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RESEARCH PAPER

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

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Abstract

Background: Orthostatic hypotension (OH) can be assessed with non-invasive continuous beat-to-beat haemodynamic monitoring during active stand (AS) testing; this yields large volumes of data outside the scope of the traditional OH definition. We explored clinical associations of different AS patterns in participants from Wave 1 of the Irish Longitudinal Study on Ageing.
Methods: AS patterns were generated based on three sequential binary systolic blood pressure features: drop ≥40 mmHg within 10 sec post-stand ("immediate deficit"), failure to return to within 20 mmHg of supine level at 40 sec after standing ("stabilisation deficit") and drop ≥20 mmHg between >40 and 120 sec post-stand ("late deficit"). Eight AS groups resulted from combining the presence/absence of these three features. The groups were cross-sectionally characterised, and their ability to independently predict orthostatic intolerance (OI) during AS, and falls or syncope in the past year, was evaluated using multivariate logistic regression models.
Results: A total of 4,899 participants were included (mean age 61), of which 3,312 (68%) had no deficits. Older age was associated with stabilisation deficit and late deficits were seen in groups with higher proportions of beta blockers and psychotropic medications. Regression models identified independent associations between OI and three immediate-deficit groups; associations seemed stronger as more deficits were present. There was a significant association between falls history and the three-deficit group (odds ratio 1.54, 95% confidence interval: 1.15–2.07, $P = 0.004$).
Conclusions: More deficits seemed associated with the higher risk of OI and falls history. Observations are not causal but the recognition of these patterns may help clinicians focus on careful prescribing.

Keywords: physiologic monitoring, active stand, orthostatic hypotension, orthostatic intolerance, falls, older people

Key Points

- Immediate, stabilisation and late BP deficits can be seen during the continuous orthostatic AS test.
- We characterised eight AS groups resulting from simultaneous consideration of those three deficits.
- Late deficits were seen with higher proportions of beta blockers and psychotropic medications.
- More deficits seemed associated with the higher risk of OI and the history of falls.
- The recognition of continuous AS patterns may help clinicians focus on careful prescribing.

Introduction

Orthostatic hypotension (OH) increases with age [1] and is associated with falls [2], cognitive decline [3] and mortality [4]. OH is traditionally defined as a reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (BP) of at least 10 mmHg within 3 min of standing [5]. This definition is based on intermittent BP measurements via sphygmomanometer during a 3-min assessment.

Non-invasive continuous beat-to-beat hemodynamic monitoring during active stand (AS) testing provides a more detailed picture of a person's early orthostatic BP behaviour [6] and generates data that are outside the scope of the traditional OH definition [7], requiring overall clinical interpretation.

Continuous orthostatic BP monitoring is not commonplace in most clinics, but research efforts have aimed at identifying single features of the continuous AS pattern that may be associated with increased clinical risk. Thus, there has been interest in the immediate BP drop (which takes place within the first 10–15 sec post-stand and is not captured by the traditional sphygmomanometer assessment) [8,9], and the early (i.e. within 30–40 sec) BP recovery phase [10,11], which is often missed by the traditional method. By 2–3 min post-stand, the ability of the sphygmomanometer method to detect a given BP drop is comparable to that of the AS method [12].

Continuous hemodynamic patterns following AS are morphologically heterogeneous [13,14], and the recognition of key AS features could help guide clinical risk assessment and treatments. The accumulation of health deficits is associated with worse health outcomes [15], and we hypothesised that this principle may also apply to the accumulation of adverse BP features during the AS. To test that hypothesis, we modelled AS patterns according to the presence/absence of immediate, early and late BP deficits, and explored their clinical associations in participants from Wave 1 of the Irish Longitudinal Study on Ageing (TILDA). An additional aim was to gain clinical insights into the potential pathophysiology of different continuous BP patterns.

Methods

Sample

An analysis was conducted on data from the health assessment of TILDA Wave 1 (June 2009–June 2011). Full details of the study design, sampling and methodology have been described elsewhere [16,17]. Participants who were unwilling/unable to provide informed consent or had inadequate AS data were not included.

AS protocol

Participants underwent an AS test with the Finometer MIDI device (Finapres Medical Systems BV, Amsterdam, The Netherlands), performed by trained research nurses and recorded at 200 Hz. Participants underwent the AS following approximately 10 min of supine rest. Baseline BP was calculated as the mean value between 60 and 30 sec before stand. Data were downsampled to 1 Hz. Two smoothing filters were applied, a 10-point moving average filter and an 11-point median filter. Onset of the stand was detected via an algorithm using data from the Finometer height correction unit [18]. Here we utilised BP response data up to 120 sec post-stand, at 10-sec intervals.

AS features and groupings

The decision to focus on SBP features was based on a study by Fedorowski *et al.* [19], which found that approximately 95% of patients with classical OH can be identified by SBP changes alone. Eight mutually exclusive AS patterns were manually extracted based on three sequential binary SBP deficits previously utilised by our research group: SBP drop $\geq$40 mmHg within 10 sec post-stand ("immediate drop": yes or no [20]), failure to return to within 20 mmHg of supine level at 40 sec after standing ("stabilisation failure": yes or no [11]), and drop $\geq$20 mmHg at any time between $>$40 and 120 sec post-stand ("late deficit": yes or no [21]) (Figure 1).

Clinical characterisation variables

The following variables were used to characterise the eight AS patterns: age (years), sex, a binary Fried's frailty phenotype category (non-frail vs. pre-frail/frail) [22], time taken to stand during the AS [18], cognition as per mini-mental state examination (MMSE) score, multimorbidity (the history of two or more self-reported diseases among the following: myocardial infarction, heart failure, angina, atrial fibrillation, hypertension, hypercholesterolemia, stroke, diabetes mellitus (DM), chronic obstructive pulmonary disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease and hip fracture). We also characterised the groups according to the usage of antihypertensive and psychotropic medications. Polypharmacy was defined as concomitant use of five or more regular medications.

Although there are many clinical variants of orthostatic intolerance (OI) [23], our study defined it as present if participants self-reported dizziness, light-headedness or unsteadiness during the AS. Participants were also asked about the history of falls in the past 12 months (yes or no), and blackouts in the past 12 months (i.e. recent syncope: yes or no).

Statistical analyses

Statistical analyses were performed in Stata version 14.1 (Stata Corp., College Station, TX, USA). The graphical visualisation of the eight AS patterns was performed with IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA), using mean SBP $\pm$ 1 standard error (SE) for each group.

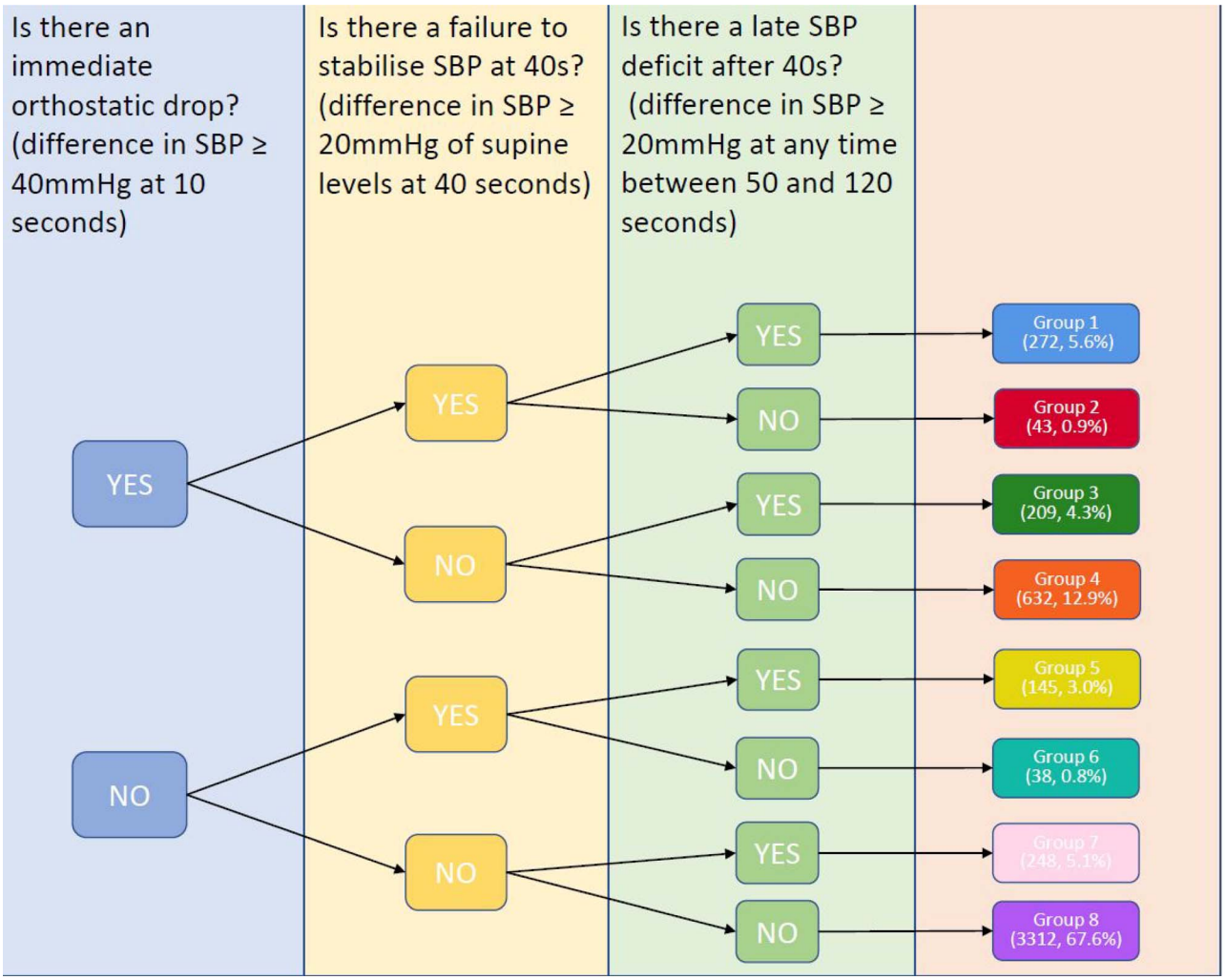

Figure 1. Hypothesised eight mutually exclusive groups based on three sequential SBP features during the AS. The column on the right shows the classification result (in brackets: number of participants in the group, percentage of the total sample).

Descriptive statistics were given as mean with standard deviation (SD), median with interquartile range (IQR) or number (*n*) with percentage (%). Overall differences between the eight AS groups (as nominal variable) were assessed using analysis of variance in the case of normally distributed continuous variables, or the Kruskal–Wallis test in the case of interval, non-normal variables; for categorical (e.g. dichotomous) variables, the Chi-squared test was used. Given the projected number of comparisons (around 30), and considering an Alpha level of 0.05, a Bonferroni's adjustment calculation recommended to lower $P < 0.05$ to $P < 0.001$ to detect statistical significance during the characterisation of the sample.

For the cross-sectional associations between the AS groups and OI, falls and syncope, three logistic regression models were fitted for each outcome:

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

In these models, the threshold for statistical significance was set at $P < 0.05$.

Ethics

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

Results

In total, 8,174 participants over the age of 50 were recruited to wave 1 of the TILDA study, of whom 5,034 attended the

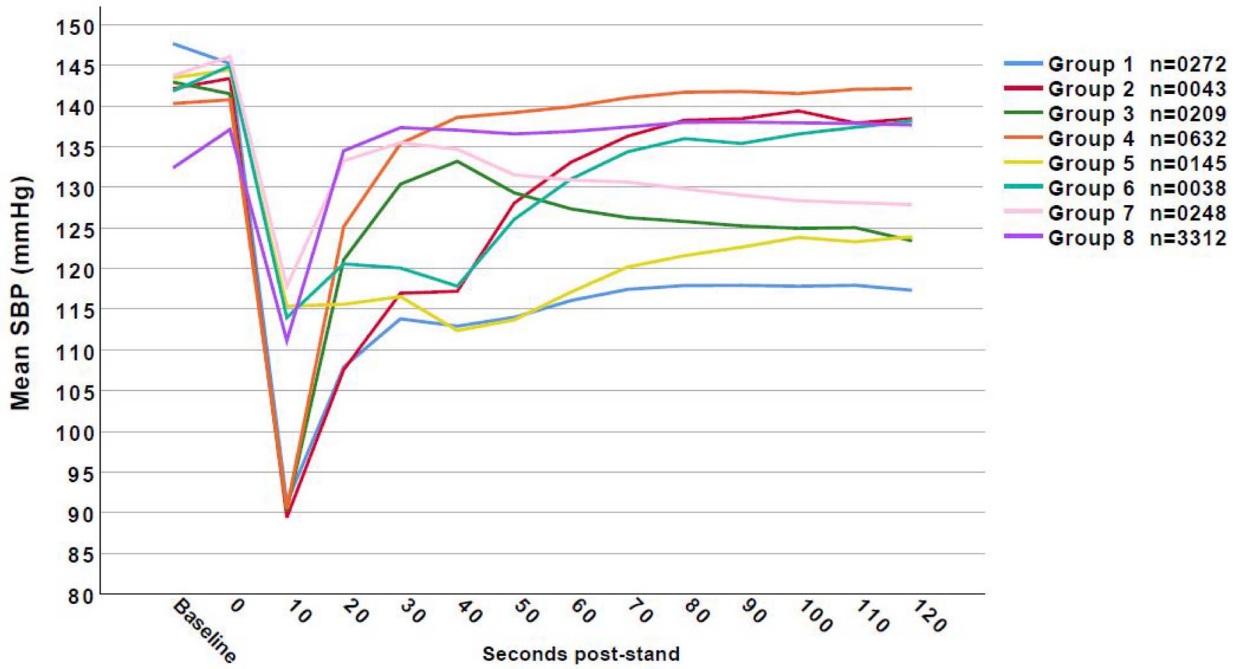

Figure 2. Graphical visualisation of the eight AS groups.

health assessment centre. There were 4,905 participants with adequate AS data for analysis, of whom 4,899 had complete data for the generation of the eight AS groups using the decision tool in Figure 1. Overall, the mean age was 61, and 55% were female.

As Figure 1 shows, the largest group was the one with no deficits (68%), followed by immediate deficit only (13%), all three deficits (6%) and late deficit only (5%). The other groups contained fewer than 5% of participants each. The graphical visualisation of the groups (mean SBP) is presented in Figure 2. An interactive version with SEs is available as Appendix 2, available in *Age and Ageing* online.

The clinical characteristics of the total sample and the eight AS groups are summarised in Table 1. Overall, OI was reported by 38% of participants; 20% had the history of falls and 5% reported recent syncope.

Participants in the largest group with no deficits had the lowest baseline SBP and were among the youngest, least frail, least comorbid and least medicated. They were also among the groups with lowest proportion of OI (Table 1).

The group with all three deficits was not among the oldest but seemed to have the highest use of beta-blockers, benzodiazepines, antidepressants, highest baseline SBP, highest proportion of falls and one of the highest proportions of OI (Table 1). Groups 2, 5 and 6 (older and with impaired stabilisation) had proportions of DM over 10%.

The results of the three logistic regression models for the prediction of OI, falls and syncope (Models C) are shown in Table 2; full information for Models A, B and C is available in Appendix 1 available in *Age and Ageing* online.

In models C (Table 2), there were statistically significant associations between OI and three groups with immediate deficit, with a seemingly incremental odds ratio (OR) according to the number of deficits: OR 1.42 [95% confidence interval (CI): 1.19–1.70, $P < 0.001$] for immediate only; OR 1.60 (95% CI: 1.20–2.13, $P = 0.001$) for immediate and late; and OR 1.83 (95% CI: 1.41–2.38, $P < 0.001$) for immediate, stabilisation and late. There was also a statistically significant association between the group with all three deficits and falls (OR 1.54, 95% CI: 1.15–2.07, $P = 0.004$).

Discussion

In this large population-based study of Irish participants aged 50+ undergoing continuous orthostatic BP measurements, we showed eight different orthostatic BP patterns based on three sequential SBP deficits. We showed that the most common patterns were characterised by no deficits or an immediate deficit only. Groups with an immediate deficit had the higher risk of OI, with a seemingly incremental OI risk as more deficits were present. The group with all three deficits was associated with recent falls. Our findings confirm and expand previous observations that hemodynamic AS patterns are heterogeneous [14], highlighting the need to take a nuanced approach to the interpretation of the AS that considers potentially different pathophysiological mechanisms and clinical associations. To our knowledge, ours is the largest study to date and may serve as a population-wide reference to help clinicians identify normal and abnormal AS responses, inform their bedside interpretation and potentially lead to more personalised medical care.

Table 1. Characterisation of the overall sample and the eight AS groups

	Overall	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	*P*
Number (%)	4,899 (100.0)	272 (5.6)	43 (0.9)	209 (4.3)	632 (12.9)	145 (3.0)	38 (0.8)	248 (5.1)	3,312 (67.6)	
Mean age in years (SD)	61.0 (8.8)	64.5 (9.3)	68.1 (10.5)	60.3 (7.7)	61.6 (8.6)	66.9 (9.2)	68.8 (9.5)	61.3 (9.2)	60.2 (8.5)	<0.001*
Female gender, *n* (%)	2,703 (55.2)	172 (63.2)	23 (53.5)	142 (67.9)	364 (57.6)	101 (69.7)	18 (47.4)	153 (61.7)	1730 (52.2)	<0.001#
Non-frail, *n* (%)	3,471 (72.6)	174 (65.4)	31 (75.6)	155 (74.9)	448 (72.4)	80 (57.6)	24 (64.9)	156 (65.3)	2,403 (74.3)	<0.001#
Pre-frail or frail, *n* (%)	1,313 (27.5)	92 (34.6)	10 (24.4)	52 (25.1)	171 (27.6)	59 (42.5)	13 (35.1)	83 (34.7)	833 (25.7)	<0.001#
Mean time to stand in seconds (SD)	7.6 (3.0)	7.9 (2.7)	8.3 (3.5)	7.3 (2.3)	7.5 (2.8)	9.7 (4.5)	9 (3.8)	8.1 (3.2)	7.5 (2.9)	<0.001*
Median MMSE (IQR)	29 (2)	29 (2)	28 (3)	29 (2)	29 (2)	29 (2)	29 (3)	29 (2)	29 (2)	<0.001*
Multimorbidity, *n* (%)	2,236 (45.6)	132 (48.5)	22 (51.2)	85 (40.7)	303 (47.9)	92 (63.5)	27 (71.1)	113 (45.6)	1,462 (44.1)	<0.001#
Atrial fibrillation, *n* (%)	109 (2.3)	7 (2.6)	2 (4.7)	2 (1.0)	16 (2.6)	3 (2.1)	4 (10.5)	3 (1.2)	72 (2.2)	0.024#
Parkinson's disease, *n* (%)	15 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.1)	0 (0.0)	3 (1.2)	7 (0.2)	<0.001#
Diabetes mellitus, *n* (%)	300 (6.1)	17 (6.3)	5 (11.6)	7 (3.4)	35 (5.5)	15 (10.3)	5 (13.2)	14 (5.7)	202 (6.1)	0.065#
Hypertension, *n* (%)	1934 (39.7)	119 (44.1)	24 (57.1)	98 (47.1)	294 (46.9)	63 (43.8)	16 (42.1)	108 (43.9)	1,212 (36.7)	0.001#
Polypharmacy, *n* (%)	830 (17.0)	68 (25.1)	13 (30.2)	25 (12.0)	98 (15.6)	46 (32.4)	9 (24.3)	55 (22.4)	516 (15.6)	<0.001#
Anti-hypertensive medications, *n* (%)										
Overall	1,553 (31.7)	99 (36.4)	16 (37.2)	60 (28.7)	211 (33.4)	67 (46.2)	19 (50.0)	77 (31.1)	1,004 (30.3)	<0.001#
Beta blockers	563 (11.5)	55 (20.3)	7 (16.3)	28 (13.5)	81 (12.9)	27 (19.0)	3 (8.1)	26 (10.6)	336 (10.2)	<0.001#
Diuretics	289 (5.9)	17 (6.3)	5 (11.6)	7 (3.4)	35 (5.0)	13 (9.2)	4 (10.8)	16 (6.5)	192 (5.8)	0.211#
Angiotensin-Converting Enzyme (ACE) inhibitors/Angiotensin receptor blockers	1,047 (21.5)	53 (19.6)	13 (30.2)	33 (15.9)	150 (23.9)	44 (31.0)	10 (27.0)	54 (22.0)	690 (20.9)	0.014#
Calcium channel blockers	402 (8.2)	23 (8.5)	6 (14.0)	11 (5.3)	38 (6.0)	19 (13.4)	11 (29.7)	22 (8.9)	272 (8.2)	<0.001#
Alpha blockers	71 (1.5)	8 (3.0)	1 (2.3)	0 (0)	9 (1.4)	6 (4.2)	0 (0)	6 (2.4)	41 (1.2)	0.010#
Psychoactive medications, *n* (%)										
Overall	444 (9.1)	46 (16.9)	6 (14.0)	16 (7.7)	67 (10.6)	21 (14.5)	3 (7.9)	28 (11.3)	257 (7.8)	<0.001#
Z-drugs	109 (2.2)	12 (4.4)	2 (4.7)	3 (1.4)	14 (2.2)	11 (7.8)	1 (2.7)	5 (2.0)	61 (1.9)	<0.001#
Benzodiazepines	140 (2.9)	17 (6.3)	0 (0.0)	9 (4.3)	15 (2.4)	5 (3.5)	2 (5.4)	10 (4.1)	82 (2.5)	0.009#
Antidepressants	281 (5.7)	35 (12.9)	4 (9.3)	9 (4.3)	47 (7.4)	12 (8.3)	1 (2.6)	15 (6.1)	158 (4.8)	<0.001#
OI during AS, *n* (%)	1880 (38.4)	130 (47.8)	21 (48.8)	93 (44.5)	271 (42.9)	57 (39.3)	13 (34.2)	103 (41.7)	1,192 (36.0)	<0.001#
At least 1 fall in the past 12 months, *n* (%)	960 (19.6)	77 (28.3)	6 (14.0)	36 (17.3)	125 (19.8)	32 (22.1)	7 (18.4)	47 (19.0)	630 (19.0)	0.025#
At least 1 syncope in the past 12 months, *n* (%)	226 (4.62)	13 (4.8)	1 (2.3)	11 (5.3)	23 (3.7)	11 (7.8)	2 (5.3)	9 (3.6)	156 (4.7)	0.585#
Mean baseline SBP, mmHg (SD)	135.8 (22.3)	147.7 (24.9)	142.1 (27.9)	142.9 (25.0)	140.3 (23.0)	143.5 (23.0)	141.8 (19.1)	143.8 (24.3)	132.4 (20.6)	<0.001*
Mean baseline heart rate (HR), beats per minute (SD)	65.0 (9.9)	61.9 (9.9)	63.5 (9.8)	61.2 (9.2)	63.1 (9.5)	67.1 (11.7)	69.9 (10.9)	65.0 (9.9)	65.7 (9.7)	<0.001*

*Kruskal–Wallis test, #Chi-square test.

Table 2. Results of the fully adjusted logistic regression models (Models C)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
	OR (95% CI)*P*	OR (95% CI)*P*	OR (95% CI)*P*	OR (95% CI)*P*	OR (95% CI)*P*	OR (95% CI)*P*	OR (95% CI)*P*	
OI	**1.83 (1.41, 2.38) <0.001**	1.85 (0.98, 3.47) 0.056	**1.60 (1.20, 2.13) 0.001**	**1.42 (1.19, 1.70) <0.001**	1.20 (0.84, 1.73) 0.314	0.99 (0.49, 20.3) 0.981	**1.32 (1.00, 1.74) 0.048**	(Base)
Falls	**1.54 (1.15, 2.07) 0.004**	0.64 (0.27, 1.56) 0.326	0.86 (0.58, 1.26) 0.440	1.00 (0.80, 1.26) 0.957	0.90 (0.58, 1.40) 0.641	0.91 (0.39, 2.12) 0.824	0.94 (0.67, 1.33) 0.732	(Base)
Recent syncope	0.91 (0.49, 1.66) 0.750	0.56 (0.05, 4,21) 0.658	1.27 (0.67, 2.41) 0.464	0.72 (0.45, 1.16) 0.180	1.29 (0.64, 2.58) 0.478	0.60 (0.80, 4.47) 0.616	0.74 (0.37, 1.50) 0.409	(Base)

Statistically significant results are highlighted in bold.

Our results are consistent with the definition of initial OH in that the immediate SBP drop is associated with OI [8]; however, our results underscore the merit of considering the immediate BP drop and OI separately. Indeed, the fact that the strength of the association with OI seemed stronger as more deficits were seen in the AS pattern acknowledges the importance of not just the immediate BP change but also the recovery phase [7]. In addition, this finding is consistent with the theory of the accumulation of health deficits [15,25], which postulates that deficit accumulation may be a useful measure of biological age and thus of increased clinical risk [26]. Interestingly, the three-deficit pattern was not seen in the oldest group, perhaps in keeping with the principle that accumulation of health deficits is heterogeneous resulting in poor correlation with chronological age [25].

In terms of the pathophysiology behind the accumulation of deficits effect in association with OI, some studies have suggested that the presence of an isolated immediate BP deficit (without OI symptoms) may not be pathological and is often seen in young healthy people [27]. However, in older people who may be affected by comorbidities, initial OH may be a risk factor for unexplained syncope [28]. Our study suggests that an isolated immediate BP deficit is common in a healthier group of older people, but it is seen with other deficits in less healthy groups. A possible explanation for the variable relationship between immediate SBP drops and health status is that the healthier the person is, the faster they are generally able to stand up [18]. This increased speed in changing from supine to standing gives the body less time to compensate for the stress of orthostasis and, as a result, there

may be a greater immediate SBP drop. Therefore, the clinical significance of an immediate BP deficit needs to be assessed in the context of the subsequent SBP recovery. Cooke *et al*. came to a similar conclusion in their study that attempted to classify OH into three different subtypes based on how the SBP responded to the initial SBP drop. They similarly found a wide range of SBP response patterns and felt that the recovery patterns may guide predicting future adverse outcomes in OH [29].

Looking at the groups with immediate deficit, 3 and 4 were younger and tended to stand quicker, which may explain their immediate drop; whilst 4 fully recovered, 3's late deficit might be due to a marginally higher proportion of beta-blockers (lowest baseline heart rate) and benzodiazepines. Groups 1 and 2 were older, which is associated with impaired BP stabilisation [11,12]. Group 1 is the reminiscent of the syndrome of supine hypertension with OH, in which baseline hypertension is followed by a marked late deficit possibly due to pharmacological influences (e.g. beta blockers, antidepressants and benzodiazepines) [13,24]; in group 2 (older than 1), late recovery seemed to occur in the context of a lower SBP baseline and less of the latter pharmacological influences (e.g. none on benzodiazepines).

Looking at the groups without an immediate deficit, 8 and 7 were younger and did not fail to stabilise, but 7's late deficit was in the context of a higher proportion of benzodiazepines and antidepressants. Groups 5 and 6 (with stabilisation failure) were older and had proportions of DM over 10%. DM can cause orthostatic hypertension, which might appear as better late recoveries (this also applies to group 2) [30]. Again, a difference between 5 and 6 was that 5's late deficit was seen with a higher burden of beta blockers and antidepressants.

Our study has limitations. Firstly, it is of cross-sectional nature and observations do not imply causality. Further research is necessary to establish the longitudinal stability of the AS patterns and their association with future health outcomes. Future research will consider more objective health outcomes such as incident diagnosed disease, objective disability or mortality.

As regards clinical outcomes, our definitions of falls and syncope are limited by recall bias. In addition, our binary OI variable is limited in that postural dizziness is very common in older people and is often multifactorial [23]. Despite not being the oldest, the group with all three deficits had one of the highest OI proportions and the highest use of beta-blockers, benzodiazepines and antidepressants; the latter medications may independently contribute to OI [13,24] and in this regard clinicians should retain a high level of clinical alertness.

Finally, the method of classifying individuals is open to bias as this was done manually without blinding. However, our classification method is not intended to represent a gold standard, as some of the resulting groups were small and there may have been some clinical overlap between them. In practice, some individuals may fit into more than one category, or there may be a spectrum of risk rather than discrete categories. Our data invite hypotheses but cannot answer them.

Further research will apply artificial intelligence techniques, which we hope will more efficiently divide the sample into a smaller number of more different groups. Automatic clustering approaches could be compared with manual approaches in their ability to predict outcomes.

Conclusion

The interpretation of AS patterns requires the consideration of immediate, stabilisation and late deficits simultaneously. Older age was associated with stabilisation deficits and late deficits were seen with a higher burden of beta blockers and psychotropic medications. Whilst observations are not causal and longitudinal research is required, the recognition of continuous AS patterns could help personalise prescribing.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

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