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Autonomic nervous system and postural control regulation during orthostatic test as putative markers of physical resilience among community-dwelling older adults

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ABSTRACT

Introduction: We examined whether autonomic nervous system (ANS) and postural control regulation during orthostatic test reflect physical resilience by studying their associations with maximal walking speed and mortality.

Methods: The participants were community-dwelling Finnish men ($n = 303$) and women ($n = 386$) aged 75, 80, and 85 years at baseline. Systolic and diastolic blood pressure (BP), heart rate, heart rate variability (HRV), respiratory rate, and postural sway were obtained using a digital sphygmomanometer, a single-channel ECG, and thigh- and chest-worn accelerometers. Linear and Cox regression models were used to estimate the associations of the physiological indices with maximal 10-m walking speed and 5-year mortality separately for sexes.

Results: Better maintenance of BP under orthostatic stress was associated with faster walking speed in women and lower mortality hazard in men. Greater HRV in terms of low frequency power and lower respiration rate in supine position and smaller orthostatic changes in these were associated with faster walking speed especially in women. Less postural sway after standing up was associated with faster walking speed in women (−0.057, SE 0.022, $p = 0.011$) and more postural sway with increased mortality hazard in men (HR 1.71, 95 % CI 1.20–2.43) even after controlling for BP responses.

Conclusions: In addition to ANS regulation at rest and under stress, adaptation of postural control system to orthostasis may be used in quantifying older adults' physical resilience. Wearable sensors capturing stimulus-response patterns and natural fluctuations of body functions may provide opportunities to monitor and incorporate different subsystems' resilience also in free-living conditions.

1. Introduction

Resilience refers to the dynamic ability of a system to recover or restore optimal functioning following stressors. When facing disturbance, the system may either restore its current equilibrium state or quickly recover to it, or it may be pushed over a tipping point into another, possibly more unfavorable equilibrium state (Scheffer et al., 2018). In aging research, the concept of physical resilience has gained increasing interest as older individuals frequently experience sudden transitions in health and functioning, such as delirium, syncope, acute loss of mobility, and finally also death (Olde Rikkert and Melis, 2019). Improving the identification of older adults' capacity to resist and recover from critical health transitions may greatly benefit promoting healthy aging.

Stimulus-response patterns following standardized stress-tests as well as natural fluctuations of physiological parameters derived from time series data that aim to capture impaired homeostatic regulation may signal declining physical resilience of a person or their subsystems (Varadhan et al., 2008). Stressing the system may reveal “hidden” vulnerability, which may not appear in normal conditions (Álvarez-Millán et al., 2022). A well-known example of stimulus-response patterns is impaired blood pressure (BP) response to orthostasis when the fast change in posture disturbs the autonomic nervous system (ANS) regulating BP. Upon standing the blood volume towards the lower body

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increases due to gravity and vasodilation. This leads to reduced venous return and a decrease in BP. Subsequently, cardiac output and vasoconstriction increase to restore BP to the optimal level. When the regulatory processes are unable to counterbalance the BP, the system may be pushed over a tipping point, and orthostatic hypotension may occur (Scheffer et al., 2018). Orthostatic intolerance reflecting impaired ANS function may also be a marker of a multi-level and multi-organ dysregulation underlying poor health and functioning (Fried et al., 2021; Romero-Ortuño et al., 2021). Research has provided evidence that non-adaptive responses after orthostatic test are valuable in evaluating the likelihood of current and future health outcomes, such as lower cognitive performance (Frewen et al., 2014), lower physical performance, frailty, and falls (Mol et al., 2021) as well as mortality (Fedorowski et al., 2010; Lagro et al., 2014).

Monitoring the dynamics of several physiological subsystem parameters during stress-tests may improve the quantification of an individual's physical resilience and prediction of decline in health and functioning. Assessments of heart rate (HR) and heart rate variability (HRV) at resting conditions or in response to stressors (e.g. changing body positions, such as standing up, or doing physical performance tests) are commonly used to measure the activity of the ANS and its sympathetic and parasympathetic branches regulating the vital functions of the body (Berntson et al., 1997). For example, studies have shown that orthostatic HR response tends to attenuate with age and among individuals with compromised heath (Cybulski and Niewiadomski, 2003; Romero-Ortuno et al., 2011). As heart rate needs to adapt flexibly to stressors, also higher within-person variability and complexity are considered as signs of healthy and resilient function of the ANS even without intentionally stressing the system (Costa et al., 2002; Goldberger et al., 2002; Rector et al., 2021). Previous studies have also demonstrated that monitoring respiration rate, which is one fundamental vital sign and closely linked to cardiovascular responses, may predict adverse health events and mortality (Cretikos et al., 2008; Takayama et al., 2022). However, respiration rate in rest or in response to stress has received less attention in non-clinical, population-based samples among older adults. HR, HRV and respiration rate can all be obtained from single-channel ECG measurements.

In addition to perturbing the cardiorespiratory system, the orthostatic test posture transition perturbs postural balance. The postural balance regulation associated with the perturbance could also be used in evaluating physiological resilience akin to the previous art with the cardiorespiratory system. Maintenance of the upright posture involves multiple physiological systems including the somatosensory, vestibular, and visual systems as well as the cardiovascular control (Garg et al., 2014). When standing still, postural sway needs to be controlled within a narrow range, and in contrast to HR, high magnitude fluctuations and increased self-similarity of the system's dynamics is considered to reflect slower recovery rate from disturbances and more fragile function of the contributing subsystems (Fossion et al., 2018; Gijzel et al., 2019).

In this study, we examined whether the autonomic nervous system (ANS) and postural control regulation during orthostatic test reflect physical resilience among older men and women. To this end, we studied associations of these putative resilience indicators with maximal walking speed and 5-year mortality. Walking speed is an integrative measure of health as it reflects multiple underlying physiological systems that constantly strive for homeostasis in response to incoming stressors (Studenski et al., 2011). Consequently, better walking speed may indicate greater physiological reserve capacity to respond effectively to stressors (Koivunen et al., 2020). Mortality, in turn, is a powerful indicator of health decline and failure of the system.

2. Materials and methods

2.1. Study design and participants

Baseline and follow-up data from the population-based “Active aging - resilience and external support as modifiers of the disablement outcome’ (AGNES) study (Rantanen et al., 2018) were used in the current study. The sampling protocol and participation in the baseline study are reported in detail elsewhere (Portegijs et al., 2019; Rantanen et al., 2018). Briefly, at baseline in 2017–2018, the participants were 75-, 80-, and 85-year-old community-dwelling adults living in the city of Jyväskylä, Central Finland. The participants were recruited after obtaining their contact information from the population register of the national Digital and Population Services Agency. Not living independently in the recruitment area and inability to communicate were the exclusion criteria. Of the contacted people, 36.6 % (n = 1021) participated in the study and formed the baseline sample (Portegijs et al., 2019). At baseline, a computer-assisted personal interview (CAPI) was conducted in participants' homes and in the end of the interview, assessments in the research center were scheduled. In total, 910 of the participants attended the functional assessments in the research center.

In the current study, two analytical samples were used (Fig. 1). Orthostatic BP and HR responses were available for 811, of whom 689 had also a postural sway recording, and they formed the larger sample used for the BP, HR, and postural sway analyses. BP and HR responses were missing mainly because the participants did not perform the orthostatic test or the BP measurement failed. Data were missing in the postural sway analysis for different reasons. A walking test, which was used as a reference to identify the upright posture in the orthostatic test, was missing for 31 participants. Other reasons for missing data were that accelerometer device was not attached, or data were lost (n = 38), delayed standing up or support while standing (n = 12), and recording and processing error (n = 40). A subsample (n = 483) of the larger analytical sample was used for the HRV and respiratory rate analyses. Of the 698 participants, 11 had missing data in ECG recordings completely or at some test phase. Further, HRV indices could not be derived for 195 participants due to excessive amount of irregular heart rhythms, such as atrial fibrillation, or noisy data.

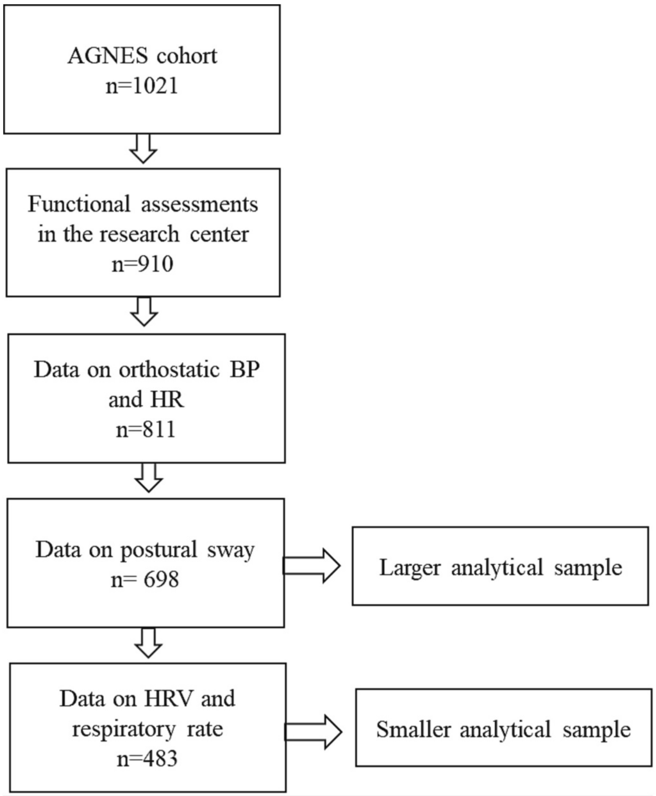

Fig. 1. Flow chart of the study participants. BP = blood pressure, HR = heart rate, HRV = heart rate variability.

2.2. Measurements

Orthostatic test was performed by a research nurse in a quiet, private room at the research center. The participants were instructed to avoid additional strain, staying up late and consuming alcohol during the day before the assessments. Also, the use of caffeine-containing beverages, such as coffee, tea, or soft cola drinks, as well as smoking was to be avoided for two hours before the assessments. In addition, the participants were instructed to take their medication as usual and to eat a light breakfast or lunch at least one hour before the start of the measurements.

In the test, the participants remained in supine position for at least 10 min and then maintained a quiet stance for six minutes after active standing up. A digital sphygmomanometer was used to measure BP during the test. In addition, participants wore two tri-axial accelerometers, both sampling continuously at 100 Hz (13-bit±16 g) UKK RM42 (UKK Terveyspalvelut Oy, Tampere, Finland) and (14-bit±16 g) eMotion Faros 180 (Bittium Technologies Oy, Oulu, Finland) including an additional single-channel electrocardiography (ECG) recorder. The accelerometers were attached to the thigh of the dominant leg and the sternum or diagonally on the left side of the chest under the breast for the ECG recording.

2.2.1. Blood pressure, heart rate, and dizziness

BP was measured during supine rest one minute before standing up, immediately after active standing up, and three and five minutes after standing up. In the present analyses, only the supine measurement and the first BP measurement in standing position were used because the orthostatic stabilization of BP is normally achieved in one minute or less (Finucane et al., 2014). The orthostatic response was defined as the difference between the BP immediately after standing up and the BP in supine. Orthostatic hypotension was defined as a systolic drop of at least 20 mmHg and/or a diastolic drop of at least 10 mmHg BP relative to baseline after standing up (Freeman et al., 2011). HR in supine and after standing up was assessed together with the BP measurements. Participants reported whether they perceived dizziness after standing up, and the response was coded as yes or no.

2.2.2. HRV and respiratory rate

HRV and respiratory rate parameters were calculated using continuous ECG recording for four minutes in supine and for four minutes in standing position, excluding the last 20 s before and the first minute and 20 s immediately after standing up. For each parameter, the difference between standing and supine positions was calculated. All HRV and respiration rate calculations were performed with Kubios HRV Premium analysis software (version 3.2.0., Kubios Oy, Kuopio, Finland). The software uses an automatic QRS detection algorithm, from which beat-to-beat RR intervals were calculated. RR intervals were edited for removal of artifacts using an automatic correction algorithm (Lipponen and Tarvainen, 2019). Subsequently, visual evaluation was conducted to confirm that the software has appropriately identified the R peaks, and that the RR interval time series is free from misaligned beat detections and ectopic beats. HRV analysis was not performed if 1) excessive amount ($>$20 %) of artifact was detected, or 2) signal strength was weak or absent (i.e., QRS complexes were not correctly detected). Time-domain and frequency-domain HRV parameters were calculated. Mean (RR) and standard deviation of normal-to-normal sinus beat intervals (SDNN, ms) were selected from time-domain indices as they quantify overall RR interval length and HRV including fluctuations at all frequencies, respectively. Frequency-domain (power spectral) analysis allows evaluation of fluctuation at different frequency bands including high frequency and low frequency spectral components. The spectrum was calculated using Lomb-Scargle periodogram. High frequency power (HFP; 0.15–0.40 Hz) reflects the modulation of parasympathetic (vagal) activity and the low frequency power (LFP; 0.04–0.15 Hz) represents both sympathetic and parasympathetic activity (Shaffer and Ginsberg, 2017). HFP and LFP were expressed as absolute units (milliseconds squared, ms^2). Electrocardiogram-derived respiration (EDR) was used to estimate the respiration rate based on R-wave amplitudes which reflect the motion of the electrodes with respect to the heart (Moody et al., 1985). The respiration rate is expressed in Hertz (Hz) and cycles per minute.

2.2.3. Postural sway

Postural sway was calculated only for the participants who could stand up immediately after being supine and who did not use an aid during standing. The postural sway analysis was done using a custom-written Matlab code. As the participants wore the accelerometers in supine and standing positions during the orthostatic test, we needed to identify the upright orientation of the thigh from the raw accelerometer data after standing up. The transition from supine to a standing position was detected using a posture equation by Vähä-Ypyä et al. (2018). Posture reference values were determined from a standardized walking bout, where all participants were known to be in standing position and the orientation was calculated in 1 s epochs. Previously, we have validated and used the same method to detect sit-to-stand transitions in free-living conditions (Löppönen et al., 2022; Löppönen et al., 2021). The transition from lying down to standing up was recorded when the orientation of accelerometer exceeded the threshold value ($\pi/4$). We skipped the first five seconds after standing up to allow the participant to reach a steady upright position. Then postural sway was analyzed for 30 s period using the magnitude of the resultant of the horizontal acceleration (i.e., movement only in the horizontal plane). First, the vertical acceleration was extracted by filtering raw acceleration data using low-pass filter with a 2nd order Butterworth with a cutoff frequency of 0.5 Hz (Vähä-Ypyä et al., 2018). This vertical acceleration was separated from the resultant calculated from the raw accelerometer data to obtain only the magnitude of the resultant of the horizontal acceleration.

The 30-s Root Mean Square (RMS) (Ghislieri et al., 2019) was calculated for this resultant acceleration using Matlab's rms-function in 0.33-s bouts indicating the overall fluctuation. The RMS of the acceleration was multiplied by 100 for the analyses. Also, temporal autocorrelation of the 0.33-s bouts was calculated (Gijzel et al., 2019), which indicates the similarity of the system's dynamics in consecutive states (lags). Autocorrelation was calculated using the “R” statistical environment (version 4.2.1) and auto- and cross-covariance and -correlation function estimation (acf-function, argument lag.max = 1) of the stats (version 3.6.2) library.

2.2.4. Outcomes

Maximal walking speed was assessed by measuring the time to walk 10-m distance in the study center corridor using photocells. The participants were instructed to walk as fast as possible without compromising safety. Five meters was allowed for acceleration before the first photocell and the walking continued well past the finish line after the second photocell to ensure that deceleration commenced only after exiting the measurement area. The participants wore walking shoes or sneakers and were allowed to use a walking aid if necessary. Walking speed was calculated in m/s.

Information on death dates were obtained from the Finnish Digital and Population Data Services Agency. The participants were followed up from baseline until the first of August 2022 for mortality.

2.2.5. Covariates

Potential confounders were selected based on their possible association with the predictors and gait speed or mortality. These variables included sex assigned at birth (male/female), age, body height, the number of chronic conditions, and the number of medications that are known to affect BP and HR (Joseph et al., 2017). Body height was measured at the research center. The number of chronic conditions and medications were calculated based on participants' responses to a questionnaire, which was subsequently reviewed by a research nurse (Rantanen et al., 2018).

2.3. Statistical analyses

Before constructing the statistical models, logarithm transformation was applied to the frequency-domain HRV variables (LFP, HFP) to normalize the distribution. We applied a paired *t*-test to study the average changes in BP, HR, HRV and respiratory rate from supine to standing position separately for men and women. Two-way repeated measures analysis of variance (ANOVA) was used to study potential differences in the orthostatic responses between sexes. The response in the observed parameters was calculated and reported as the difference in parameters between supine and standing positions except for postural sway and dizziness, which were examined only in standing position. We used a chi-square test to analyze sex differences in orthostatic hypotension and dizziness and an independent samples t-test in postural sway.

Due to a high number of parameters tested ($n = 18$), in the first phase, several linear regression models were conducted to explore the possible associations of supine and response values of ANS and postural sway with maximal walking speed separately in men and women (in total 36 models). The models were adjusted for age, body height, number of chronic conditions, and number of medications (+ supine values in models evaluating responses in BP, HR, HRV and respiratory rate). Similarly, 18 Cox regression models for each sex were performed to explore the association of the predictors with all-cause mortality adjusted for age, number of chronic conditions, and number of medications (+ supine values in models evaluating responses in BP, HR, HRV and respiratory rate). The Benjamini-Hochberg procedure was used to adjust for multiple comparisons with a false discovery rate of 0.10 (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001).

In the second phase, multivariate linear and Cox regression models including only the statistically significant predictors from the first phase were constructed to test whether the associations remain significant independent of other predictors. The multivariate models were conducted with the smaller analytical sample ($n = 483$) and were adjusted for age, body height, number of chronic conditions, and number of medications (+ supine values if orthostatic responses were included in the model). Statistical significance was set at $p < .05$ and the data were analyzed using the SPSS 28 for Windows.

3. Results

Table 1 shows the characteristics of the larger analytical sample used in this study. In comparison to women, men were taller and had faster walking speed. Men also had fewer chronic conditions than women but no sex differences were observed in the number of medications affecting BP and HR. The smaller subsample used in the HRV and respiratory rate analyses did not differ substantially from the larger sample in terms of the background characteristics or the proportion of the participants who died during the follow-up.

Table 1
Participant characteristics stratified by sex.

	Men (n = 303)	Women (n = 386)
	n (%)	n (%)
Age group		
75 years	153 (51)	207 (54)
80 years	97 (32)	120 (31)
85 years	53 (18)	59 (15)
Died during the follow-up	23 (8)	20 (5)

	Mean (SD)	Mean (SD)
Walking speed, [m/s]	1.9 (0.4)	1.7 (0.3) [a]
Body height, [cm]	172.4 (6.0)	158.5 (5.3) [a]
Number of chronic conditions	2.9 (1.7)	3.3 (1.9) [a]
Number of medications	1.4 (1.2)	1.3 (1.2)

Notes. SD = standard deviation.

[a] $p < .05$, men vs women.

3.1. Orthostatic responses

Immediately upon standing, SBP decreased and HR increased in both sexes, but the changes were more prominent in men compared to women (Table 2). In women, DBP was higher in standing position in relation to supine whereas in men, the DBP values were similar in supine and standing. Orthostatic hypotension was more common in men. With decreased RR interval, HRV reduced in both sexes, which was shown as decreased SDNN, LFP, and HFP. Decrease in LFP was greater in men in comparison to women. Respiratory rate in supine was on average 14.4 cycles per minute in men and 13.8 cycles per minute in women, and it increased by slightly more than one cycle per minute in both sexes. In standing position, the amount of postural sway or temporal autocorrelation in the time series of postural sway did not differ between sexes.

3.2. Linear regression analyses with walking speed as an outcome

After accounting for multiple comparison, we found statistically significant associations of ANS and postural sway with walking speed only in women in the separate linear regression models. Lower HR and respiratory rate, and higher LFP in supine position were associated with faster walking speed when adjusted for covariates (Table 3). After standing up, better maintenance of DBP, a smaller decrease in LFP, a smaller increase in respiratory rate, not feeling dizziness, less postural sway and lower temporal autocorrelation in the consecutive time lags of 0.33 s were also associated with faster walking speed. All the significant predictors associated with walking speed were entered into the multivariate regression model with the covariates and supine DBP values (Table 4). In women, higher supine LFP and lower supine respiratory rate remained associated with faster walking speed independent of other regulatory indicators. Of the orthostatic response indicators, a smaller increase in respiratory rate and a smaller increase in LFP and less postural sway also remained associated with faster walking speed.

3.3. Mortality analyses

In the larger analytical sample ($n = 689$), the 5-year follow-up encompassed 1231 person-years of surveillance among men and 1592 person-years among women. During the follow-up, 23 men and 20 women died. The crude mortality rate for men was 1,9/100 person-years and for women 1,3/100 person-years. In the smaller analytical subsample ($n = 483$) the corresponding mortality rates were similar as in the larger sample (1,9/100 person-years in men and 1,3/100 in women).

The associations of the supine and response values of ANS and postural sway with mortality hazard are reported in Table 5. After accounting for the covariates and multiple comparison, in men, better maintenance of DBP upon standing was associated with decreased mortality hazard and more postural sway with increased mortality hazard. Both indices remained associated with mortality risk also when entered in the same Cox regression model (Table 6).

4. Discussion

Our results suggest that even minor deficits in regulatory systems of ANS and postural balance, evident after a modest physiological perturbation, capture meaningful information about physiological resilience. For example, the observed changes in BP upon standing up did not meet on average the orthostatic hypotension criteria, and the increase in respiratory rate was less than two respiratory cycles per minute. Given the relatively high walking speed and low mortality rate in our sample and the absence of a major health event stressing the system, it is notable that such small stress responses may be used to quantify physical

Table 2

Autonomic nervous system and postural control regulation responses during the orthostatic test in men and women.

	Sex	Supine	Standing up	Response	*p*-value[*]
		Mean (SD)	Mean (SD)	Mean (SD)	
SBP, [mmHg]	Men	144.8 (18.08)	136.6 (22.2)	−8.1 (15.4)[a]	**<0.001**
	Women	152.8 (19.7)	149.0 (24.2)	−3.8 (16.3)	**<0.001**
DBP, [mmHg]	Men	77.1 (9.4)	77.2 (11.3)	0.2 (7.7)[a]	0.735
	Women	78.9 (9.1)	82.3 (11.0)	3.3 (7.6)	**<0.001**
HR, [bpm]	Men	60.8 (10.2)	71.8 (12.9)	11.00 (8.6)[a]	**<0.001**
	Women	63.4 (9.9)	71.4 (11.3)	8.0 (6.9)	**<0.001**
OH, [yes], n (%)	Men	–	–	74 (25)[b]	
	Women	–	–	68 (18)	
Dizziness, [yes], n (%)	Men	–	–	58 (20)	
	Women	–	–	75 (20)	

		Supine 4 min	Standing 4 min	Response	
RR, [ms]	Men	99.6 (15.4)	86.6 (14.7)	−13.00 (7.9) [a]	**<0.001**
	Women	96.1 (14.3)	86.4 (13.5)	−9.7 (6.7)	**<0.001**
SDNN, [ms]	Men	24.9 (19.5)	21.0 (16.6)	−3.9 (16.6)	**<0.001**
	Women	24.6 (19.7)	22.0 (18.1)	−2.6 (16.4)	**0.009**
LFP, [ms^2]	Men	461 (837)	303 (503)	−159 (757)	
	Women	408 (835)	333 (628)	−74 (694)	
LFP, [ln(ms^2)]	Men	5.4 (1.1)	5.0 (1.1)	−0.4 (1.1) [a]	**<0.001**
	Women	5.3 (1.1)	5.1 (1.1)	−0.1 (1.0)	**0.018**
HFP, [ms^2]	Men	430 (2056)	231 (743)	−199 (1896)	
	Women	420.5 (1370)	315.3 (1540)	−105.3 (1421)	
HFP, [ln(ms^2)]	Men	4.7 (1.3)	4.1 (1.4)	−0.6 (1.2)	**<0.001**
	Women	4.8 (1.3)	4.3 (1.3)	−0.5 (1.1)	**<0.001**
EDR, [Hz]	Men	0.24 (0.06)	0.26 (0.06)	0.02 (0.06)	**<0.001**
	Women	0.23 (0.06)	0.26 (0.06)	0.02 (0.06)	**<0.001**
Sway RMS [cm/s^2]	Men	–	–	3.25 (1.09)	
	Women	–	–	3.30 (1.10)	
Sway, temporal autocorrelation	Men	–	–	0.66 (0.17)	
	Women	–	–	0.67 (0.17)	

Notes. Supine = one minute before standing up; Standing up = immediately after active standing up; Supine 4 min = four minutes period in supine, Standing 4 min = four minutes period in standing position, Response = standing – supine. BP, HR, and postural sway indices (n = 698), HRV and respiratory rate indices (n = 538), HR = heart rate, bpm = beats per minute, SBP = systolic blood pressure, DBP = diastolic blood pressure, OH = orthostatic hypotension; HRV = heart rate variability, SDNN = standard deviation of normal-to-normal intervals, LFP = low frequency power, HFP = high frequency power, ms^2 = milliseconds squared, EDR = ECG-derived respiration, Hz = Hertz, RMS = root mean square.

[*] Analyzed with a paired t-test.

[a] $p < .05$ position-by-sex interaction (analyzed with repeated ANOVA).

[b] $p < .05$, men vs. women group comparison (analyzed with chi-square test / *t*-test).

resilience. While previous studies on orthostatic stress responses have mainly focused on ANS, to the authors' best knowledge, this study is the first to investigate also postural sway as a measure of adaptation in population-based sample of older adults by using accelerometer data. The current results contribute to the shift towards studying the dynamic functions of different systems in understanding physical resilience during aging (Cohen et al., 2022).

Our findings accord with those previous studies showing that poorer autonomic compensation mechanisms to restore BP during orthostasis is associated with lower walking speed (O'Connell et al., 2018) and mortality (Fedorowski et al., 2010; Lagro et al., 2014). Impaired BP response to active standing reflects especially baroreflex sensitivity, which is responsible for short-term regulation of arterial BP and its assessment is commonly used to evaluate the overall state of the ANS (Tank et al., 2000). Compromised ANS function has been suggested to indicate widespread alterations in physiological systems because ANS regulates every organ of the body (Karemaker, 2017; Ziemssen and Siepmann, 2019). In addition to ANS function, orthostatic intolerance has also been related to other more specific mechanisms, such as poor peripheral motor nerve function (Lange-Maia et al., 2017) and decreased skeletal muscle pump activity (Stewart et al., 2004), which both affect walking ability.

In addition to stress responses, spontaneous fluctuations in biological markers, such as in HR, have been suggested to reflect resilience of the system without purposely stressing it as natural systems are inherently non-stationary and permanently subject to stochastic small-scale stressors (Olde Rikkert and Melis, 2019; Scheffer et al., 2018). Thus, important findings of this study were that higher LFP and lower respiratory rate at rest were associated with faster walking speed in women while no such associations were observed for HFP or overall HRV (SDNN) of the HRV spectrum. The observed associations are consistent with earlier studies reporting trends towards higher resting LFP and lower resting respiratory rates in non-frail than frail older adults (Álvarez-Millán et al., 2022; Chaves et al., 2008; Katayama et al., 2015). We also found that under a standardized orthostatic stress exposure, a smaller decrease in LFP and a smaller increase in respiratory rate in women were associated with faster walking speed supporting the idea that these indicators may be informative about subsystems' resilience underlying functional capacity. While lower HRV and higher respiratory rate have also been linked to increased mortality particularly in clinical populations (Kleiger et al., 1987; Stein et al., 2005; Takayama et al., 2022), we did not observe such associations in this population sample of older adults, in which mortality was still low.

In resting conditions, LFP captures HR fluctuations occurring at the wavelength of 7 and 25 s, and is considered to indicate the function of baroreflex feedback loop, which is affected by both, the sympathetic and parasympathetic activation and inhibition (Rahman et al., 2011). Sometimes when the respiration rate is slow, below 7 s, also the vagal nerve activity may cause fluctuations in the heart rate in the LF band of the HRV spectrum (Shaffer and Ginsberg, 2017). In our sample, HR fluctuations crossed over into the LF band due to slow respiration in around 5 % of the participants in supine and 3 % during standing. Respiration indeed has an integral role in the cardiovascular and autonomic function, where the effects are reciprocal. Despite the substantial evidence of the relationship between abnormal respiratory and adverse outcomes, respiration rate has received less attention alongside with the cardiovascular and HRV indices in studies assessing ANS function among older adults. However, assessment of respiratory rate holds a great potential and warrants further investigation as a marker of physical resilience and health in older adults as it is relatively easy to perform at least in rest without any devices, and novel technical solutions can make the monitoring feasible also during experimental procedures or in daily life.

The observed negative association between postural sway and walking speed is well known from the literature as postural balance is a one of the key factors influencing walking ability (Earhart, 2013). In

Table 3
Associations of autonomic nervous system regulation and postural control indices with maximal walking speed in men and women.

	Men			Women		
	B (SE)	p	R^2	B (SE)	p	R^2
Supine						
SBP, [per 10 mmHg]	0.013 (0.012)	0.291	0.151	−0.003 (0.008)	0.742	0.161
DBP, [per 10 mmHg]	0.019 (0.023)	0.403	0.150	−0.025 (0.017)	0.150	0.165
HR, [per 10 bpm]	−0.027 (0.021)	0.194	0.148	−0.033 (0.016)	**0.041**	0.170
SDNN, [per 10 ms]	−0.002 (0.015)	0.868	0.146	0.010 (0.010)	0.278	0.149
LFP, [per 1 ln(ms^2)]	0.033 (0.023)	0.153	0.132	0.045 (0.017)	**0.010**	0.151
HFP, [per 1 ln(ms^2)]	0.017 (0.021)	0.421	0.125	0.024 (0.015)	0.107	0.137
EDR, [per 0.1 Hz]	−0.033 (0.046)	0.473	0.125	−0.116 (0.033)	**<0.001**	0.169
Response						
ΔSBP, [per 10 mmHg]	0.010 (0.014)	0.470	0.150	0.017 (0.010)	0.078	0.163
ΔDBP, [per 10 mmHg]	0.071 (0.029)	0.015	0.166	0.042 (0.020)	**0.044**	0.173
ΔHR, [per 10 bpm]	−0.043 (0.026)	0.097	0.154	−0.017 (0.023)	0.453	0.169
ΔSDNN, [per 10 ms]	−0.003 (0.019)	0.888	0.146	0.011 (0.013)	0.295	0.152
ΔLFP, [per 1 ln(ms^2)]	0.007 (0.028)	0.790	0.127	0.055 (0.021)	**0.009**	0.171
ΔHFP, [per 1 ln(ms^2)]	−0.021 (0.023)	0.359	0.125	0.007 (0.019)	0.381	0.134
ΔEDR, [per 0.1 Hz]	−0.114 (0.052)	0.032	0.142	−0.116 (0.038)	**0.002**	0.196
OH, [yes vs. no]	0.013 (0.050)	0.792	0.148	−0.036 (0.041)	0.379	0.162
Dizziness, [yes vs. no]	−0.125 (0.054)	0.022	0.166	−0.088 (0.040)	**0.027**	0.174
Sway RMS, [per 1 cm/s^2]	−0.037 (0.022)	0.089	0.156	−0.042 (0.014)	**0.003**	0.179
Sway autocorrelation, [per 0.1]	0.035 (0.019)	0.783	0.148	−0.023 (0.009)	**0.011**	0.173

Notes. BP, HR, and postural sway indices (n = 698), HRV and respiratory rate indices (n = 438), SBP = systolic blood pressure, DBP = diastolic blood pressure, OH = orthostatic hypotension, HR = heart rate, bpm = beats per minute, SDNN = standard deviation of normal-to-normal intervals, LFP = low frequency power, HFP = high frequency power; EDR = ECG-derived respiration, Hz = Hertz; RMS = root mean square. B = unstandardized beta, models adjusted for age, body height, number of chronic conditions, and number of medication (+ supine values for models evaluating responses), Response = standing – supine, Bolded *p*-values remained statistically significant after the Benjamini-Hochberg procedure, R^2 = adjusted coefficient of determination.

Table 4
Multivariate linear regression analysis of the associations of autonomic nervous system and postural sway indices with walking speed stratified by sex.

	Men (n = 204)		Women (n = 279)	
	B (SE)	p	B (SE)	p
Supine				
HR, [per 10 bpm]	−0.038 (0.031)	0.216	0.005 (0.022)	0.835
LFP, [per 1 ln(ms^2)]	0.037 (0.029)	0.204	0.058 (0.020)	**0.004**
EDR, [per 0.1 Hz]	−0.072 (0.057)	0.205	−0.163 (0.036)	**<0.001**
Response				
ΔDPB, [per 10 mmHg]	0.050 (0.034)	0.142	0.045 (0.024)	0.067
ΔLFP, [per 1 ln(ms^2)]	−0.000 (0.029)	1.00	0.047 (0.021)	**0.026**
ΔEDR, [per 0.1 Hz]	−0.118 (0.054)	**0.031**	−0.109 (0.038)	**0.005**
Dizziness, [yes vs. no]	−0.047 (0.067)	0.482	−0.058 (0.049)	0.237
Sway RMS, [per 1 cm/s^2]	−0.060 (0.032)	0.068	−0.057 (0.022)	**0.011**
Sway autocorrelation, [per 0.1]	0.004 (0.017)	0.808	−0.008 (0.011)	0.501
R^2, adjusted	0.183		0.258	

Note. DBP = diastolic blood pressure, HR = heart rate, bpm = beats per minute, LFP = low frequency power, EDR = ECG-derived respiration, Hz = Hertz; RMS = root mean square. B = unstandardized beta, models adjusted for age, body height, number of chronic conditions, number of medications and DPB supine values; Response = standing – supine. Bolded p-values statistically significant <0.05, R^2 = adjusted coefficient of determination.

Table 5
Associations of autonomic nervous system regulation and postural control indices with mortality hazard in men and women.

	Men	Women
	HR (95 % CI)	(HR 95 % CI)
Supine		
SBP, [per 10 mmHg]	1.02 (0.82–1.29)	0.89 (0.71–1.11)
DBP, [per 10 mmHg]	0.68 (0.42–1-12)	0.99 (0.61–1.62)
HR, [per 10 bpm]	1.02 (0.69–1.50)	0.66 (0.39–1.12)
SDNN, [per 10 ms]	1.09 (0.85–1.40)	0.65 (0.34–1.21)
LFP, [per 1 ln(ms^2)]	0.85 (0.54–1.34)	0.74 (0.46–1.20)
HFP, [per 1 ln(ms^2)]	0.95 (0.63–1.44)	0.80 (0.51–1.26)
EDR, [per 0.1 Hz]	1.73 (0.76–3.92)	1.57 (0.63–3.92)
Response		
ΔSBP, [per 10 mmHg]	0.76 (0.58–0.99)	0.79 (0.64–0.98)
ΔDBP, [per 10 mmHg]	**0.35 (0.19–0.64)**	0.75 (0.41–1.40)
ΔHR, [per 10 bpm]	0.99 (0.61–1.61)	1.03 (0.52–2.02)
ΔSDNN, [per 10 ms]	0.90 (0.60–1.35)	1.06 (0.63–1.77)
ΔLFP, [per 1 ln(ms^2)]	0.81 (0.46–1.41)	1.08 (0.61–1.89)
ΔHFP, [per 1 ln(ms2)]	1.03 (0.65–1.63)	0.94 (0.54–1.65)
ΔEDR, [per 0.1 Hz]	0.98 (0.38–2.54)	1.94 (0.60–6.40)
OH, [yes vs. no]	1.40 (0.58–3.35)	1.96 (0.74–5.19)
Dizziness, [yes vs. no]	2.85 (1.19–6.83)	1.22 (0.43–3.47)
Sway RMS, [per 1 cm/s^2]	**1.76 (1.26–2.53)**	0.80 (0.48–1.35)
Sway autocorrelation, [per 0.1]	1.01 (0.78–1.31)	0.95 (0.75–1.20)

Notes. Hemodynamic and postural sway indices (n = 698), HRV and respiratory rate indices (n = 483), HR = hazard ratio, CI = confidence interval; SBP = systolic blood pressure, DBP = diastolic blood pressure, OH = orthostatic hypotension; HR = heart rate, bpm = beats per minute, SDNN = standard deviation of normal-to-normal intervals, ms = milliseconds, LFP = low frequency power, HFP = high frequency power, ms^2 = milliseconds squared; EDR = ECG-derived respiration, Hz = Hertz; RMS = root mean square; Models adjusted for age, number of chronic conditions, and number of medication (+ supine values for models evaluating responses upon standing), Response = standing – supine. Bolded hazard ratios statistically significant after the Benjamini-Hochberg procedure.

addition, the hypothesized direction between increased temporal autocorrelation of postural sway and slower walking speed was shown in our analyses among women suggesting that decreased temporal independence of fluctuations around an equilibrium in response to perturbation indicate loss of stability and resilience. Although extracting the patterns of fluctuations may provide meaningful insight into systems' resilience,

Table 6
Multivariate Cox regression analysis of the associations of DBP responses and postural sway with mortality hazard stratified by sex.

	Men (n = 204)	Women (n = 279)
	HR (95 % CI)	HR (95 % CI)
ΔDPB, [per 10 mmHg]	**0.37 (0.21–0.67)**	0.73 (0.39–1.35)
Sway RMS, [per 1 cm/s^2]	**1.71 (1.20–2.43)**	0.78 (0.46–1.32)

Note. ΔDBP = diastolic blood pressure response (standing – supine), RMS = root mean square; Models adjusted for age, number of chronic conditions, number of medication, and supine values for DBP, bolded hazard ratios statistically significant <0.05.

in our analyses, the temporal autocorrelation of postural sway did not outperform the average overall sway in predicting walking speed and mortality. However, it should be kept in mind that only one time lag of 0.33 s was explored based on a previous study by Gijzel et al. (2019) and also different intervals could be studied.

Under orthostatic stress, increased postural sway has also been proposed as a compensation mechanism to maintain BP through skeletal muscle pump activation when the ANS compensation mechanisms are compromised (Claydon and Hainsworth, 2006; Garg et al., 2014). In the current analyses, the associations of postural sway or BP responses with walking speed or mortality hazard did not attenuate when both postural sway and BP were added in the same multivariate model proposing that the regulation of the systems may not be dependent of each other. However, in future studies it could be worth investigating the possible interplay between the physiological control systems within subjects, such as the interdependence of the cardiovascular and postural control systems or cardiorespiratory coupling as indicators of resilience as the patterns and dysfunctions within the subsystems' interactions as the functioning of the system depends on the complex interactions between its components (Cohen et al., 2022).

We conducted the analyses separately to men and women due to reported sex differences in autonomic cardiovascular regulation (Evans et al., 2001; Ramaekers, 1998), which was also shown in our results by more prominent ANS responses in men. This is in line with a previous study reporting higher orthostatic hypotension prevalence in men than in women among adults older than 75 years (Méndez et al., 2018). It may be possible that this decreased physical resilience to regulate the basal body functions under stress also underlies men's higher mortality rates compared to women. In turn, in women, the studied regulatory indicators were more often associated with walking speed than with mortality, which may be explained by the fact that depleted physiological resilience mechanisms in women is more likely to be manifested in reduced functional capacity than in increased mortality (Oksuzyan et al., 2008). It is important to note, however, that analyzing men and women separately reduced the analytical sample sizes and may have caused the statistical analyses to be underpowered for finding significant results. In particular, the results of the Cox regression analysis must be interpreted with caution due to the small number of events. Hence, the presented findings and the observed sex differences should be tested with larger samples.

While most previous research has focused on investigating orthostatic BP responses, a major strength of this study is that it extends on exploring different systems' dynamics during the standardized orthostatic test as putative indicators of physical resilience. Although the orthostatic test procedure of the study was not originally designed to measure postural control, we were able to successfully measure postural sway from wearable accelerometers using an algorithm based on a custom-written algorithm, which identifies supine and upright postures. While wearable inertial measurement unit-based balance assessments have shown reasonable concurrent criterion validity with force platform-based posturography (Gawronska et al., 2020), the latter is considered the more precise method and the reliability of the assessment with accelerometers remains to be established. On the other hand, accelerometer-based measurements may open new possibilities to measure postural control regulation also in daily life.

Moreover, examination of HRV yielded important results as it has been less studied in population-based samples of older people. However, incorporating HRV measurements to analyses also meant limitations to the study as it is highly sensitive to inaccurate calculations due to e.g., artifacts or atrial fibrillation, which led to excluding a high number of participants from the analyses. Thus, the participants may have represented a healthier section of the same-aged population. It is, therefore, possible that the observed associations are underestimates and they would have been stronger if those with poorer health had also participated. However, the participants of the HRV sample did not differ substantially from the larger sample in terms of the background characteristics or mortality. We also used population-based and heterogeneous sample instead of a self-selected convenience sample and there was variation in many background characteristics of the participants. In addition, investigating sensitive and discriminating resilience markers in high-functioning older adults is particularly important to find early-warning signs of functional decline.

Another measurement-related limitation of this study was that the discrete BP measurement may not have captured the full orthostatic response, especially in DBP, as generally the orthostatic stabilization of BP is achieved in one minute or less (Finucane et al., 2014). In the first BP measurement upon standing, DBP showed to be on average at the same level in men and higher in women when compared to the supine position although decrease may have occurred. Thus, the future studies may choose to use continuous BP monitoring, if possible. We were also not able to standardize the posture of the feet or visual target during standing as the analyses were secondary in nature. We believe that the lack of standardized base of support and visual target may have weakened the found associations between postural sway, walking speed and mortality as the measurement may not have been as sensitive (as a measurement with controlled posture) in discriminating between participants who differed in their postural control. The results showed that the postural sway indicators were associated with walking speed and mortality in the hypothesized direction, which gives us confidence about the validity of the measurement and that we were able to capture postural control regulation. We also had no information about possible vestibular disorders, which could also underlie increased postural sway during standing. Finally, in this study we could not investigate whether the functioning of dynamic physiological systems is associated with better ability to tolerate and respond to a major scale clinical stressor, such as surgery. However, the observed associations with walking speed and mortality risk provided a valuable basis for this initial investigation.

5. Conclusions

In addition to orthostatic BP, dynamics of respiration rate, HRV, and postural sway may reflect the regulatory subsystems' resilience and overall health among community-dwelling older adults. Alongside to the static approach of assessing functional reserve capacities, wearable sensors capturing stimulus-response patterns and natural fluctuations in time series of body functions may provide opportunities to monitor and incorporate different subsystems' resilience in daily life.

Author statement

We confirm that this work has not been published nor is it currently under consideration for publication elsewhere. All authors have contributed to the work and the final version of the manuscript has been read and approved by all authors.

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CRediT authorship contribution statement

Kaisa Koivunen: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Funding acquisition. **Antti Löppönen:** Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing. **Lotta Palmberg:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Timo Rantalainen:** Methodology, Software, Writing – review & editing, Funding acquisition. **Taina Rantanen:** Resources, Writing – original draft, Writing – review & editing, Funding acquisition. **Laura Karavirta:** Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing, Funding acquisition.

Declaration of competing interest

None.

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