be a *biological*, rather than a *chronological*, marker of ageing, in keeping with the frailty paradigm.

- In the face of frailty (which had a significant correlation with previous falls), OI had a modest ($P < 0.05$) independent association with previous falls.

- Considered as a screening tool for the presence of pre-frailty or frailty, OI had in the sample a positive predictive value (PPV) of 69.0% (with the modified Fried's classification) and 81.7% (with TRIL-FI). An alternative tool based on the *presence of OI during stand* and *at least one fall in the last six months* had a PPV of 88.9% and 96.3%, respectively. If externally replicated, the latter screening tool would be of potential use in primary care settings.

Personal perspective and future research

The candidate's self-assessment is that, through this doctoral investigation (2007–2010), he has achieved a good systematic comprehension of the complex field of orthostatic hemodynamics and frailty in older people, and has learned and implemented advanced quantitative research methods that had not been previously applied in this field (e.g. cluster analysis, SEM). The investigation has contributed original findings that have merited publication in international peer-reviewed journals. The candidate will pursue further research in the context of The Irish Longitudinal Study on Ageing (TILDA), to address many of the limitations of this initial investigation.

Based on the main limitations of this investigation, some themes for further research are outlined below:

- *Reproducibility of the orthostatic hemodynamic responses*. To address the issue of the potential lack of reproducibility of the Finometer® readings, further research should standardise the assessment conditions (e.g. timing, medications, meals and lifestyle habits) and repeat the assessments at least twice in each subject.

- *Correlation of 'chronic OI' symptoms with 'active stand OI'*. As explained above, this would enhance the internal validity of the correlation between frailty and active stand OI, and shed light on the issue of the reproducibility of active stand OI.

- *Assessment of cerebral blood flow during OI*. This would require cerebral Doppler equipment and ideally, as outlined above, a prospective method of reporting OI.

This design would also allow the testing of the hypothesis that frailty is associated with an impairment of the cerebral autoregulation.

- *Longitudinal prognosis of the MOH classification*. This would be the candidate's preferred post-doctoral area of study, and would be highly suited to the design of The Irish Longitudinal Study on Ageing (TILDA, http://www.tcd.ie/tilda/), which is a prospective, population-based study, incorporating Finometer® active stands to a comprehensive assessment protocol. The aim would be to replicate the MOH classification in the baseline sample (with similar autonomic exclusion criteria) and study the different trajectories of the three MOH groups, not only with an emphasis on mortality but also on the incidence of falls, neurological disease (e.g. cognitive impairment) and autonomic-related disorders (e.g. Parkinson's disease, diabetes).

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Appendices

Appendix 1. TRIL Clinic leaflet.

Would you like to participate in a research programme that aims to develop technologies to help older persons live independently at home?

Falls, memory loss and social isolation are three of the main factors that have an adverse impact on the quality of life of the older persons.

The TRIL programme is looking for 600 participants who are healthy or had a previous fall or near fall.

You are suitable for the research programme if you are

- Aged 60 and over
- Able to walk and look after yourself independently (you may have a walking stick)
- Do not have significant memory problems
- Willing to take part in research

Your participation in this study will contribute greatly towards our knowledge to promote healthy and independent future for many older people.

What is involved?

If you have been troubled by falls or stumbles and would like to participate in this research, please ask your doctor to refer you to our facility at St. James Hospital (at the address below). We will be happy to speak to your doctor if he/she needs further information. Once we have received the referral letter, an experienced nurse will ring you at home who will explain to you the nature of the project and answer any questions you may have. She will also arrange a clinic appointment that is suitable for you. The research clinic is situated in Hospital 4 top floor in **St James's Hospital** and it is closely linked to the Falls and Blackout Unit. If you haven't had issues with falls but would like to volunteer as a healthy control, please contact us directly using the contact details below (GP referral not necessary). On the day you visit the clinic, you will be met by the secretary who will register you into the system. You will then meet a doctor on the research team who will explain the research in greater detail and take consent from you. There are three stages to your visit.

Medical

A doctor will ask about your medical conditions and your previous falls and stumbles (if you have any). You will then undergo a series of tests including a brief physical check-up, tracing of your heart (ECG), blood pressure measurement, vision test, blood test and a walking test. A senior physiotherapist will also look at your balance and muscle strength. You will also have a hearing test. After that you may be invited to take part in any of the following sections.

Cognition

This part of the research is to help develop a recorder to detect memory function and mood through *voice patterns*. The researcher will ask permission to *record your voice* while they ask you some questions about your *memory* and *mood* and then ask you to read a series of words and to use words to describe pictures.

Social interview

This part of the research looks at how *social networks influence health*. In addition to a set of multiple-choice questions, you will have a 30-minute interview where the researchers ask about your life and social support.

Ethnography

This part of the research allows us to have a greater understanding of how you live from day to day and your viewpoints about how technology affects your life.

Confidentiality

The information that we gather about you will be treated with the strictest confidence and will only be used with your permission and fully anonymized.

Contact Details

If you would like further information, please ring us at

Tel: 01-4103863 or 01-4284614

Address: TRIL programme office, Hospital 4 Top Floor, St James's Hospital, Dublin 8.

E-mail: tril@stjames.ie or www.trilcentre.org

The TRIL programme is a collection of joint research projects from Trinity College, University College Dublin (UCD), NUI Galway and is funded by Intel Corporation and IDA as part of the research and development programme of the department of Enterprise, Trade and Employment.

"The TRIL Centre brings together world-class industry and academic experts who are inventing and testing new technologies with older people, and their families, to support them in continuing to live independently. The TRIL Centre will focus on three key areas: improving social health and community engagement for older people, detecting and preventing falls in the home, and helping those with memory loss to maintain their independence." 30/1/2007, Press release at launch of TRIL centre.

Appendix 2. Referral form for St James's Hospital Emergency Department.

Patient Suitable for TRIL falls assessment

ST JAMES'S HOSPITAL

Falls Assessment Referral Form

Name: _____ Address: _____ _____ Telephone number: _____ M.R.N._____ D.O.B._____	Next of kin:_____ NOK Tel No: _____ Date seen in Emergency Department: _____ **Patient informed of referral: Yes ☐ No ☐** Consultant(s) _____

The aim of the pathway is:
To facilitate follow up **falls assessment** following discharge from the Emergency Department (ED) of a selected group of older patients (≥ 60 years) presenting with falls. Early (within 2 weeks) comprehensive assessment will be offered at TRIL clinical research facility (Hospital 4 top floor).

Patients presenting with a **FALL** who fulfil the following criteria (Inclusion criteria)

- ☐ Over 60 years old
- ☐ Medically stable (for e.g. no acute infection, stroke, myocardial infarction)
- ☐ **Able to walk on their own <u>with or without</u> an aid** (stick, zimmer frame)
- ☐ Do not have significant memory problems
- ☐ Discharged from emergency department

This falls pathway **DOES NOT** apply to patients who (exclusion criteria)

- Loss of consciousness (Refer to FABU – yellow form)
- Require Hospital admission
- Moderate to severe cognitive impairment
- Unable to walk independently
- Require **acute** multidisciplinary input (including medical social worker)
- **Require** acute **medicine of the elderly department input**

History of fall
Mobility: Independent □ Stick □ Frame □ **Please complete medication list on the back page**

Past Medical History	
❑ Previous Falls ❑ Stroke ❑ Parkinson Disease ❑ Osteoarthritis ❑ Faints	❑ Injuries ❑ Alcohol taken ❑ Medications implicated for falls Other significant history

Signature and contact number: _____ **Date:** _____

To discuss a case please ring ext 3863 TRIL centre, Hospital 4 top Floor.

Medication List

Medication	Dosage	Frequency

Record of patients presenting with falls but not suitable for TRIL assessment

Name: _____ Address: _____ _____ Telephone number: _____ M.R.N._____ D.O.B._____	Next of kin:_____ NOK Tel No: _____ Date seen in Emergency Department: _____

Reasons patient were not suitable for TRIL falls assessment

- ❑ Loss of consciousness (Refer to FABU – yellow form)
- ❑ Require Hospital admission
- ❑ Moderate to severe cognitive impairment
- ❑ Unable to walk independently
- ❑ Require **acute** multidisciplinary input (including medical social worker)
- ❑ **Require** acute **medicine of the elderly department input**
- ❑ Admission to hospital
    - Medically unwell, expand
      _____
    - Injuries
    - Fracture, expand
      _____
    - Soft tissue injuries
    - State other reasons for admission

Thank you. Please leave completed form in box provided.

Appendix 3. Letter to General Practitioners from the Emergency Department.

Emergency Department,

St James's Hospital,

James's Street,

Dublin 8.

Date:

Dear Doctor,

Patient addressograph
MRN:
Name
Address

Your patient was seen in the Emergency Department of St James Hospital on _____

with a fall. If you think your patient needs further falls assessment, please refer patient to the Medicine of the Elderly Medical Outpatient.

Write to:

TRIL Clinic

St James's Hospital,

James's Street,

Dublin 8.

Yours truly,

Appendix 4. Clinical Nurse Manager phone call script.

Hello, my name is Clodagh Cunningham. I am a nurse from St James's Hospital. You attended casualty on the __date___ with a fall. I would appreciate if you can take a few minutes to answer a few questions.

1. What are you like on your feet? Independent/ walks with stick/ walks with frame/ immobile
2. Is this your first fall? Yes/No
3. How many falls have you had in the past year? _____
4. Did you injury yourself when you fell?
5. How is your health at the moment?

Does the patient appear confused? Yes/No

If suitable, I would like to offer you an opportunity to have an assessment to find out why you are falling and if there's anything we can do to prevent you from further falls. The assessment will be carried out by doctors, nurses, physiotherapist and with the assistance of scientist. We will be using some new technology to assess your walking. Your eyesight and hearing will also be tested. We will also check your blood pressure and take some blood samples. You will also have your memory checked. This is a research clinic and we are developing new technology to improve diagnosis of falls risk and aim to prevent future falls. If you like to attend, we can offer you an appointment and arrange the transport if you like.

We will inform you of some of the results on the day and write to your GP. We will refer you for rehabilitation and OPD follow up if required.

If not suitable, and falling a lot since attending ED or become chair bound since the fall, that is high risk. Have you ever been to the MedEL OPD? Then you say that if you like to we will offer you an appointment in the Medicine of the Elderly OPD for assessment. A nurse will ring you to arrange a visit.

What is unsuitable?
Confused
Immobile

High risk of falls:
At least 2 falls in last month
Fall frequency have increased

Notes from phone call

Date:
Name: MRN:

Person spoken to: Patient / Care-giver _____

What are you like on your feet? Independent/ walks with stick/ walks with frame/ immobile
Is this your first fall? Yes/No
How many falls have you had in the past year? _____
Did you injury yourself when you fell?
How is your health at the moment?

Does the patient appear confused? Yes/No

Outcome

Suitable

Appointment arranged	**☐ Yes ☐ No**
Date of Appointment	_____
Transport required	☐ Yes ☐ No
Appointment booked on system	☐ Yes ☐ No
Letter sent to patients by Brian	☐ Yes ☐ No

Not suitable

Ring in a month
Arrange OPD ☐ New ☐ Return
Letter to GP ☐ Yes ☐ No

Comments

Appendix 5. Informed consent form.

SJH / AMNCH RESEARCH ETHICS COMMITTEE CONSENT FORM

Title of research study: Comprehensive assessment using existing and innovative technologies in older people who are at risk of falls and in healthy older controls

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date::
Date on which the participant was first furnished with this form:

Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person competent to give consent to his or her participation in the research study (other than a person who applied to undertake or conduct the study). If the subject is a minor (under 18 years old) the signature of parent or guardian must be obtained:-

NAME OF CONSENTOR, PARENT or GUARDIAN:
SIGNATURE:
RELATION TO PARTICIPANT:

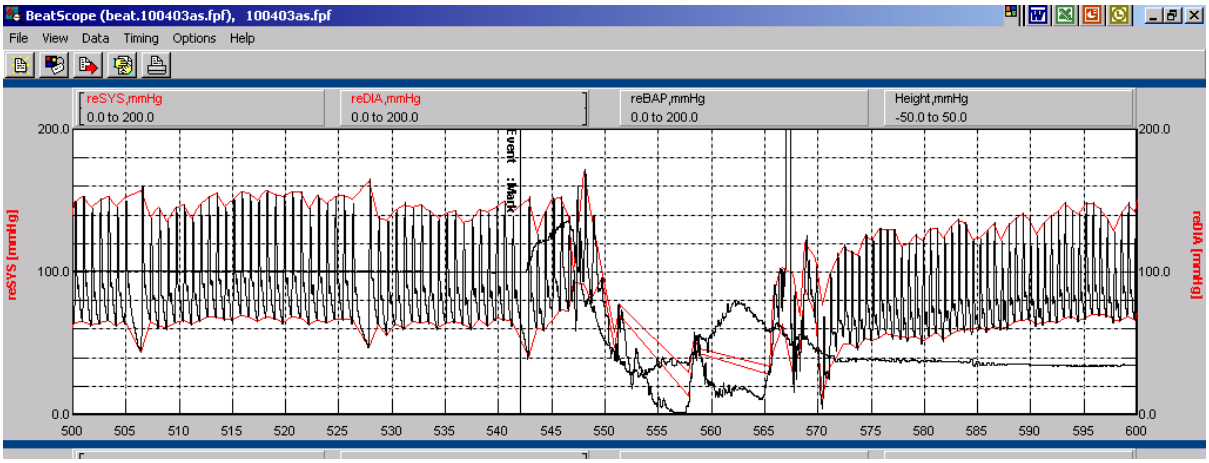
Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS: SIGNATURE:
NAME OF SECOND WITNESS: SIGNATURE:

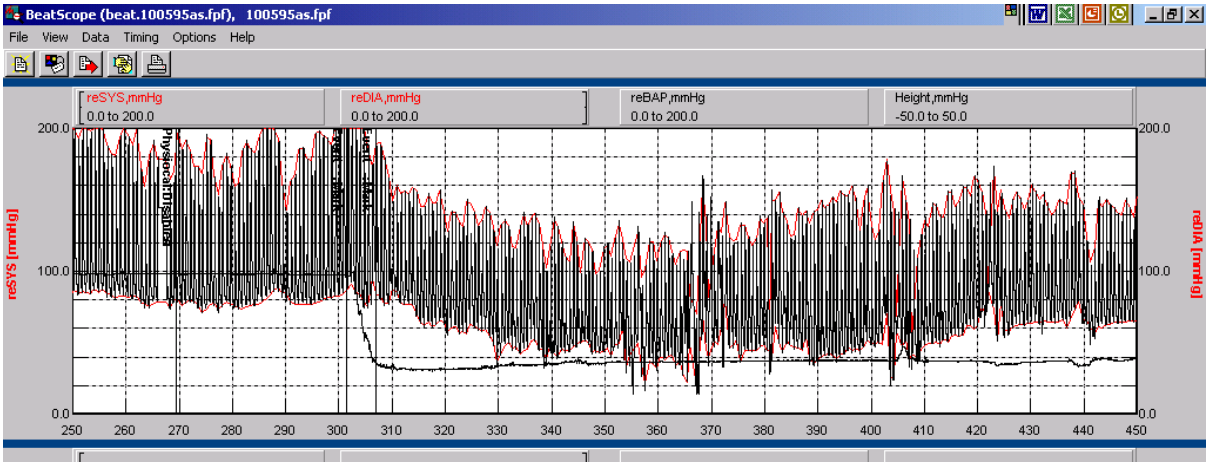
Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature: **Date:**
(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records, and send one copy to the sponsor (if there is a sponsor).

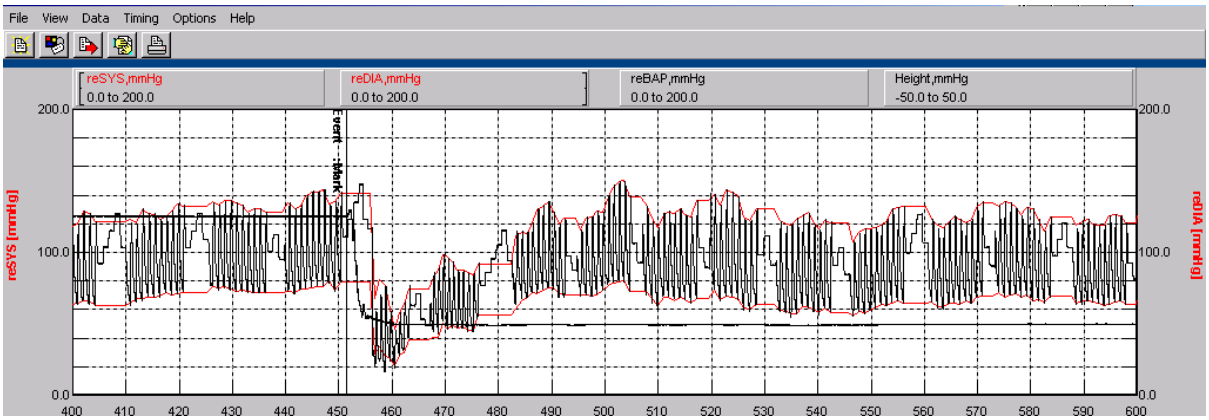
Appendix 6. Examples of files excluded as part of the quality checks.



Example 1. Signal lost during active stand (nadir not interpretable).



Example 2. Excessive signal fluctuation, apparent nadir at >30 seconds after stand, suggests signal drift (Physiocal off).



Example 3. The Physiocal occurs every less than 40 beats prior to stand, suggesting poor quality signal at baseline. Moreover, the Physiocal was not switched off before the active stand.

Appendix 7. Structural equation models by the *Markov chain Monte Carlo* (MCMC) estimation method.

In AMOS 16.0, when models contain categorical *response* (i.e. *dependent*) variables, the use of the *Markov chain Monte Carlo* (MCMC) option, as opposed to *Maximum Likelihood* (ML) estimation, is advocated (1, 2). The MCMC estimation uses a *probit* model that links the predictor to the categorical response using a cumulative normal probability function. For the purpose of consistency, this appendix shows the results of all the models shown in the main text of the thesis using the MCMC (instead of the ML) estimation method.

In AMOS, *probit* modelling is specified by selecting the option 'allow non-numeric data' when selecting the working data file. The next step is to recode the categorical response variables to 'ordered-categorical' (under the 'tools' menu). If the categorical outcome variable is dichotomous, the variance of its error term needs to be set to 1.0 in order to achieve identification, but the latter is not required for categorical variables having more than two levels. In the 'analysis properties' menu, the option 'estimate means and intercepts' is selected, and both 'standardized estimates' and 'indirect, direct & total effects' are requested. MCMC estimation is then initiated, and the user stops the estimation when the automatic indicator shows a satisfactory convergence. The output includes the regression weights and the standardised path coefficients. In terms of fit measures for *probit* modelling, the posterior predictive *P* value provides information on overall model fit to data, with values closer to 0.50 being better than ones larger or smaller.

SEM in figure 7.3. Structural equation model (SEM) with postulated relationships between the consensus classification of orthostatic hypotension (COH), orthostatic intolerance (OI), falls and age.

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
OI←COH	0.49	0.01	1.00	-0.09	1.11	0.11	-0.03	-0.69	1.63
Faller←OI	0.31	0.00	1.00	0.11	0.53	0.14	0.03	-0.03	0.71
Faller←Age	0.03	0.00	1.00	0.01	0.06	0.04	-0.04	0.00	0.08
Faller←COH	0.31	0.01	1.00	-0.44	1.16	0.24	0.02	-1.01	2.10
Means									
COH	0.94	0.00	1.00	0.92	0.96	0.02	-0.05	0.90	0.98
Age	72.07	0.00	1.00	71.40	72.75	0.00	-0.04	70.82	73.35
Intercepts									
Faller	-3.82	0.02	1.00	-5.68	-2.07	-0.13	0.08	-7.57	-0.49
OI	-1.03	0.01	1.00	-1.63	-0.47	-0.14	0.00	-2.22	0.09
Covariances									
Age↔COH	-0.13	0.00	1.00	-0.29	0.03	-0.05	0.04	-0.51	0.17
Variances									
COH	0.06	0.00	1.00	0.05	0.06	0.33	0.26	0.04	0.07
Age	51.61	0.04	1.00	45.21	58.77	0.26	0.10	39.46	69.52

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	COH	Age	OI
OI	0.11		
Faller	0.07	**0.23**	**0.28**

Posterior Predictive $P = 0.50$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 7.4. Structural equation model (SEM) with postulated relationships between the Fedorowski-modified classification of orthostatic hypotension (FOH), orthostatic intolerance (OI), falls and age.

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
OI←FOH	0.46	0.01	1.00	-0.07	1.03	0.14	-0.02	-0.49	1.46
Faller←OI	0.31	0.00	1.00	0.09	0.53	-0.01	-0.07	-0.06	0.66
Faller←Age	0.03	0.00	1.00	0.01	0.05	0.03	0.04	0.00	0.08
Faller←FOH	0.36	0.01	1.00	-0.35	1.16	0.15	-0.08	-1.05	1.72
Means									
FOH	0.93	0.00	1.00	0.91	0.96	0.02	0.09	0.88	0.98
Age	72.06	0.01	1.00	71.37	72.74	0.01	-0.02	70.61	73.28
Intercepts									
Faller	-3.85	0.03	1.00	-5.56	-2.13	-0.03	0.15	-7.71	-0.40
OI	-1.00	0.01	1.00	-1.55	-0.48	-0.13	-0.02	-1.95	0.03
Covariances									
Age↔FOH	-0.08	0.00	1.00	-0.26	0.09	-0.04	-0.01	-0.44	0.23
Variances									
FOH	0.06	0.00	1.00	0.06	0.07	0.26	0.11	0.05	0.08
Age	51.70	0.07	1.00	45.34	58.82	0.29	0.21	40.27	69.77

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	FOH	Age	OI
OI	0.11		
Faller	0.08	**0.22**	**0.28**

Posterior Predictive $P = 0.51$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 7.5. Structural equation model (SEM) with postulated relationships between the initial orthostatic hypotension classification (IOH), orthostatic intolerance (OI), falls and age.

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
OI←IOH	Regression weight fixed at 1 in the model (lack of model convergence if not fixed)								
Faller←OI	0.19	0.01	1.00	-0.12	0.52	0.06	-0.05	-0.37	0.74
Faller←Age	0.03	0.00	1.00	0.01	0.05	0.02	-0.04	-0.01	0.08
Faller←IOH	0.22	0.01	1.00	-0.42	0.88	0.08	0.06	-1.07	1.64
Means									
IOH	0.19	0.00	1.00	0.16	0.23	0.05	0.06	0.12	0.27
Age	72.06	0.00	1.00	71.39	72.73	0.05	-0.04	70.69	73.30
Intercepts									
Faller	-3.48	0.02	1.00	-5.04	-1.93	-0.03	0.02	-7.06	0.02
OI	-0.81	0.00	1.00	-0.94	-0.68	-0.03	-0.11	-1.06	-0.56
Covariances									
Age↔IOH	0.20	0.00	1.00	-0.07	0.48	0.00	0.04	-0.29	0.75
Variances									
IOH	0.16	0.00	1.00	0.14	0.18	0.26	0.14	0.13	0.20
Age	51.70	0.05	1.00	45.12	59.29	0.28	0.21	40.52	67.68

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	IOH	Age	OI
OI	**0.37**		
Faller	0.08	**0.22**	0.19

Posterior Predictive $P = 0.00$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 7.6. Structural equation model (SEM) with postulated relationships between the morphological classification of orthostatic hypotension (MOH), orthostatic intolerance (OI), falls and age.

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
OI←MOH	0.39	0.00	1.00	0.21	0.59	0.06	0.04	0.02	0.75
Faller←OI	0.30	0.00	1.00	0.08	0.52	0.06	0.12	-0.10	0.70
Faller←Age	0.03	0.00	1.00	0.01	0.05	0.00	-0.04	-0.01	0.07
Faller←MOH	0.05	0.00	1.00	-0.19	0.29	0.02	-0.02	-0.42	0.50
Means									
MOH	1.95	0.00	1.00	1.89	2.02	0.03	0.03	1.82	2.08
Age	72.06	0.01	1.00	71.39	72.73	-0.01	-0.07	70.74	73.30
Intercepts									
Faller	-3.54	0.03	1.00	-5.14	-1.93	-0.02	-0.08	-6.56	-0.82
OI	-1.35	0.00	1.00	-1.77	-0.96	-0.04	0.07	-2.12	-0.55
Covariances									
Age↔MOH	0.33	0.00	1.00	-0.13	0.80	0.05	0.25	-0.68	1.44
Variances									
MOH	0.47	0.00	1.00	0.41	0.53	0.29	0.12	0.36	0.60
Age	51.56	0.06	1.00	45.14	59.12	0.32	0.20	39.70	67.86

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	MOH	Age	OI
OI	**0.26**		
Faller	0.03	**0.22**	**0.28**

Posterior Predictive $P = 0.52$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 7.7. Structural equation model (SEM) with postulated relationships between a modified version of the initial OH classification (i.e. IOH without OI: mIOH), orthostatic intolerance (OI), falls and age.

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
OI←mIOH	0.30	0.00	1.00	0.04	0.57	0.04	-0.03	-0.17	0.81
Faller←OI	0.31	0.00	1.00	0.11	0.53	0.17	0.18	-0.08	0.74
Faller←Age	0.03	0.00	1.00	0.01	0.05	0.01	0.03	-0.01	0.08
Faller←mIOH	0.00	0.00	1.00	-0.33	0.33	0.07	-0.01	-0.68	0.60
Means									
mIOH	0.59	0.00	1.00	0.54	0.64	0.00	0.07	0.50	0.69
Age	72.07	0.00	1.00	71.41	72.75	0.03	0.00	70.86	73.38
Intercepts									
Faller	-3.47	0.02	1.00	-4.98	-1.95	-0.01	0.04	-6.89	-0.51
OI	-0.75	0.00	1.00	-0.95	-0.54	-0.03	-0.09	-1.19	-0.39
Covariances									
Age↔mIOH	0.12	0.00	1.00	-0.22	0.46	0.00	0.01	-0.50	0.80
Variances									
mIOH	0.25	0.00	1.00	0.22	0.28	0.29	0.21	0.19	0.31
Age	51.60	0.07	1.00	45.14	58.88	0.25	0.08	41.04	65.64

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	mIOH	Age	OI
OI	*0.15*		
Faller	0.00	**0.22**	**0.29**

Posterior Predictive $P = 0.52$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 7.8. Structural equation modelling (SEM) with postulated relationships between systolic orthostatic hemodynamic variables, orthostatic intolerance (OI), and falls.

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
OI←Perc30	-0.02	0.00	1.00	-0.03	0.00	0.03	0.03	-0.05	0.01
OI←Delta	0.00	0.00	1.00	-0.01	0.01	0.02	0.07	-0.02	0.02
Perc30←Delta	-0.48	0.00	1.00	-0.53	-0.44	0.01	0.03	-0.57	-0.40
Faller←OI	0.28	0.00	1.00	0.07	0.50	0.11	0.08	-0.08	0.75
Delta←Baseline	0.20	0.00	1.00	0.13	0.27	0.02	0.07	0.06	0.34
Faller←Delta	0.00	0.00	1.00	-0.01	0.01	0.02	0.04	-0.03	0.02
Faller←Perc30	-0.01	0.00	1.00	-0.03	0.01	-0.02	0.25	-0.06	0.03
Means									
Baseline	160.37	0.02	1.00	158.10	162.64	-0.01	0.05	155.84	164.63
Intercepts									
Delta	3.64	0.07	1.00	-7.57	14.77	-0.02	0.07	-18.73	26.18
Perc30	113.35	0.02	1.00	111.47	115.19	-0.04	0.04	109.83	117.07
OI	0.86	0.02	1.00	-0.74	2.43	-0.04	0.01	-2.47	4.39
Faller	0.04	0.02	1.00	-1.88	1.94	0.03	0.22	-4.10	5.25
Variances									
Baseline	598.87	0.69	1.00	525.92	684.69	0.32	0.12	475.09	815.97
e1	323.37	0.32	1.00	282.43	369.65	0.26	0.20	249.93	429.56
e2	80.21	0.10	1.00	70.29	91.54	0.28	0.14	62.60	102.79

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Baseline	Delta	Perc30	OI
Delta	**0.26**			
Perc30		**-0.71**		
OI		0.06	*-0.20*	
Faller		-0.06	-0.12	**0.27**

Posterior Predictive $P = 0.51$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 8.1. Internal validation of the modified Fried's definition using a structural equation model (AMOS 16.0).

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
Grip strength←Frailty	-4.66	0.02	1.00	-6.17	-3.22	-0.06	0.04	-7.66	-1.87
Weight loss←Frailty	0.31	0.00	1.00	0.09	0.56	0.32	0.27	-0.08	0.83
Walking speed←Frailty	-0.17	0.00	1.00	-0.21	-0.12	-0.06	0.01	-0.27	-0.09
Exhaustion←Frailty	0.83	0.01	1.00	0.49	1.28	0.59	0.49	0.23	1.79
Physical activity←Frailty	-1.01	0.00	1.00	-1.34	-0.69	-0.08	0.06	-1.65	-0.34
Intercepts									
Exhaustion	-1.09	0.01	1.00	-1.40	-0.86	-0.62	0.72	-1.81	-0.69
Grip strength	23.06	0.01	1.00	22.12	24.02	0.03	0.00	20.41	24.89
Walking speed	1.23	0.00	1.00	1.20	1.26	0.04	-0.02	1.16	1.29
Weight loss	-1.08	0.00	1.00	-1.25	-0.92	-0.17	0.20	-1.48	-0.77
Physical activity	4.04	0.00	1.00	3.81	4.26	-0.01	0.01	3.58	4.50
Variances									
e2	84.48	0.18	1.00	69.07	100.59	0.07	0.09	55.89	116.83
e3	0.07	0.00	1.00	0.05	0.08	-0.05	0.23	0.03	0.10
e5	4.80	0.01	1.00	4.03	5.65	0.17	0.08	3.26	6.50

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Frailty
Physical activity	**-0.42**
Exhaustion	**0.63**
Walking speed	**-0.54**
Weight loss	*0.29*
Grip strength	**-0.45**

Posterior Predictive $P = 0.44$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 10a. SEM with the OH classifications as indicators of frailty (modified Fried's classification).

Estimates:

	Mean	S.E.	S.D.	C.S.	Skewness	Kurtosis	Min.	Max.
Regression weights								
MOH←Frailty	0.12	0.00	0.07	1.00	0.00	0.02	-0.18	0.42
OI←Frailty	0.60	0.01	0.13	1.00	0.08	-0.13	0.07	1.14
COH←Frailty	0.08	0.01	0.17	1.00	-0.03	-0.12	-0.67	0.72
FOH←Frailty	-0.04	0.01	0.17	1.00	0.01	0.27	-0.83	0.73
Faller←Frailty	0.69	0.01	0.16	1.00	0.36	0.05	0.08	1.45
IOH←Frailty	0.51	0.01	0.13	1.00	0.05	0.02	-0.01	1.09
Means								
Frailty	0.08	0.00	0.04	1.00	-0.13	0.05	-0.08	0.22
Intercepts								
COH	1.61	0.00	0.09	1.00	0.06	0.06	1.18	1.99
FOH	1.53	0.01	0.09	1.00	0.05	-0.05	1.17	1.86
IOH	-0.95	0.00	0.08	1.00	-0.09	0.14	-1.26	-0.67
MOH	0.44	0.00	0.04	1.00	-0.01	0.07	0.29	0.61
OI	-0.65	0.00	0.07	1.00	0.00	0.41	-0.93	-0.36
Faller	-1.28	0.01	0.09	1.00	-0.23	0.22	-1.75	-0.92
Covariances								
e1↔e2	0.98	0.00	0.01	1.00	-2.08	7.40	0.90	1.00
e3↔e5	0.95	0.00	0.02	1.00	-0.62	0.24	0.88	0.99
e1↔e3	0.45	0.01	0.11	1.00	-0.28	0.03	-0.02	0.80
e1↔e4	0.44	0.00	0.06	1.00	-0.13	0.16	0.22	0.63
e1↔e5	0.29	0.01	0.12	1.00	-0.40	0.27	-0.18	0.65
e2↔e3	0.44	0.01	0.11	1.00	-0.12	-0.32	-0.06	0.80
e3↔e4	0.33	0.00	0.05	1.00	0.02	-0.08	0.10	0.50
e4↔e5	0.17	0.00	0.05	1.00	0.22	0.12	-0.01	0.39
e2↔e4	0.41	0.00	0.06	1.00	0.02	-0.05	0.19	0.62
e2↔e5	0.29	0.01	0.11	1.00	-0.03	-0.17	-0.18	0.68
Variances								
Frailty	0.39	0.00	0.04	1.00	0.44	0.20	0.24	0.62
e4	0.47	0.00	0.05	1.00	0.30	0.08	0.30	0.69

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	Frailty
Faller	**0.39**
OI	**0.35**
MOH	0.10
IOH	**0.30**
FOH	-0.02
COH	0.05

Posterior Predictive $P = 0.47$.

S.E.: standard error; S.D.: standard deviation; C.S.: convergence statistic.

SEM in figure 10.1b. SEM with the OH classifications as indicators of frailty (modified Fried's classification). The significant indicators were postulated as independent risk factor for falls.

Estimates:

	Mean	S.E.	S.D.	C.S.	Skewness	Kurtosis	Min.	Max.
Regression weights								
MOH←Frailty	0.12	0.01	0.07	1.00	0.07	-0.09	-0.15	0.41
OI←Frailty	0.58	0.01	0.12	1.00	-0.02	0.11	0.13	1.15
COH←Frailty	0.08	0.02	0.17	1.00	0.03	-0.39	-0.57	0.63
FOH←Frailty	-0.05	0.02	0.17	1.00	-0.05	-0.27	-0.68	0.56
Faller←Frailty	0.60	0.02	0.20	1.00	-0.02	0.04	-0.09	1.58
IOH←Frailty	0.49	0.01	0.12	1.00	0.01	0.07	-0.05	1.11
Means								
Frailty	0.09	0.00	0.03	1.00	-0.18	0.16	-0.09	0.22
Intercepts								
COH	1.59	0.01	0.11	1.00	-0.01	0.44	1.22	2.01
FOH	1.53	0.01	0.11	1.01	-0.20	-0.24	1.16	1.93
IOH	-0.95	0.01	0.07	1.00	0.24	0.31	-1.23	-0.66
MOH	0.44	0.00	0.04	1.00	0.06	-0.08	0.28	0.60
OI	-0.65	0.00	0.07	1.00	0.13	0.05	-0.97	-0.32
Faller	-1.09	0.02	0.18	1.01	0.27	0.11	-1.83	-0.23
Covariances								
e1↔e2	0.98	0.00	0.01	1.01	-0.86	0.77	0.93	1.00
e3↔e5	0.96	0.00	0.02	1.01	-1.37	1.91	0.86	0.99
e1↔e3	0.43	0.01	0.11	1.01	-0.30	0.20	0.00	0.77
e1↔e4	0.46	0.01	0.06	1.01	-0.29	0.07	0.20	0.65
e1↔e5	0.27	0.01	0.12	1.01	-0.30	0.24	-0.20	0.67
e2↔e3	0.43	0.01	0.10	1.01	-0.15	0.06	0.06	0.77
e3↔e4	0.32	0.01	0.06	1.01	0.00	-0.22	0.09	0.51
e4↔e5	0.18	0.00	0.05	1.00	0.21	0.01	0.01	0.40
e2↔e4	0.43	0.01	0.06	1.01	0.02	-0.48	0.21	0.62
e2↔e5	0.28	0.01	0.10	1.00	-0.16	0.22	-0.13	0.66
Variances								
Frailty	0.39	0.00	0.05	1.00	0.19	0.11	0.25	0.63
e4	0.48	0.00	0.05	1.00	0.29	-0.04	0.31	0.71

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	Frailty	OI	IOH
OI	**0.34**		
IOH	**0.29**		
Faller	**0.32**	-0.06	0.27
MOH	0.10		
FOH	-0.03		
COH	0.05		

Posterior Predictive $P = 0.49$.

S.E.: standard error; S.D.: standard deviation; C.S.: convergence statistic.

SEM in figure 10.2a. SEM with the OH classifications as indicators of frailty (TRIL-FI).

Estimates:

	Mean	S.E.	S.D.	C.S.	Skewness	Kurtosis	Min.	Max.
Regression weights								
MOH←Frailty	0.08	0.00	0.05	1.00	0.16	0.49	-0.11	0.30
OI←Frailty	0.43	0.01	0.10	1.00	0.30	0.59	0.06	0.85
COH←Frailty	0.09	0.02	0.14	1.01	-0.10	0.13	-0.39	0.57
FOH←Frailty	0.04	0.01	0.13	1.00	-0.52	2.08	-0.53	0.50
Faller←Frailty	0.75	0.01	0.13	1.01	0.10	-0.14	0.24	1.26
IOH←Frailty	0.34	0.01	0.10	1.00	0.07	-0.15	0.00	0.70
Means								
Frailty	0.30	0.00	0.04	1.00	0.07	0.26	0.08	0.46
Intercepts								
COH	1.60	0.01	0.10	1.00	0.10	0.32	1.22	2.00
FOH	1.51	0.01	0.10	1.00	0.06	0.47	1.15	1.89
IOH	-1.02	0.01	0.09	1.01	-0.10	-0.16	-1.34	-0.68
MOH	0.43	0.00	0.04	1.00	-0.04	-0.19	0.27	0.58
OI	-0.73	0.01	0.08	1.00	-0.13	0.35	-1.08	-0.44
Faller	-1.55	0.02	0.13	1.01	-0.25	0.05	-2.05	-1.13
Covariances								
e1↔e2	0.97	0.00	0.02	1.02	-1.39	1.70	0.88	1.00
e3↔e5	0.96	0.00	0.02	1.01	-0.01	-0.28	0.91	0.99
e1↔e3	0.32	0.02	0.13	1.01	0.01	-0.47	0.00	0.76
e1↔e4	0.43	0.01	0.07	1.01	-0.23	0.21	0.14	0.66
e1↔e5	0.16	0.02	0.13	1.01	0.03	-0.36	-0.23	0.62
e2↔e3	0.34	0.02	0.12	1.01	-0.03	-0.51	0.02	0.69
e3↔e4	0.33	0.01	0.05	1.01	0.14	-0.38	0.15	0.48
e4↔e5	0.18	0.01	0.05	1.01	0.12	-0.01	-0.03	0.32
e2↔e4	0.40	0.01	0.07	1.01	-0.14	0.07	0.15	0.62
e2↔e5	0.18	0.02	0.13	1.01	-0.11	-0.52	-0.21	0.58
Variances								
Frailty	0.65	0.01	0.08	1.00	0.09	0.19	0.40	0.98
e4	0.47	0.01	0.05	1.00	0.40	0.36	0.33	0.68

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	Frailty
Faller	**0.51**
OI	**0.33**
MOH	0.09
IOH	**0.26**
FOH	0.03
COH	0.07

Posterior Predictive $P = 0.47$.

S.E.: standard error; S.D.: standard deviation; C.S.: convergence statistic.

SEM in figure 10.2b. SEM with the OH classifications as indicators of frailty (TRIL-FI). The significant indicators were postulated as independent risk factor for falls.

Estimates:

	Mean	S.E.	S.D.	C.S.	Skewness	Kurtosis	Min.	Max.
Regression weights								
MOH←Frailty	0.08	0.00	0.05	1.00	-0.16	0.30	-0.21	0.27
OI←Frailty	0.41	0.01	0.09	1.00	0.33	0.39	0.02	0.88
COH←Frailty	0.07	0.02	0.14	1.01	0.01	-0.22	-0.33	0.63
FOH←Frailty	0.03	0.01	0.12	1.01	-0.09	0.00	-0.38	0.43
Faller←Frailty	0.71	0.02	0.16	1.01	0.24	-0.37	0.20	1.39
IOH←Frailty	0.32	0.01	0.10	1.01	0.26	0.06	-0.06	0.79
Means								
Frailty	0.30	0.00	0.04	1.00	-0.07	0.14	0.12	0.47
Intercepts								
COH	1.57	0.01	0.10	1.01	0.13	-0.03	1.22	1.90
FOH	1.50	0.01	0.09	1.00	0.02	0.27	1.14	1.89
IOH	-1.01	0.01	0.08	1.01	0.05	0.27	-1.35	-0.67
MOH	0.42	0.00	0.04	1.00	-0.06	0.07	0.27	0.58
OI	-0.73	0.00	0.07	1.00	-0.22	0.17	-1.01	-0.40
Faller	-1.33	0.02	0.17	1.00	0.05	0.51	-2.13	-0.65
Covariances								
e1↔e2	0.98	0.00	0.01	1.01	-1.64	2.94	0.92	1.00
e3↔e5	0.96	0.00	0.01	1.01	-1.05	0.91	0.91	0.99
e1↔e3	0.41	0.02	0.11	1.01	-0.39	-0.32	0.08	0.69
e1↔e4	0.45	0.01	0.06	1.01	-0.55	-0.10	0.25	0.64
e1↔e5	0.23	0.03	0.15	1.02	-1.11	0.97	-0.21	0.57
e2↔e3	0.41	0.02	0.10	1.01	0.16	-0.26	0.05	0.74
e3↔e4	0.32	0.00	0.04	1.01	0.09	-0.17	0.15	0.47
e4↔e5	0.18	0.01	0.04	1.01	-0.03	0.06	0.05	0.38
e2↔e4	0.43	0.01	0.06	1.01	-0.13	0.02	0.21	0.62
e2↔e5	0.24	0.02	0.13	1.02	-0.50	0.10	-0.13	0.60
Variances								
Frailty	0.66	0.01	0.08	1.01	0.52	-0.08	0.43	1.00
e4	0.47	0.00	0.05	1.00	0.45	0.10	0.33	0.69

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	Frailty	OI	IOH
OI	**0.31**		
IOH	**0.25**		
Faller	**0.47**	-0.12	0.30
MOH	0.09		
FOH	0.03		
COH	0.05		

Posterior Predictive $P = 0.50$.

S.E.: standard error; S.D.: standard deviation; C.S.: convergence statistic.

SEM in figure 10.3a. SEM with the OH classifications (IOH modified) as indicators of frailty (modified Fried's classification).

Estimates:

	Mean	S.E.	S.D.	C.S.	Skewness	Kurtosis	Min.	Max.
Regression weights								
MOH←Frailty	0.13	0.01	0.07	1.00	-0.04	0.30	-0.14	0.36
OI←Frailty	0.61	0.02	0.14	1.01	0.07	-0.45	0.15	1.09
COH←Frailty	0.15	0.04	0.22	1.01	-0.02	-0.92	-0.63	0.74
FOH←Frailty	-0.01	0.03	0.17	1.01	0.01	-0.58	-0.59	0.55
Faller←Frailty	0.67	0.01	0.15	1.00	0.07	0.34	0.16	1.32
mIOH←Frailty	0.00	0.01	0.12	1.01	0.14	0.43	-0.46	0.43
Means								
Frailty	0.08	0.00	0.04	1.00	-0.23	-0.19	-0.07	0.22
Intercepts								
COH	1.62	0.01	0.09	1.01	0.37	1.42	1.29	2.22
FOH	1.51	0.01	0.09	1.01	0.38	0.52	1.25	1.98
mIOH	0.23	0.01	0.06	1.00	0.02	-0.18	-0.01	0.48
MOH	0.44	0.00	0.04	1.00	0.03	0.08	0.29	0.58
OI	-0.63	0.01	0.07	1.01	-0.39	-0.12	-1.00	-0.35
Faller	-1.27	0.01	0.09	1.00	-0.16	0.16	-1.66	-0.98
Covariances								
e1↔e2	0.98	0.00	0.02	1.02	-1.71	3.29	0.90	1.00
e3↔e5	0.18	0.01	0.07	1.00	0.08	0.07	-0.12	0.49
e1↔e3	0.83	0.01	0.07	1.02	-0.07	-0.30	0.61	0.98
e1↔e4	0.44	0.01	0.05	1.01	0.17	0.39	0.24	0.62
e1↔e5	0.16	0.01	0.11	1.01	0.10	-0.05	-0.17	0.62
e2↔e3	0.82	0.02	0.08	1.02	0.25	-0.72	0.60	0.98
e3↔e4	0.52	0.00	0.04	1.01	-0.24	-0.14	0.36	0.66
e4↔e5	0.17	0.00	0.05	1.00	-0.16	0.27	0.00	0.37
e2↔e4	0.42	0.01	0.05	1.01	-0.02	0.37	0.20	0.64
e2↔e5	0.16	0.02	0.12	1.01	-0.10	-0.15	-0.19	0.55
Variances								
Frailty	0.39	0.00	0.04	1.00	0.61	0.90	0.24	0.65
e4	0.47	0.01	0.05	1.01	0.01	-0.60	0.31	0.65

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	Frailty
Faller	**0.38**
OI	**0.35**
MOH	0.11
mIOH	0.00
FOH	0.00
COH	0.09

Posterior Predictive $P = 0.48$.

S.E.: standard error; S.D.: standard deviation; C.S.: convergence statistic.

SEM in figure 10.3b. SEM with the OH classifications (IOH modified) as indicators of frailty (modified Fried's classification). The significant indicators were postulated as independent risk factor for falls.

Estimates:

	Mean	S.E.	S.D.	C.S.	Skewness	Kurtosis	Min.	Max.
Regression weights								
MOH←Frailty	0.12	0.01	0.07	1.00	-0.13	0.32	-0.13	0.37
OI←Frailty	0.58	0.01	0.13	1.00	0.06	-0.06	0.16	1.14
COH<--Frailty	0.11	0.02	0.17	1.01	0.36	0.29	-0.43	0.89
FOH←Frailty	-0.03	0.03	0.18	1.01	-0.36	0.31	-0.69	0.53
Faller←Frailty	0.57	0.02	0.17	1.01	-0.03	0.07	-0.07	1.11
mIOH←Frailty	-0.04	0.01	0.11	1.00	0.06	-0.02	-0.50	0.42
Faller←OI	0.21	0.01	0.11	1.00	0.14	0.09	-0.22	0.65
Means								
Frailty	0.08	0.00	0.03	1.00	0.01	0.08	-0.06	0.22
Intercepts								
COH	1.61	0.02	0.10	1.01	-0.05	-0.13	1.27	1.93
FOH	1.52	0.01	0.09	1.01	0.03	0.10	1.19	1.84
mIOH	0.23	0.01	0.06	1.00	-0.16	-0.17	0.00	0.45
MOH	0.44	0.00	0.04	1.00	-0.12	-0.27	0.28	0.57
OI	-0.64	0.01	0.07	1.00	-0.07	-0.32	-0.92	-0.41
Faller	-1.18	0.01	0.10	1.00	0.09	-0.17	-1.51	-0.82
Covariances								
e1↔e2	0.98	0.00	0.01	1.02	-0.92	-0.06	0.94	1.00
e3↔e5	0.19	0.01	0.08	1.01	-0.25	0.15	-0.07	0.51
e1↔e3	0.83	0.01	0.07	1.02	-0.82	0.56	0.56	0.97
e1↔e4	0.44	0.01	0.06	1.01	-0.07	-0.09	0.21	0.62
e1↔e5	0.19	0.02	0.14	1.02	-0.46	0.03	-0.19	0.59
e2↔e3	0.83	0.01	0.06	1.01	-0.51	-0.02	0.61	0.95
e3↔e4	0.52	0.00	0.04	1.00	0.15	-0.10	0.39	0.68
e4↔e5	0.18	0.00	0.05	1.00	-0.08	0.04	-0.02	0.32
e2↔e4	0.42	0.01	0.06	1.01	-0.24	0.20	0.19	0.57
e2↔e5	0.20	0.02	0.14	1.02	-0.53	-0.01	-0.19	0.59
Variances								
Frailty	0.39	0.00	0.04	1.00	0.36	0.11	0.25	0.56
e4	0.47	0.01	0.05	1.01	0.41	-0.30	0.34	0.68

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Frailty	OI
OI	**0.34**	
Faller	**0.32**	*0.20*
MOH	0.11	
mIOH	-0.02	
FOH	-0.01	
COH	0.07	

Posterior Predictive $P = 0.51$.

S.E.: standard error; S.D.: standard deviation; C.S.: convergence statistic.

SEM in figure 10.4a. SEM with the OH classifications (IOH modified) as indicators of frailty (TRIL-FI).

Estimates:

	Mean	S.E.	S.D.	C.S.	Skewness	Kurtosis	Min.	Max.
Regression weights								
MOH←Frailty	0.08	0.00	0.05	1.00	0.08	-0.05	-0.12	0.27
OI←Frailty	0.44	0.01	0.10	1.01	-0.23	-0.23	0.11	0.76
COH←Frailty	0.15	0.02	0.14	1.01	0.07	-0.34	-0.33	0.66
FOH←Frailty	0.06	0.01	0.12	1.01	-0.19	0.59	-0.48	0.53
Faller←Frailty	0.74	0.01	0.14	1.01	0.00	-0.08	0.29	1.33
mIOH←Frailty	-0.05	0.01	0.09	1.01	0.04	0.12	-0.37	0.38
Means								
Frailty	0.30	0.00	0.04	1.00	-0.13	0.19	0.14	0.45
Intercepts								
COH	1.59	0.01	0.09	1.01	0.16	-0.03	1.27	1.96
FOH	1.52	0.01	0.09	1.00	0.14	0.55	1.15	1.94
mIOH	0.23	0.01	0.06	1.00	0.11	-0.17	-0.06	0.46
MOH	0.42	0.00	0.04	1.00	0.03	-0.23	0.27	0.63
OI	-0.73	0.00	0.07	1.00	0.18	0.25	-0.98	-0.39
Faller	-1.51	0.02	0.13	1.01	-0.03	-0.44	-2.02	-1.03
Covariances								
e1↔e2	0.98	0.00	0.01	1.02	-0.63	0.13	0.92	1.00
e3↔e5	0.19	0.01	0.08	1.01	0.34	-0.18	-0.08	0.49
e1↔e3	0.84	0.02	0.08	1.02	-0.88	0.43	0.54	0.97
e1↔e4	0.43	0.01	0.05	1.01	-0.24	0.39	0.21	0.60
e1↔e5	0.23	0.02	0.13	1.01	-0.28	-0.54	-0.18	0.53
e2↔e3	0.84	0.01	0.07	1.02	-0.53	-0.26	0.60	0.96
e3↔e4	0.50	0.00	0.04	1.00	0.44	0.17	0.37	0.67
e4↔e5	0.18	0.01	0.05	1.00	0.11	0.11	0.01	0.36
e2↔e4	0.41	0.01	0.05	1.01	0.23	-0.05	0.23	0.61
e2↔e5	0.25	0.02	0.13	1.02	-0.01	-0.45	-0.22	0.52
Variances								
Frailty	0.65	0.01	0.07	1.00	0.68	1.45	0.40	1.01
e4	0.46	0.00	0.05	1.00	0.59	0.31	0.33	0.66

Standardised regression coefficients (the ones that were significant by the ML method are in bold):

	Frailty
Faller	**0.51**
OI	**0.33**
MOH	0.09
mIOH	-0.04
FOH	0.05
COH	0.12

Posterior Predictive $P = 0.48$.

S.E.: standard error; S.D.: standard deviation; C.S.: convergence statistic.

SEM in figure 10.4b. SEM with the OH classifications (IOH modified) as indicators of frailty (TRIL-FI). The significant indicators were postulated as independent risk factor for falls.

Estimates:

	Mean	S.E.	S.D.	C.S.	Skewness	Kurtosis	Min.	Max.
Regression weights								
MOH←Frailty	0.09	0.01	0.05	1.01	0.20	-0.18	-0.08	0.27
OI←Frailty	0.40	0.01	0.10	1.01	0.24	-0.26	0.05	0.80
COH<--Frailty	0.11	0.02	0.14	1.01	0.22	0.34	-0.33	0.62
FOH←Frailty	0.05	0.02	0.13	1.01	0.05	-0.12	-0.34	0.42
Faller←Frailty	0.71	0.01	0.13	1.01	-0.05	-0.10	0.13	1.15
mIOH←Frailty	-0.04	0.01	0.08	1.00	-0.19	0.08	-0.38	0.27
Faller←OI	0.18	0.01	0.11	1.01	0.32	-0.27	-0.16	0.53
Means								
Frailty	0.31	0.00	0.04	1.00	0.00	-0.05	0.17	0.49
Intercepts								
COH	1.60	0.01	0.09	1.01	0.06	0.19	1.26	1.94
FOH	1.52	0.01	0.09	1.01	0.19	0.25	1.16	1.82
mIOH	0.24	0.01	0.07	1.00	-0.15	0.15	-0.01	0.53
MOH	0.42	0.00	0.04	1.00	-0.04	-0.11	0.28	0.58
OI	-0.72	0.01	0.08	1.00	0.06	-0.07	-1.04	-0.44
Faller	-1.46	0.01	0.13	1.01	0.03	0.08	-1.90	-0.90
Covariances								
e1↔e2	0.98	0.00	0.01	1.02	-1.13	1.10	0.94	1.00
e3↔e5	0.19	0.01	0.08	1.01	0.00	-0.23	-0.07	0.42
e1↔e3	0.86	0.02	0.09	1.02	-1.03	1.17	0.53	0.98
e1↔e4	0.47	0.01	0.05	1.01	-0.13	-0.15	0.26	0.65
e1↔e5	0.19	0.02	0.10	1.01	-0.02	0.27	-0.29	0.52
e2↔e3	0.86	0.01	0.07	1.02	-0.68	0.10	0.62	0.98
e3↔e4	0.51	0.01	0.04	1.01	0.00	-0.36	0.38	0.67
e4↔e5	0.17	0.00	0.05	1.00	0.14	0.43	0.00	0.36
e2↔e4	0.44	0.01	0.04	1.01	-0.09	-0.30	0.29	0.60
e2↔e5	0.21	0.01	0.10	1.01	-0.14	-0.23	-0.14	0.53
Variances								
Frailty	0.65	0.00	0.08	1.00	0.08	-0.21	0.41	0.94
e4	0.47	0.01	0.05	1.01	0.37	0.24	0.32	0.76

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Frailty	OI
OI	**0.30**	
Faller	**0.47**	*0.16*
MOH	0.10	
mIOH	-0.03	
FOH	0.04	
COH	0.09	

Posterior Predictive $P = 0.50$.

S.E.: standard error; S.D.: standard deviation; C.S.: convergence statistic.

SEM in figure 10.6a. SEM with medication burden being postulated as a confounder of the association between frailty (modified Fried's classification) and orthostatic intolerance (OI).

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
OI←Polypharmacy	0.11	0.00	1.00	-0.20	0.40	-0.05	-0.10	-0.40	0.66
Faller←OI	0.22	0.01	1.00	0.01	0.43	0.15	0.20	-0.19	0.69
OI←Psychotropes	0.12	0.01	1.00	-0.43	0.66	-0.03	-0.08	-0.92	1.06
Faller←Anti-hypertensives	0.05	0.01	1.00	-0.34	0.43	-0.05	-0.10	-0.66	0.82
OI←Anti-hypertensives	0.05	0.00	1.00	-0.28	0.38	0.04	-0.04	-0.61	0.73
OI←Frailty	0.46	0.00	1.00	0.25	0.67	0.05	0.08	0.07	0.88
Faller←Frailty	0.43	0.00	1.00	0.15	0.69	-0.02	-0.02	-0.11	0.90
Faller←Polypharmacy	0.19	0.01	1.00	-0.19	0.55	-0.07	0.07	-0.59	0.96
Faller←Psychotropes	0.01	0.01	1.00	-0.64	0.64	-0.10	-0.04	-1.14	1.08
Means									
Polypharmacy	0.41	0.00	1.00	0.37	0.46	-0.04	-0.07	0.32	0.49
Antihypertensives	0.25	0.00	1.00	0.20	0.29	-0.08	0.09	0.16	0.33
Psychotropes	0.05	0.00	1.00	0.03	0.08	-0.02	0.00	0.01	0.09
Frailty	0.62	0.00	1.00	0.57	0.68	-0.03	0.10	0.50	0.76
Intercepts									
OI	-0.94	0.00	1.00	-1.14	-0.73	0.02	-0.10	-1.37	-0.54
Faller	-1.46	0.01	1.00	-1.77	-1.16	-0.07	0.06	-2.16	-0.89
Covariances									
Polypharmacy↔Anti-hypertensives	0.10	0.00	1.00	0.08	0.13	0.23	0.08	0.06	0.15
Polypharmacy↔Frailty	0.05	0.00	1.00	0.03	0.08	0.07	0.01	0.00	0.11
Frailty↔Psychotropes	0.03	0.00	1.00	0.01	0.04	0.07	0.04	0.00	0.05
Antihypertensives ↔Frailty	0.03	0.00	1.00	0.00	0.05	0.03	0.03	-0.03	0.08
Polypharmacy ↔Psychotropes	0.02	0.00	1.00	0.01	0.03	0.03	0.03	0.00	0.04
Variances									
Polypharmacy	0.25	0.00	1.00	0.22	0.28	0.31	0.26	0.19	0.33
Antihypertensives	0.19	0.00	1.00	0.17	0.22	0.22	0.06	0.15	0.24
Frailty	0.38	0.00	1.00	0.34	0.44	0.35	0.39	0.29	0.53
Psychotropes	0.05	0.00	1.00	0.05	0.06	0.29	0.00	0.04	0.07

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Psychotropes	Frailty	Antihypertensives	Polypharmacy	OI
OI	0.03	**0.27**	0.02	0.05	
Faller	0.00	**0.24**	0.02	0.08	*0.21*

Posterior Predictive $P = 0.52$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 10.6b. SEM with medication burden being postulated as a confounder of the association between frailty (TRIL-FI) and orthostatic intolerance (OI).

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
OI←Polypharmacy	-0.04	0.00	1.00	-0.36	0.27	0.03	-0.02	-0.64	0.56
Faller←OI	0.21	0.01	1.00	0.01	0.43	0.18	0.45	-0.17	0.73
OI←Psychotropes	0.02	0.01	1.00	-0.55	0.60	0.07	-0.11	-1.00	1.12
Faller←Anti-hypertensives	-0.26	0.01	1.00	-0.65	0.14	0.02	0.29	-1.04	0.56
OI←Anti-hypertensives	-0.13	0.01	1.00	-0.46	0.20	-0.02	-0.08	-0.74	0.57
OI←Frailty	0.45	0.00	1.00	0.23	0.67	-0.04	0.16	0.01	0.87
Faller←Frailty	0.77	0.01	1.00	0.48	1.07	0.02	-0.04	0.25	1.34
Faller←Polypharmacy	-0.12	0.01	1.00	-0.50	0.26	-0.08	0.15	-0.92	0.55
Faller←Psychotropes	-0.26	0.01	1.00	-0.89	0.37	0.01	0.11	-1.46	0.95
Means									
Polypharmacy	0.41	0.00	1.00	0.37	0.46	-0.01	-0.06	0.32	0.50
Antihypertensives	0.25	0.00	1.00	0.21	0.29	-0.03	0.08	0.16	0.33
Psychotropes	0.05	0.00	1.00	0.03	0.08	0.01	-0.08	0.01	0.10
Frailty	1.84	0.00	1.00	1.78	1.91	-0.04	0.04	1.71	1.96
Intercepts									
OI	-1.37	0.01	1.00	-1.76	-0.98	0.01	0.17	-2.15	-0.66
Faller	-2.48	0.02	1.00	-3.08	-1.93	-0.09	0.07	-3.58	-1.32
Covariances									
Polypharmacy↔Anti-hypertensives	0.10	0.00	1.00	0.08	0.13	0.26	0.31	0.06	0.15
Polypharmacy↔Frailty	0.19	0.00	1.00	0.16	0.23	0.25	0.11	0.12	0.26
Frailty↔Psychotropes	0.05	0.00	1.00	0.03	0.06	0.21	0.20	0.02	0.08
Antihypertensives ↔Frailty	0.14	0.00	1.00	0.11	0.18	0.17	0.09	0.08	0.21
Polypharmacy ↔Psychotropes	0.02	0.00	1.00	0.02	0.03	0.18	0.09	0.01	0.04
Variances									
Polypharmacy	0.25	0.00	1.00	0.22	0.28	0.32	0.20	0.20	0.32
Antihypertensives	0.19	0.00	1.00	0.17	0.22	0.24	0.26	0.15	0.25
Frailty	0.53	0.00	1.00	0.47	0.60	0.28	0.09	0.41	0.67
Psychotropes	0.05	0.00	1.00	0.05	0.06	0.33	0.14	0.04	0.07

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Psychotropes	Frailty	Antihypertensives	Polypharmacy	OI
OI	0.00	**0.31**	-0.05	-0.02	
Faller	-0.05	**0.48**	-0.10	-0.05	*0.19*

Posterior Predictive $P = 0.53$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 10.8a. Postulating interplays between frailty (modified Fried's definition), orthostatic hemodynamics, orthostatic intolerance and falls.

Estimates:

	Mean	S.E.	C.S.	95% Lower	95% Upper	Skewness	Kurtosis	Min.	Max.
Regression weights									
Faller←IOH-SBP	-0.42	0.02	1.00	-1.23	0.40	0.01	-0.09	-1.99	1.28
MOH3←Delta HR	-0.01	0.00	1.00	-0.04	0.00	-0.24	0.15	-0.06	0.03
OI←MOH3	0.28	0.01	1.00	0.03	0.56	0.16	0.10	-0.20	0.84
OI←Delta HR	0.02	0.00	1.00	0.00	0.04	0.21	0.00	-0.01	0.06
OI←IOH-SBP	-0.28	0.02	1.00	-0.99	0.38	-0.10	0.02	-1.67	0.93
MOH3←IOH-SBP	2.44	0.01	1.00	2.02	2.93	0.27	0.16	1.59	3.38
Faller←OI	0.19	0.00	1.00	-0.03	0.42	0.10	-0.03	-0.24	0.65
Baseline SBP←Frailty	2.43	0.02	1.00	-1.23	6.06	0.01	-0.04	-5.14	9.99
Faller←Frailty	0.46	0.00	1.00	0.19	0.74	0.03	-0.01	-0.07	1.01
IOH-SBP←Frailty	0.02	0.00	1.00	-0.05	0.10	0.02	0.04	-0.14	0.18
MOH3←Frailty	0.10	0.01	1.00	-0.18	0.39	0.02	-0.09	-0.44	0.76
Delta HR←Frailty	-1.19	0.01	1.00	-2.48	0.12	0.02	0.03	-3.83	1.56
OI←Frailty	0.50	0.00	1.00	0.28	0.72	0.03	-0.02	0.08	0.98
Delta HR←Baseline HR	-0.09	0.00	1.00	-0.17	-0.02	-0.01	0.04	-0.25	0.06
Delta HR←IOH-SBP	-0.25	0.01	1.00	-1.97	1.46	-0.02	0.07	-3.80	3.14
Faller←MOH3	0.14	0.01	1.00	-0.17	0.46	0.07	-0.03	-0.41	0.71
Baseline HR←Frailty	1.87	0.01	1.00	0.25	3.49	0.00	-0.01	-1.60	5.39
IOH-SBP←Baseline SBP	0.00	0.00	1.00	0.00	0.00	0.06	0.02	0.00	0.01
Delta HR←Baseline SBP	-0.05	0.00	1.00	-0.08	-0.01	-0.03	0.07	-0.12	0.03
MOH3← Baseline SBP	0.00	0.00	1.00	0.00	0.01	0.05	0.08	-0.01	0.02
Means									
Frailty	0.62	0.00	1.00	0.56	0.68	-0.01	0.06	0.49	0.74
Intercepts									
Baseline SBP	158.86	0.02	1.00	155.68	162.07	0.02	0.00	152.24	166.60
IOH-SBP	-0.17	0.00	1.00	-0.47	0.12	-0.05	0.01	-0.81	0.40
MOH3	-2.69	0.03	1.00	-4.04	-1.40	-0.09	-0.03	-5.60	-0.18
Delta HR	29.37	0.06	1.00	21.77	37.10	0.05	0.01	13.69	45.83
OI	-0.71	0.01	1.00	-1.30	-0.11	0.02	-0.02	-2.01	0.46
Faller	-1.07	0.02	1.00	-1.77	-0.40	-0.09	-0.10	-2.30	0.12
Baseline HR	67.47	0.01	1.00	66.08	68.87	0.00	0.04	64.41	70.35

Variances									
Frailty	0.38	0.00	1.00	0.33	0.43	0.28	0.14	0.29	0.49
e6	598.83	0.59	1.00	525.39	684.56	0.32	0.34	431.17	795.42
e1	0.22	0.00	1.00	0.19	0.25	0.27	0.21	0.17	0.30
e7	111.57	0.10	1.00	97.62	127.39	0.30	0.26	86.59	152.11
e3	73.31	0.09	1.00	64.06	83.88	0.29	0.23	56.07	96.87

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Frailty	Baseline SBP	Baseline HR	IOH-SBP	Delta HR	MOH3	OI
Baseline SBP	0.06						
Baseline HR	*0.11*						
IOH-SBP	0.03	**0.16**					
Delta HR	-0.08	**-0.13**	*-0.11*	-0.01			
MOH3	0.04	0.05		**0.74**	-0.08		
OI	**0.27**			-0.12	*0.15*	*0.39*	
Faller	**0.25**			-0.18	0.00	0.19	*0.19*

Posterior Predictive $P = 0.40$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 10.8b. Postulating interplays between frailty (TRIL-FI), orthostatic hemodynamics, orthostatic intolerance and falls.

Estimates:

	Mean	S.E.	C.S.	95% Lower	95% Upper	Skewness	Kurtosis	Min.	Max.
Regression weights									
Faller←IOH-SBP	-0.10	0.03	1.00	-0.98	0.85	0.13	-0.04	-1.68	1.75
MOH3←Delta HR	-0.01	0.00	1.00	-0.03	0.01	-0.32	0.36	-0.06	0.03
OI←MOH3	0.23	0.01	1.00	-0.03	0.49	0.07	-0.10	-0.19	0.76
OI←Delta HR	0.02	0.00	1.00	0.00	0.04	0.24	0.26	-0.01	0.06
OI←IOH-SBP	-0.16	0.02	1.00	-0.86	0.54	-0.04	-0.04	-1.64	1.12
MOH3←IOH-SBP	2.57	0.01	1.00	2.13	3.07	0.22	0.05	1.80	3.64
Faller←OI	0.22	0.00	1.00	0.01	0.44	0.00	0.01	-0.20	0.61
Baseline SBP←Frailty	3.99	0.03	1.00	0.84	7.16	0.03	-0.04	-1.73	10.00
Faller←Frailty	0.63	0.01	1.00	0.34	0.91	0.07	0.27	-0.03	1.26
IOH-SBP←Frailty	-0.01	0.00	1.00	-0.08	0.05	0.00	0.03	-0.13	0.11
MOH3←Frailty	0.36	0.01	1.00	0.10	0.63	0.03	-0.02	-0.24	0.85
Delta HR←Frailty	-1.75	0.01	1.00	-2.86	-0.62	0.02	0.05	-4.48	0.43
OI←Frailty	0.38	0.00	1.00	0.17	0.60	0.01	-0.02	-0.06	0.80
Delta HR←Baseline HR	-0.10	0.00	1.00	-0.17	-0.02	0.00	0.05	-0.24	0.05
Delta HR←IOH-SBP	-0.34	0.01	1.00	-2.01	1.36	0.01	-0.01	-3.75	3.05
Faller←MOH3	0.02	0.01	1.00	-0.32	0.35	-0.05	-0.15	-0.56	0.59
Baseline HR←Frailty	0.68	0.01	1.00	-0.70	2.07	0.00	0.03	-2.47	3.43
IOH-SBP←Baseline SBP	0.00	0.00	1.00	0.00	0.01	0.05	0.05	0.00	0.01
Delta HR←Baseline SBP	-0.04	0.00	1.00	-0.08	-0.01	-0.03	-0.01	-0.10	0.03
MOH3← Baseline SBP	0.00	0.00	1.00	-0.01	0.01	0.03	0.02	-0.01	0.02
Means									
Frailty	1.84	0.00	1.00	1.77	1.91	0.00	0.03	1.70	1.99
Intercepts									
Baseline SBP	153.06	0.05	1.00	146.72	159.37	-0.04	-0.07	139.28	164.30
IOH-SBP	-0.14	0.00	1.00	-0.45	0.15	-0.07	0.05	-0.79	0.49
MOH3	-3.20	0.03	1.00	-4.61	-1.86	-0.12	-0.02	-5.80	-0.92
Delta HR	31.27	0.08	1.00	23.78	38.85	0.01	0.01	16.72	47.90
OI	-1.22	0.02	1.00	-2.09	-0.38	-0.07	-0.03	-2.98	0.45
Faller	-2.28	0.03	1.00	-3.48	-1.19	-0.21	-0.04	-4.22	-0.14
Baseline HR	67.39	0.02	1.00	64.59	70.14	0.00	0.04	61.76	74.30

Variances									
Frailty	0.53	0.00	1.00	0.46	0.60	0.22	0.03	0.39	0.70
e6	590.90	0.76	1.00	519.05	673.61	0.24	0.01	456.38	763.27
e1	0.22	0.00	1.00	0.20	0.26	0.25	0.11	0.17	0.29
e7	112.69	0.18	1.00	98.68	128.94	0.28	0.12	86.15	147.43
e3	72.00	0.08	1.00	63.10	82.45	0.32	0.18	55.38	94.76

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Frailty	Baseline SBP	Baseline HR	IOH-SBP	Delta HR	MOH3	OI
Baseline SBP	*0.12*						
Baseline HR	0.05						
IOH-SBP	-0.02	**0.16**					
Delta HR	**-0.15**	*-0.12*	*-0.12*	-0.02			
MOH3	**0.16**	0.03		**0.75**	-0.05		
OI	**0.25**			-0.06	*0.16*	*0.33*	
Faller	**0.38**			-0.04	0.00	0.02	*0.21*

Posterior Predictive $P = 0.38$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 10.9a. Postulating interplays between frailty (modified Fried's definition), orthostatic hemodynamics, orthostatic intolerance and falls, in the presence of polypharmacy.

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
Faller←IOHSBP	-0.46	0.03	1.00	-1.30	0.42	0.08	0.11	-2.28	1.27
MOH3←Delta HR	-0.01	0.00	1.00	-0.04	0.01	-0.32	0.17	-0.07	0.02
OI←MOH3	0.26	0.01	1.00	0.00	0.56	0.15	-0.07	-0.23	0.78
OI←Delta HR	0.02	0.00	1.00	0.00	0.04	0.25	0.11	-0.02	0.06
OI←IOH-SBP	-0.27	0.02	1.00	-1.02	0.44	-0.06	-0.02	-1.61	1.15
Faller←OI	0.18	0.01	1.00	-0.04	0.40	0.01	-0.02	-0.24	0.62
Faller←Frailty	0.44	0.00	1.00	0.16	0.74	0.12	0.17	-0.18	1.05
IOH-SBP←Frailty	0.03	0.00	1.00	-0.05	0.10	-0.03	-0.01	-0.13	0.19
MOH3←Frailty	-0.02	0.01	1.00	-0.33	0.30	0.14	0.34	-0.72	0.83
Delta HR←Frailty	-0.99	0.01	1.00	-2.39	0.37	-0.03	0.04	-3.85	1.49
OI←Frailty	0.50	0.00	1.00	0.27	0.74	0.05	-0.06	-0.01	0.96
Delta HR←Baseline HR	-0.10	0.00	1.00	-0.18	-0.03	-0.05	-0.08	-0.25	0.08
Delta HR←IOH-SBP	-0.29	0.02	1.00	-2.03	1.44	-0.01	0.00	-3.73	3.21
Faller←MOH3	0.15	0.01	1.00	-0.17	0.46	-0.09	0.12	-0.55	0.79
Baseline HR←Frailty	2.49	0.02	1.00	0.79	4.20	0.02	0.01	-0.93	6.35
Polypharmacy ←Frailty	0.37	0.00	1.00	0.17	0.57	0.04	-0.04	-0.02	0.85
IOHSBP ←Baseline SBP	0.00	0.00	1.00	0.00	0.00	-0.04	0.05	0.00	0.01
IOH-SBP ←Polypharmacy	-0.01	0.00	1.00	-0.07	0.05	-0.02	0.04	-0.13	0.13
Baseline HR ←Polypharmacy	-1.66	0.01	1.00	-2.93	-0.39	-0.04	0.06	-4.55	0.86
Baseline SBP ←Polypharmacy	1.49	0.03	1.00	-1.44	4.44	-0.04	0.06	-4.44	7.58
Baseline SBP←Frailty	1.86	0.04	1.00	-2.06	5.68	-0.04	0.01	-7.56	9.25
Delta HR← Baseline SBP	-0.05	0.00	1.00	-0.08	-0.01	0.02	-0.04	-0.12	0.02
MOH3 ←Polypharmacy	0.28	0.01	1.00	0.01	0.55	0.05	-0.01	-0.17	0.83
Faller ←Polypharmacy	0.09	0.00	1.00	-0.15	0.32	0.03	0.04	-0.46	0.53
MOH3 ←Baseline SBP	0.00	0.00	1.00	-0.01	0.01	0.05	0.04	-0.01	0.02
OI ←Polypharmacy	0.03	0.00	1.00	-0.17	0.21	-0.15	0.08	-0.38	0.46
Delta HR ←Polypharmacy	-0.47	0.01	1.00	-1.45	0.55	0.06	-0.01	-2.51	1.97
MOH3←IOHSBP	2.55	0.02	1.00	2.09	3.08	0.22	-0.12	1.74	3.57

Means									
Frailty	0.62	0.00	1.00	0.57	0.68	0.04	-0.06	0.51	0.74
Intercepts									
Baseline SBP	159.52	0.04	1.00	156.04	163.02	0.01	0.00	152.23	166.14
IOH-SBP	-0.18	0.00	1.00	-0.47	0.12	0.04	0.05	-0.86	0.53
MOH3	-2.34	0.02	1.00	-3.65	-1.03	-0.02	0.00	-4.91	0.03
Delta HR	29.56	0.06	1.00	21.93	37.24	0.03	-0.01	14.12	45.05
OI	-0.73	0.02	1.00	-1.33	-0.12	-0.04	0.12	-2.00	0.53
Faller	-1.02	0.02	1.00	-1.75	-0.38	-0.23	0.09	-2.50	0.19
Baseline HR	66.71	0.01	1.00	65.19	68.23	-0.04	-0.02	63.54	69.73
Polypharmacy	-0.45	0.00	1.00	-0.63	-0.28	0.00	-0.08	-0.79	-0.09
Variances									
Frailty	0.38	0.00	1.00	0.33	0.43	0.28	0.15	0.29	0.51
e6	596.46	0.83	1.00	522.08	682.48	0.30	0.22	453.72	795.44
e1	0.22	0.00	1.00	0.20	0.26	0.25	0.16	0.17	0.31
e7	108.95	0.16	1.00	95.25	124.83	0.28	0.07	83.64	148.32
e3	73.08	0.10	1.00	63.91	83.28	0.24	0.12	52.92	98.04

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Frailty	Poly-pharmacy	Baseline SBP	Baseline HR	IOH-SBP	Delta HR	MOH3	OI
Poly-pharmacy	**0.22**							
Baseline SBP	0.05	0.06						
Baseline HR	**0.14**	**-0.16**						
IOH-SBP	0.04	-0.02	**0.16**					
Delta HR	-0.07	-0.05	**-0.13**	*-0.12*	-0.02			
MOH3	-0.01	*0.17*	0.02		**0.75**	-0.07		
OI	**0.27**	0.03			-0.11	*0.15*	*0.37*	
Faller	**0.24**	0.08			-0.19		0.21	*0.18*

Posterior Predictive $P = 0.40$.

S.E.: standard error; C.S.: convergence statistic.

SEM in figure 10.9b. Postulating interplays between frailty (TRIL-FI), orthostatic hemodynamics, orthostatic intolerance and falls, in the presence of polypharmacy.

Estimates:

	Mean	S.E.	C.S.	95% Lower bound	95% Upper bound	Skewness	Kurtosis	Min.	Max.
Regression weights									
Faller←IOHSBP	-0.17	0.02	1.00	-1.17	0.77	-0.15	0.15	-2.30	1.71
MOH3←Delta HR	-0.01	0.00	1.00	-0.03	0.01	-0.26	0.22	-0.06	0.03
OI←MOH3	0.23	0.01	1.00	-0.04	0.51	0.09	0.50	-0.32	0.89
OI←Delta HR	0.02	0.00	1.00	0.00	0.04	0.34	0.27	-0.01	0.06
OI←IOH-SBP	-0.16	0.02	1.00	-0.90	0.58	-0.01	0.35	-1.93	1.35
Faller←OI	0.22	0.01	1.00	0.00	0.46	0.13	0.10	-0.21	0.68
Faller←Frailty	0.79	0.01	1.00	0.42	1.19	0.10	-0.07	0.08	1.57
IOH-SBP←Frailty	-0.02	0.00	1.00	-0.11	0.08	-0.01	0.06	-0.22	0.19
MOH3←Frailty	0.19	0.01	1.00	-0.24	0.64	0.03	0.25	-0.73	1.16
Delta HR←Frailty	-2.05	0.02	1.00	-3.77	-0.38	-0.07	-0.03	-5.34	1.78
OI←Frailty	0.46	0.01	1.00	0.17	0.77	0.02	0.12	-0.26	1.05
Delta HR←Baseline HR	-0.09	0.00	1.00	-0.17	-0.01	0.01	0.04	-0.27	0.07
Delta HR←IOH-SBP	-0.37	0.01	1.00	-2.08	1.34	-0.01	-0.06	-4.12	2.90
Faller←MOH3	0.04	0.01	1.00	-0.29	0.42	0.22	0.08	-0.64	0.76
Baseline HR←Frailty	3.27	0.02	1.00	1.15	5.37	-0.02	0.09	-1.46	7.18
Polypharmacy ←Frailty	1.12	0.00	1.00	0.92	1.33	0.04	0.04	0.73	1.54
IOHSBP ←Baseline SBP	0.00	0.00	1.00	0.00	0.01	0.04	0.11	0.00	0.01
IOH-SBP ←Polypharmacy	0.00	0.00	1.00	-0.06	0.07	0.01	-0.07	-0.12	0.12
Baseline HR ←Polypharmacy	-2.30	0.02	1.00	-3.68	-0.89	0.07	-0.03	-5.11	0.44
Baseline SBP ←Polypharmacy	0.35	0.03	1.00	-2.91	3.63	0.01	0.11	-5.97	6.64
Baseline SBP←Frailty	3.59	0.04	1.00	-1.25	8.42	-0.02	-0.02	-6.40	13.23
Delta HR← Baseline SBP	-0.04	0.00	1.00	-0.08	-0.01	0.01	0.10	-0.11	0.03
MOH3 ←Polypharmacy	0.14	0.01	1.00	-0.15	0.44	0.09	0.28	-0.43	0.85
Faller ←Polypharmacy	-0.15	0.01	1.00	-0.40	0.09	-0.07	-0.10	-0.61	0.35
MOH3 ←Baseline SBP	0.00	0.00	1.00	-0.01	0.01	0.04	-0.07	-0.01	0.02
OI ←Polypharmacy	-0.07	0.00	1.00	-0.28	0.12	-0.14	0.27	-0.56	0.33
Delta HR ←Polypharmacy	0.25	0.01	1.00	-0.89	1.43	0.10	0.09	-2.14	2.88
MOH3←IOHSBP	2.57	0.01	1.00	2.13	3.07	0.25	0.20	1.67	3.61

Means									
Frailty	1.84	0.00	1.00	1.78	1.91	-0.02	0.06	1.68	1.99
Intercepts									
Baseline SBP	153.87	0.09	1.00	144.08	163.67	0.03	-0.01	134.19	173.26
IOH-SBP	-0.14	0.00	1.00	-0.48	0.20	-0.02	0.11	-0.87	0.67
MOH3	-2.79	0.04	1.00	-4.54	-1.17	-0.13	0.09	-6.12	0.51
Delta HR	31.51	0.07	1.00	23.72	39.16	-0.01	0.02	14.22	47.63
OI	-1.41	0.02	1.00	-2.34	-0.47	-0.04	0.34	-3.53	0.50
Faller	-2.58	0.03	1.00	-3.86	-1.35	-0.14	0.12	-5.19	-0.26
Baseline HR	61.98	0.04	1.00	57.70	66.25	0.03	0.06	54.34	72.00
Polypharmacy	-2.34	0.00	1.00	-2.76	-1.93	-0.05	0.04	-3.14	-1.56
Variances									
Frailty	0.53	0.00	1.00	0.46	0.60	0.26	0.00	0.40	0.68
e6	591.49	0.57	1.00	518.84	675.84	0.28	0.05	455.68	759.54
e1	0.22	0.00	1.00	0.19	0.25	0.28	0.13	0.17	0.29
e7	107.45	0.11	1.00	93.41	123.09	0.23	0.13	78.46	142.16
e3	72.02	0.08	1.00	62.91	82.23	0.26	0.20	55.71	100.81

Standardised regression coefficients (the ones that were significant by the ML method are in bold; the ones that tended towards significance are in italics):

	Frailty	Poly-pharmacy	Baseline SBP	Baseline HR	IOH-SBP	Delta HR	MOH3	OI
Poly-pharmacy	**0.63**							
Baseline SBP	0.11	0.02						
Baseline HR	**0.22**	**-0.28**						
IOH-SBP	-0.03	0.01	**0.16**					
Delta HR	-0.17	0.04	**-0.12**	*-0.11*	-0.02			
MOH3	0.08	*0.11*	0.02		**0.75**	-0.06		
OI	**0.30**	-0.08			-0.07	*0.17*	*0.33*	
Faller	**0.48**	-0.16			-0.06		0.06	*0.20*

Posterior Predictive $P = 0.41$.

S.E.: standard error; C.S.: convergence statistic.

Appendix 7 References:

1. Grace J. SEM Tutorials. 2010 [updated 2010; cited December 29]; Available from: http://www.structuralequations.com/3.html.

2. Arbuckle JL. Amos™ 16.0 User's Guide. Available online: http://www.amosdevelopment.com/download/Amos%2016.0%20User's%20Guide.pdf. Ambler, Pennsylvania: AMOS Development Corporation & SPSS, Inc.; 2007.