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# Clinical and demographic correlates of accelerometer-measured physical activity in participants enrolled in the OPTIMISE HFpEF study

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Aims	This study aimed to measure physical activity (PA) in participants with suspected heart failure with preserved ejection fraction (HFpEF) and assess associations between PA and participant characteristics.
Methods and results	Adults with presumed HFpEF were recruited and received diagnostic evaluation and clinical assessment. Physical activity was objectively measured using accelerometers over 7 days. To examine predictors of PA, a best subset analysis was used, with the optimal model defined as that with the lowest Bayesian information criterion. One hundred and twenty-four participants with presumed HFpEF who had valid accelerometer data were included in this study. Seventy-six were confirmed by a cardiologist as meeting the European Society of Cardiology diagnosis criteria for HFpEF. The median age of all participants was 80.1 years, and 47.4% were female. Patients spent most of each 24-h period at low-intensity PA and few or no durations at high-intensity PA, with lower activity for those with HFpEF. Gait speed was the best univariate correlate of activity levels (adjusted $R^2$ 0.29). The optimal model using best subsets regression included six variables and improved adjusted $R^2$ to 0.47. In the model, lower levels of PA were associated with slower gait speed, lower levels of anxiety, higher levels of depression, past smoking history, a confirmed HFpEF diagnosis, and higher body mass index.
Conclusion	Participants demonstrated very low PA levels. The study has identified important patient characteristics associated with PA, which may help to identify those most in need of interventions. Notably, participants with confirmed HFpEF were more inactive than participants with other heart failure phenotypes.
Keywords	Heart failure with preserved ejection fraction • Activities • Lifestyle • Sedentary • Accelerometer

## **Implications for Practice**

- Patients with HFpEF had very low levels of physical activity and represent a group requiring support to increase physical activity.
- Some factors associated with low physical activity levels such as slow gait speed, increased BMI, and depression identify patients at risk of sedentary behaviour and are potentially modifiable.
- Physical activity has been shown to improve fitness and quality of life in HFpEF and innovative interventions are needed to support patients with HFpEF to be active.

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## Introduction

Heart failure (HF) is a syndrome caused by structural and/or functional defects of the heart, leading to reduced cardiac output and/or raised intracardiac pressures.<sup>1</sup> Heart failure is a serious public health concern in the UK, affecting over 920 000 people,<sup>2</sup> and accounting for 2% of NHS expenditure and 5% of emergency hospitalizations.<sup>3</sup> Approximately half of all cases are attributable to the phenotype heart failure with preserved ejection fraction (HFpEF), which is more difficult to diagnose and has so far proved refractory to traditional HF pharmacotherapy.

Heart failure with preserved ejection fraction is conceptually defined as the presence of an ejection fraction (EF) greater than 50% alongside objective evidence of a reduced capacity to eject blood adequately at normal diastolic filling pressures.<sup>4</sup> The development of HFpEF is driven by a pro-inflammatory state induced by comorbid conditions such as obesity, hypertension, diabetes mellitus, and chronic obstructive pulmonary disease.<sup>5</sup> The pro-inflammatory state leads to coronary microvascular endothelial inflammation, which begins the cascade of events leading to left ventricular stiffness and heart failure. More recently, peripheral endothelial dysfunction has been highlighted as pathophysiologically potent in HFpEF causing or contributing to a range of skeletal muscle abnormalities that contribute significantly to exercise intolerance.<sup>6</sup>

Successive failure of clinical trials of drugs to alter morbidity and mortality and emerging evidence of the role of peripheral factors has prompted an increased focus on alternative pathways of management and a call for more tangible endpoints such as improvement in the quality of life (QoL) and functional capacity.<sup>7</sup> Meta-analyses<sup>8–10</sup> have shown physical activity (PA) improves QoL and functional capacity; however, evidence of effects of PA on hospitalizations and mortality is lacking and findings have been inconsistent in relation to diastolic dysfunction.

Little is known about the quantity and quality of PA performed by those with HFpEF<sup>11</sup> and therefore the best mode and dose of PA to prescribe in HFpEF.<sup>12</sup> Cardiac rehabilitation guidelines recommend supervised aerobic exercise 3–5 times per week for 20–160 min that can be augmented by resistance exercises and is progressively increased based on baseline assessed by cardiopulmonary exercise testing. However, in the UK many cardiac rehabilitation programmes still do not accept patients with heart failure<sup>13</sup> and uptake amongst HF patients remains low ( $\leq$ 20%).<sup>14</sup> Moreover, some argue the utility of CR in HFpEF has not been established as the evidence base predominantly excludes HFpEF patients.<sup>14</sup>

Studies that quantify and explore correlations of free-living PA in HFpEF patients are valuable in informing new interventions and may even provide insights into potential barriers to PA engagement in the real-world setting.

The aim of this article is to describe PA levels in a cohort of participants recruited to a prospective observational cohort study [Optimising Management of Heart Failure with Preserved Ejection Fraction in Primary Care (Optimise HFpEF)] and the participant characteristics associated with PA levels.

## Methods

The study has been described previously<sup>15</sup> but in brief, community-dwelling older adults with suspected HFpEF (n = 152) were recruited via the primary care setting from three regions in England. Given the diagnostic challenges of HFpEF, inclusion criteria were broad: all adult patients with diagnosed or suspected HFpEF [defined as anyone diagnosed with non-valvular HF that: (i) were not diagnosed with left ventricular systolic dysfunction or had a documented ejection fraction (EF) <50%; (ii) had a reported 'normal' or preserved EF; and (iii) had an echocardiogram reporting structural heart disease or diastolic dysfunction without moderate to severe systolic dysfunction]. Patients were excluded if they could not communicate in English; or had documented: severe neurocognitive conditions that would confound outcome assessment; New York Heart Association (NYHA) Class IV classification or other life-threatening condition; or a recent (<6 weeks) heart failure exacerbations resulting in hospitalization.

Following consent, participants underwent a transthoracic echocardiogram (TTE) and were clinically phenotyped. The primary aim was to characterize a cohort of patients with HFpEF recruited from primary care; the secondary aim was to follow-them longitudinally for 1 year to assess change over time. A component of the phenotyping was assessment of objective measurement of PA via 7-day accelerometery wear. Clinical parameters and TTEs were assessed by an experienced cardiologist against European Society of Cardiology (ESC) diagnostic criteria for HFpEF.<sup>1</sup> This separated the cohort into two groups: those who met the ESC criteria, 'confirmed HFpEF'; and those who did not, 'non-HFpEF'. The non-HFpEF group presented with various other cardiac phenotypes. Both the confirmed HFpEF and non-HFpEF participants are included in this study. This allowed comparison between groups, and an opportunity to examine the significance of a confirmed HFpEF diagnosis on levels of PA.

## Ethics

The study was given Research Ethics Committee (REC) and regulatory approval through the Health Research Authority in England (REC reference: 17/LO/2136). All participants provided written informed consent; data were handled in line with local data protection and information governance regulations which stipulate personal identifiable data is stored separately and securely. The study conformed with the principles of the Declaration of Helsinki.

## Measurement of physical activity

All participants (n = 152) were invited to wear the Axivity AX3 tri-axial accelerometer (Axivity Ltd, Newcastle upon Tyne, UK) for seven consecutive free-living days. Participants were asked to wear the accelerometer on their non-dominant wrist; however, dominant wrist wear was allowed as previous studies found no significant difference.<sup>16</sup> Verbal and written instruction on continuous wear, normal activity, and device return were given. The accelerometers were programmed to record movement with a sampling frequency of 100 Hz and a dynamic range of  $\pm 8 \text{ g}$ . The validity of wrist-worn devices set at these frequencies has been previously established.<sup>17,18</sup> Data were collected between July 2018 and November 2019.

Non-wear of the accelerometer was defined as time periods where the standard deviation of acceleration in each axis fell below 13 mg for longer than 1 h.<sup>19</sup> Valid data were defined as at least five valid days of accelerometer wear, with each valid day having data for at least 80% of a 24-h period. The median accelerometer wear percentage was 100%. Patient flow and subsequent exclusions can be visualized in *Figure 1*; in brief 152 patients were enrolled in the study and 20 were excluded due to a lack of accelerometer data. A further eight participants without valid accelerometer data as defined above were excluded. The subsequent analyses were based on the final sample of 124 participants, of which 76 were patients with HFpEF and 48 were patients with other types of cardiovascular diseases.

#### **Clinical assessments**

Outcome measures and data sources<sup>15</sup> included the following: physical characteristics (height, weight, blood pressure, respiratory rate, pulse); past medical history and comorbidities (interview and medical record review); heart function [12-lead electrocardiogram and transthoracic echocardiogram (TTE)]; oedema assessment, breathlessness, and fatigue (modified BORG), frailty assessment [clinical frailty scale, Survey of Health, Ageing and Retirement in Europe Frailty Instrument, electronic frailty index (SHARE-FI)]; cognition assessment [Montreal Cognitive Assessment (MOCA)]; physical functioning (six-minute walk test, gait speed, 7 day accelerometer wear); laboratory testing (biochemistry, haematology, biomarkers); anxiety and depression [Hospital Anxiety and Depression Score (HADS)]; heart failure QoL [Kansas City Cardiomyopathy Questionnaire (KCCQ)], HF self-care [European Heart Failure Self-Care Behaviour Questionnaire (EHFScB)]; HF symptoms (Symptom Status Questionnaire—Heart Failure) and health-related QoL (EQ-5D-5L).

#### Accelerometer data

Accelerometer data were processed using Pampro (https://github.com/ Thomite/pampro),<sup>20</sup> an open-source software package. Machine noise was filtered out by applying a low-pass filter at 20 Hz. Raw tri-axial signals were converted into an omnidirectional acceleration signal and acceleration due to gravity was removed to isolate acceleration due to PA alone, using the procedure described by van Hees et al.<sup>21</sup> The signal, known as the Euclidean Norm Minus One, was further summarized from samplelevel data into averages over 5-s epochs. The resultant signal, expressed in milligravity units (mg) where g = 9.81 ms<sup>-2</sup>, was termed the average vector magnitude and used to represent the PA intensity.

Previous studies have extensively discussed the heterogeneity in and absence of standard methods for accelerometer data collection and processing.<sup>22</sup> This is further complicated by the application of various normative 'thresholds' to classify different categories of PA, especially in chronic disease. To avoid ambiguity and enhance comparison with other

cohorts, this study did not apply thresholds and reports average vector magnitude.

## Analysis

Statistical analyses were carried out using R statistical software version 3.6.0.<sup>23</sup> Descriptive data were expressed as median values with interquartile range (IQR) or as counts with proportions unless otherwise stated. Statistical significance was set at 5% and 95% confidence intervals are provided.

For the regression, which sought to determine associations between individual variables and daily average vector magnitude, variables with zero or near-zero variance were removed, as were variables with more than five missing values and linear dependencies. Retention and exclusion of variables at each stage can be visualized in *Figure 2*.

Univariate linear regression analysis explored the association between average vector magnitude and all of the potential predictor variables before multivariate regression models were built using best subsets regression in the 'leaps' R package.<sup>24</sup> The model used an exhaustive search. To assess for overfitting of the data, the Bayesian information criterion (BIC) was extracted. We also performed *k*-fold cross-validation (*k* = 10) to predict the different models' ability to generalize to independent data sets. The optimal model was defined as that with the lowest BIC value. The number of independent variables in the model was increased until the BIC rose.

## Results

Summary statistics of the 124 patients used for the PA analysis are described in *Table 1*. In the total sample, the majority were male (59.7%), NYHA Class II (58.9%), and pre-frail or frail (55.6%). The sample was older (median age: 79.6), more functionally impaired [median SHARE-FI frailty score: 1.1; median six-minute walk distance (6MWD): 300.0 m; median gait speed: 1.1 m/s] and had more comorbidities [median Charlson Comorbidity Index (CCI): 4] than patients typically recruited into clinical trials.<sup>25,26</sup> The higher median age was representative of the general population with HF, which has a reported median age of 75 years.<sup>27</sup> Compared to the patients with



Figure | Participant flow and exclusions.



other types of cardiovascular conditions, the HFpEF sample had more severe HF by NYHA classification (P = 0.049) and was more functionally impaired, as demonstrated by the significantly higher SHARE-FI frailty score (P = 0.043) and 6MWD (P = 0.023), and significantly lower KCCQ overall summary score (P = 0.022) and daily average vector magnitude (P = 0.018). There were also proportionally more females in the HFpEF sample, which trended towards significance (P = 0.068). The HFpEF sample was otherwise no significantly different from the non-HFpEF group in the other clinical and demographic variables.

Data on the amount of time spent above each vector magnitude are presented as boxplots in *Figure 3*. For both the total sample and the subset of HFpEF patients, the majority of each 24-h period was spent in what might be considered low or sedentary levels of PA, and only short durations were spent at high-intensity PA. The median duration spent at each vector magnitude was shorter for patients with HFpEF as compared to the total sample. The spread of durations spent above each vector magnitude was large and a small number of individuals spent significantly more time above each vector magnitude compared to the rest of the sample, as represented by the filled circles in *Figure 3*.

# Correlates of daily average vector magnitude

The univariate analyses determined 19 variables were significantly correlated with daily average vector magnitude, with two variables tending towards significance. Gait speed explained the largest amount of variance (adjusted  $R^2 = 0.29$ ) (Supplementary material online, *Table S1*). The optimal model from the best-subset analysis, as defined by the lowest BIC, was the six variable model (*Table 2*). A seven variable model did not improve the BIC and only marginally improved the adjusted  $R^2$  value. In the six variable model 'optimal' model (adj  $R^2 = 0.47$ , df = 84, P < 0.001) lower levels of activity were

associated with slower gait speed, lower levels of anxiety (as measured by the HADS), higher levels of depression (as measured by the HADS), a past smoking history, a confirmed HFpEF diagnosis, and a higher body mass index (BMI) (*Table 3*; marginal effects plot in Supplementary material online, *Figure S1*).

## Discussion

Compared to healthy individuals of equivalent age, this cohort of older, multi-morbid adults predominantly recruited from the HF registers of primary care practices appeared relatively inactive with a median average vector magnitude of 16.2 mg (IQR 12.2–20.2). Importantly, within the total sample, those with a confirmed diagnosis of HFpEF were even more inactive with a median daily average vector magnitude of 15.4 mg (IQR 6.8–18.3). In comparison, a study of UK Biobank participants found the mean acceleration vector magnitude in healthy older adults aged 75–79 years old was 23.9 mg (SD  $\pm$  6.5) for women and 22.9 mg  $(SD \pm 6.8)$  for men.<sup>28</sup> When compared with older adults with cardiovascular disease from the UK biobank (n = 7040), which reported mean activity of 25.2 mg/day (IQR 25.1-25.4), the daily average vector magnitude is still low.<sup>29</sup> A subset of biobank participants (n = 53) in the latter analysis had heart failure of unspecified phenotype. The mean daily activity in this cohort of 21.5 mg/day (IQR 20.0-23.1) was still substantially higher than the average vector magnitude reported in this study.

Only one other UK clinical study has reported accelerometerybased assessment of PA in patients with confirmed HFpEF.<sup>30</sup> The REACH-HFpEF study used a GeneActive accelerometer and similarly measured physical activity levels over 7 days. Compared to REACH-HFpEF, subjects in this cohort performed more activity at lower vector magnitudes but substantially less activity at higher vector

	Confirmed HFpEF (n = 76)	Non-HFpEF ( <i>n</i> = 48)	P-value
Domographic variables			•••••
Female	36 (47.4%)	14 (79 7%)	0.068
Age	801 (748-836)	78.2 (72.9–83.2)	0.260
$BMI (ka/m^2)$	31 2 (27 7-34 4)	28.6 (23.9–32.7)	0.200
Past smoking history	49 (64 5%)	38 (79.2%)	0.007
	30 (39 5%)	13 (27 1%)	0.721
Alcohol consumption frequency	50 (57.576)	13 (27.173)	0.566
Never	16 (21 1%)	5 (10.4%)	0.500
Monthly or less	12 (15.8%)	10 (20.8%)	
2-4 times a month	8 (10.5%)	7 (14 6%)	
2-3 times a week	15 (19.7%)	11 (22 9%)	
4 or more times a week	25 (32.9%)	15 (31.3%)	
Previously attended cardiac rehabilitation programme	11 (14.5%)	7 (14 6%)	1,000
Clinical variables	(	<i>(</i> (), ((), (), (), (), (), (), (), (), (),	
NYHA classification			0.049
Class	10 (13.2%)	15 (31.3%)	
Class II	49 (64.5%)	24 (50.0%)	
Class III	17 (22.4%)	9 (18.8%)	
Presence of leg oedema	39 (51.3%)	22 (45.8%)	0.682
SHARE-FI frailty score	1.6 (0.3–2.5)	0.9 (-0.2 to 1.9)	0.043
Non-frail	25 (32.9%)	26 (54.2%)	
Pre-frail	30 (39.5%)	13 (27.1%)	
Frail	19 (25.0%)	7 (14.6%)	
Not recorded	2 (2.6%)	2 (4.2%)	
Six-minute walk distance (m)	257.5 (171.8–361.5)	338.0 (237.5–414.2)	0.023
Gait speed (m/s)	1.1 (0.7–1.3)	1.1 (0.9–1.3)	0.051
Charlson Comorbidity Index (CCI)	4.0 (3.0–6.5)	4.0 (2.5–5.0)	0.231
CHA <sub>2</sub> DS <sub>2</sub> -VASc score for atrial fibrillation stroke risk	4.2 (3.0–5.0)	4.0 (3.0–5.0)	0.121
Questionnaire scores			
KCCQ			
Physical limitation score	72.9 (50.0–87.5)	87.5 (70.8–100.0)	0.001
Total symptom score	78.1 (59.6–89.6)	91.7 (61.7–100.0)	0.066
Quality of life score	83.3 (41.7–91.7)	83.3 (62.5–100.0)	0.110
Social limitation score	82.5 (50.0–100.0)	90.0 (65.0–100.0)	0.262
Overall summary score	74.7 (53.6–88.8)	88.3 (64.1–97.8)	0.022
HADS	· · · · ·	· · · ·	
Anxiety score	4.5 (2.0–7.0)	4.0 (2.0–6.0)	0.650
Depression score	8.0 (6.0–9.0)	7.0 (5.8–8.3)	0.150
EQ-5D-5L crosswalk index value	0.7 (0.6–0.8)	0.8 (0.7–1.0)	0.205
EHFScB total score	29.0 (22.0–35.8)	32.0 (26.0–36.5)	0.270
Accelerometer data			
Daily average vector magnitude (mg)	15.4 (12.0–18.3)	18.2 (12.9–21.5)	0.018

#### Table I Summary of demographic and clinical variables for HFpEF and non-HFpEF patients

Data presented as count (percentage) or median (IQR). Independent *t*-tests were performed to compare differences in continuous variables between the HFpEF and non-HFpEF samples. Chi-squared tests were performed to compare differences in proportions of categorical variables. The bold are those that are statistically significant. BMI, body mass index; CCI, Charlson Comorbidity Index; EHFScB, European Heart Failure Self-care Behaviour Scale; HADS, Hospital Anxiety and Depression Scale; HFPEF, heart failure with preserved ejection fraction; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; SHARE-FI, Frailty Instrument of the Survey of Health, Ageing and Retirement in Europe.

magnitudes. Mean time per day spent at vector magnitudes greater than 100 mg in REACH-HFpEF was 39 min (intervention group) and 40 minutes (control group) compared to 10.52 min in this study (Supplementary material online, *Table S2*).

The findings are in line with other studies of HFpEF. A similar cross-sectional observation study (ALBERTA-HEART) found that patients with HFpEF (n = 53) had the lowest volume of activity across the four groups studied [HFpEF, heart failure with reduced ejection

fraction (HFrEF), at risk for HF, healthy control].<sup>11</sup> A *post hoc* analysis of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) study (n = 1751) found that few HFpEF patients (11%) met American Heart Association criteria



**Figure 3** Duration spent above each vector magnitude above 0 mg [all patients (n = 124); Patients with heart failure with preserved ejection fraction (n = 76)].

for ideal activity and that poor and intermediate baseline PA was associated with a higher risk of HF hospitalization and mortality.  $^{31}$ 

## **Correlates of physical activity**

In this analysis, 47% of the variance in PA was explained by gait speed, anxiety, depression, past smoking history, BMI, and HFpEF diagnosis. Even when controlling for other factors, the diagnosis of HFpEF itself was an independent predictor. Patients with HFpEF demonstrated a lower daily average vector magnitude and consistently shorter durations spent at every vector magnitude threshold in *Figure 3*. This suggests that, in this sample of participants with mixed cardiovascular pathologies, those with a diagnosis consistent with HFpEF were the most inactive.

Patients with HFpEF were more functionally impaired than those not confirmed as HFpEF. As a measure of functional impairment gait speed positively predicted daily average vector magnitude in both univariate and multivariate analyses. Previous studies have found that functional capacity correlates with total PA in mixed HF<sup>22,32</sup> and HFpEF cohorts.<sup>12,33</sup> Gait speed is a simple and reproducible measure that can be implemented within clinical practice. Given the accumulating evidence demonstrating strong associations between PA and gait speed, it could serve as a proxy measure of PA and thus identify those who would benefit most from PA interventions.

## Table 2 Parameters of models with one to seven variables generated by best subsets multivariate regression analyses

Covariates in model	Adjusted R <sup>2</sup>	R <sup>2</sup>	BIC	Mallows' Cp	<i>k</i> -fold prediction error
Gait speed	0.29	0.29	-22.57	18.56	5.53
Gait speed, weight	0.35	0.37	-28.33	9.29	5.43
Gait speed, anxiety, depression	0.39	0.41	-29.28	5.80	5.25
Gait speed, anxiety, depression, BMI	0.42	0.44	-30.55	2.34	5.23
Gait speed, anxiety, depression, past smoking history, HFpEF diagnosis	0.44	0.47	-31.37	-0.41	5.15
Gait speed, anxiety, depression, past smoking	0.47	0.50	-32.25	-2.93	5.13
history, HFpEF diagnosis, BMI					
Gait speed, anxiety, depression, past smoking history,	0.47	0.52	-29.90	-2.66	5.11
HFpEF diagnosis, BMI, CHA <sub>2</sub> DS <sub>2</sub> -VASc score for atrial fibrillation stroke risk					

Bold represents the best model.

Table 3 S	ummary of t	he optimal	six-variable	model
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Term	Estimate	Lower 95% CI	Upper 95% Cl	P-value
Gait speed	6.39	3.95	8.83	<0.001
HADS anxiety	0.46	0.19	0.74	0.001
HADS depression	-0.61	-1.12	-0.11	0.019
Past smoking history	2.66	0.41	4.91	0.021
Diagnosis of confirmed HFpEF	2.99	0.80	5.17	0.008
BMI	-0.19	-0.36	-0.02	0.026

BMI, body mass index; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; HFpEF, heart failure with preserved ejection fraction.

Past smoking history was negatively correlated with PA levels, consistent with some studies examining factors associated with PA levels in  $HF^{22}$  but not all.<sup>12,33</sup> In a recent retrospective study of 14 406 patients with coronary artery disease and HF, Grubb et al.<sup>34</sup> found that in both HFpEF and HFrEF, current smokers had a higher risk than former smokers; however, smoking history correlated with worse outcomes in HFrEF only. Links between smoking and lower PA levels have been proposed, although the exact pathophysiological mechanisms are still unclear. For instance, smoking is associated with structural and functional myocardial changes<sup>35</sup> and haemodynamic changes such as vasoconstriction and endothelial dysfunction<sup>36</sup> which can precipitate functional impairment and exercise intolerance. That smoking may be associated with physical inactivity in HF is concerning because smoking and physical inactivity are both associated with poorer outcomes in HF.<sup>37</sup> Smoking cessation in HF patients is important but only 3.2% of our cohort were current smokers. For ex-smokers, past smoking behaviour is not modifiable, but our findings suggest that these HF patients may be in greater need of PA interventions.

Similar to other studies, increasing BMI was associated with lower levels of physical activity.<sup>22,33</sup> In a study of 51 451 participants from three longitudinal cohorts, Pandey *et al.*<sup>38</sup> demonstrated a strong, dose-dependent association between lower PA levels, BMI, and risk of overall HF; with risk of developing HFpEF much lower in the context of higher PA and lower BMI. Current guidelines do not have specific recommendations for lifestyle modification in HFpEF; however, the low levels of PA observed in this study and the independent association between BMI and low PA suggested that specific targeting of these two factors in the management of HFpEF may be warranted.

Finally, both components of the HADS score appeared to be significantly associated with daily average vector magnitude. The HADS anxiety score showed a positive association, i.e., higher anxiety scores were associated with higher average daily vector magnitude. This finding is in contrast to a previous study which found higher anxiety levels were associated with lower levels of PA.<sup>32</sup> Possible explanations include anxiety resulting in patients being less likely to rest or PA exacerbating HF symptoms and increasing anxiety amongst patients.

The HADS depression score was negatively associated with PA levels, a finding consistent with some studies of HFpEF patients<sup>22</sup> but not all.<sup>33</sup> Depression can result in lower PA levels through behavioural (lower adherence to healthy behaviours including PA) and biological mechanisms (inflammation and endothelial dysfunction precipitating exercise intolerance).<sup>39</sup> In HFpEF, depression is reported to be fairly common and often goes unrecognized clinically.<sup>40</sup> Although the evidence is varied, PA interventions in HFpEF populations should perhaps include a measure of and active treatment of depression.

It is important to note that the majority of patients in this study reported low anxiety and depression levels (HADS subscale score <8) and the effect plots showed high degrees of uncertainty at high anxiety/depression levels (Supplementary material online, Figure S1). Therefore, further investigation into the relationship between anxiety and PA levels based on a larger sample with higher anxiety and depression levels representative of the general HF population is warranted. This will also be useful in examining anxiety/depression as a factor influencing PA levels, and as an outcome of PA interventions in HF patients.

### **Strengths and limitations**

Most HFpEF research is limited by the societal definition of HFpEF applied within the study, as they variably enrich for certain characteristics.<sup>41</sup> This research is no different; however, the application of the 2016 European Society of Cardiology guidelines is a strength as previous studies have employed less precise definitions which may introduce diagnostic uncertainty and/or even greater heterogeneity. Although this study assessed a large number of variables, over 50% of the variance in PA remained unexplained. Further limitations include: the cross-sectional study design, which precluded inferences of causality; lack of an external validation cohort to validate the predictive models derived; and inability to control for seasonal variation in mean temperature, which can affect daily PA in HF patients.<sup>42</sup> Finally, this study used wrist-worn accelerometers instead of hip-worn devices, which are the more traditional choice in PA research settings and may be more accurate in measuring PA.<sup>43</sup>

Despite these limitations, the use of raw acceleration signals rather than activity counts to measure PA allows our data to be compared with other studies that use different brands of accelerometers provided they produce raw acceleration output. Moreover, based on criteria outlined by Montoye *et al.*,<sup>44</sup> this study provided high-quality and complete accelerometer data.

Recently, Dibben et  $al.^{22}$  have proposed HF-specific accelerometer intensity thresholds for inactivity and MVPA as people with HF have a lower resting metabolic rate requiring greater energy expenditure for equivalent tasks. These thresholds were not applied here as the HFpEF sample used to determine thresholds was small (n=4) and the diagnostic criteria unclear; therefore, reporting average daily vector magnitude was felt to have greater comparable utility.

## Conclusion

The older, community-dwelling patients in this study demonstrated low levels of PA. The most important correlates of PA levels included past smoking history, gait speed, HFpEF diagnosis, anxiety, BMI, and depression levels. These factors can be modifiable targets or serve as a means of identifying patients most in need of PA interventions and at the highest risk of poor clinical outcomes. In particular, HFpEF patients appeared to have lower levels of PA compared to patients of other HF phenotypes and may therefore benefit more from PA interventions. This study further highlights issues in the non-standardization of measuring, reporting, and interpreting activity data, comparisons across studies are significantly limited by differences in these methods.

## Supplementary material

Supplementary material is available at European Journal of Cardiovascular Nursing.

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Conflict of interest: none declared.

## **Data availability**

The data underlying this article are available in the article and in its online supplementary material.

#### References

- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
- Taylor CJ, Ordóñez-Mena JM, Roalfe AK, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. Br Med J 2019;364:1223.
- Donkor A, McDonagh T, Hardman S. National Heart Failure Audit, April 2014 -March 2015. https://www.nicor.org.uk/wp-content/uploads/2019/02/annual\_re port\_2014\_15\_v2.pdf (last accessed December 2020); 2016.
- Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol 2020;17:559–573.
- Paulus WJ, Tschöpe C. A Novel paradigm for heart failure with preserved ejection fraction. J Am Coll Cardiol 2013;62:263–271.
- Farris SD, Moussavi-Harami F, Stempien-Otero A. Heart failure with preserved ejection fraction and skeletal muscle physiology. *Heart Fail Rev* 2017;22:141–148.
- Forman DE, Arena R, Boxer R, Dolansky MA, Eng JJ, Fleg JL, Haykowsky M, Jahangir A, Kaminsky LA, Kitzman DW, Lewis EF, Myers J, Reeves GR, Shen W-K. Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals from the American Heart Association. *Circulation* 2017;**135**: e894–e918.
- Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Eur J Prev Cardiol* 2016; 23:78–85.

- Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev* 2019;**24**:535–547.
- Leggio M, Fusco A, Loreti C, Limongelli G, Bendini MG, Mazza A, Coraci D, Padua L. Effects of exercise training in heart failure with preserved ejection fraction: an updated systematic literature review. *Heart Fail Rev* 2020;25:703–711.
- Yavari M, Haykowsky MJF, Savu A, Kaul P, Dyck JRB, Haennel RG; Alberta HEART Investigators. Volume and patterns of physical activity across the health and heart failure continuum. *Can J Cardiol* 2017;**33**:1465–1471.
- 12. Bobenko A, Bartels I, Münch M, Trippel T, Lindhorst R, Nolte K, Herrmann-Lingen C, Halle M, Duvinage A, Düngen H-D, Gelbrich G, Tschöpe C, Hasenfuss G, Wachter R, Pieske B, Edelmann F. Amount or intensity? Potential targets of exercise interventions in patients with heart failure with preserved ejection fraction: amount or intensity? Potential targets of exercise interventions in patients with heart failure with preserved ejection fraction. *ESC Heart Fail* 2018;5:53–62.
- Dalal HM, Doherty P, Taylor RS. Cardiac rehabilitation. Br Med J 2015:351: h5000.
- Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019;1:CD003331.
- Forsyth F, Mant J, Taylor CJ, Hobbs FR, Chew-Graham CA, Blakeman T, Sowden E, Long A, Hossain MZ, Edwards D, Deaton C. Optimising management of patients with heart failure with preserved ejection fraction in primary care (OPTIMISE-HFpEF): rationale and protocol for a multi-method study. *Br J Gen Pract* 2019;**3**: 1–12.
- Buchan DS, McSeveney F, McLellan G. A comparison of physical activity from Actigraph GT3X+ accelerometers worn on the dominant and non-dominant wrist. *Clin Physiol Funct Imaging* 2019;**39**:51–56.
- Esliger DW, Rowlands AV, Hurst TL, Catt M, Murray P, Eston RG. Validation of the GENEA accelerometer. *Med Sci Sports Exerc* 2011;43:1085–1093.
- White T, Westgate K, Wareham NJ, Brage S. Estimation of physical activity energy expenditure during free-living from wrist accelerometry in UK adults. *PLoS One* 2016;11:e0167472.
- van Hees VT, Renström F, Wright A, Gradmark A, Catt M, Chen KY, Löf M, Bluck L, Pomeroy J, Wareham NJ, Ekelund U, Brage S, Franks PW. Estimation of daily energy expenditure in pregnant and non-pregnant women using a wristworn tri-axial accelerometer. *PLoS One* 2011;6:e22922.
- 20. White T. *Thomite/Pampro V0.4.0.* Zenodo. Epub ahead of print 2 March 2018. doi: 10.1097/HRP.00000000000162; PMID: 29975336.
- van Hees VT, Fang Z, Langford J, Assah F, Mohammad A, da Silva ICM, Trenell MI, White T, Wareham NJ, Brage S. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. J Appl Physiol 2014;**117**:738–744.
- Dibben GO, Gandhi MM, Taylor RS, Dalal HM, Metcalf B, Doherty P, Tang LH, Kelson M, Hillsdon M. Physical activity assessment by accelerometry in people with heart failure. BMC Sports Sci Med Rehabil 2020;12:47.
- R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, https://www.R-project.org/; 2019.
- Lumley T. leaps: Regression Subset Selection. R. https://CRAN.R-project.org/pack age=leaps; 2017.
- Kitzman DW, Rich MW. Age disparities in heart failure research. J Am Med Assoc 2010;304:1950–1951.
- Khan MS, Samman Tahhan A, Vaduganathan M, Greene SJ, Alrohaibani A, Anker SD, Vardeny O, Fonarow GC, Butler J. Trends in prevalence of comorbidities in heart failure clinical trials: comorbidities in HF clinical trials. *Eur J Heart Fail* 2020; 22:1032–1042.
- Azad N, Lemay G. Management of chronic heart failure in the older population. J Geriatr Cardiol 2014;11:329–337.
- Doherty A, Jackson D, Hammerla N, Plötz T, Olivier P, Granat MH, White T, van Hees VT, Trenell MI, Owen CG, Preece SJ, Gillions R, Sheard S, Peakman T, Brage S, Wareham NJ. Large scale population assessment of physical activity using wrist worn accelerometers: the UK Biobank study. *PLoS One* 2017;**12**: e0169649.
- Barker J, Smith BK, Doherty A, et al. Physical activity of UK adults with chronic disease: cross-sectional analysis of accelerometer-measured physical activity in 96 706 UK Biobank participants. *Int J Epidem* 2019;48:1167–1174.
- 30. Lang CC, Smith K, Wingham J, Eyre V, Greaves CJ, Warren FC, Green C, Jolly K, Davis RC, Doherty PJ, Miles J, Britten N, Abraham C, Van Lingen R, Singh SJ, Paul K, Hillsdon M, Sadler S, Hayward C, Dalal HM, Taylor RS. REACH-HF Investigators. A randomised controlled trial of a facilitated home-based rehabilitation intervention in patients with heart failure with preserved ejection fraction and their caregivers: the REACH-HFpEF Pilot Study. *BMJ Open* 2018;8:e019649.
- Hegde SM, Claggett B, Shah AM, Lewis EF, Anand I, Shah SJ, Sweitzer NK, Fang JC, Pitt B, Pfeffer MA, Solomon SD. Physical activity and prognosis in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist). *Circulation* 2017;**136**:982–992.

- Pozehl BJ, Mcguire R, Duncan K, Hertzog M, Deka P, Norman J, Artinian NT, Saval MA, Keteyian SJ. Accelerometer-measured daily activity levels and related factors in patients with heart failure. J Cardiovasc Nurs 2018;33: 329–335.
- 33. Snipelisky D, Kelly J, Levine JA, Koepp GA, Anstrom KJ, McNulty SE, Zakeri R, Felker GM, Hernandez AF, Braunwald E, Redfield MM. Accelerometer-measured daily activity in heart failure with preserved ejection fraction: clinical correlates and association with standard heart failure severity indices. *Circ Heart Fail* 2017; 10:e003878.
- Grubb AF, Pumill CA, Greene SJ, et al. Tobacco smoking in patients with heart failure and coronary artery disease: a 20-year experience at Duke University Medical Center. Am Heart J 2020;230: 25–34.
- 35. Nadruz W, Claggett B, Gonçalves A, Querejeta-Roca G, Fernandes-Silva MM, Shah AM, Cheng S, Tanaka H, Heiss G, Kitzman DW, Solomon SD. Smoking and cardiac structure and function in the elderly: the ARIC study (Atherosclerosis Risk in Communities). *Circ Cardiovasc Imaging* 2016;**9**:e004950.
- Nowak A, Jonderko K, Kaczor R, Nowak S, Skrzypek D. Cigarette smoking delays gastric emptying of a radio-labelled solid food in healthy smokers. Scand J Gastroent 1987;22:54–58.
- Conard MW, Haddock CK, Poston WSC, Spertus JA; Cardiovascular Outcomes Research Consortium. The impact of smoking status on the health status of heart failure patients. *Congestive Heart Fail* 2009;15:82–86.

- Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, Berry JD. Relationship between physical activity, body mass index, and risk of heart failure. J Am Coll Cardiol 2017;69:1129–1142.
- Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and anxiety in heart failure: a review. *Harv Rev Psychiatry* 2018;26:175–184.
- 40. Warraich H, Kitzman D, Whellan D, Pamela D, Mentz R, Pastva A, Nelson B, Reeves G. Physical function, quality of life, and depression in elderly hospitalised patients with acute decompensated heart failure with preserved versus reduced ejection fraction: analysis from the REHAB-HF trial. J Am Coll Cardiol 2018;71: A1877.
- Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Nayor M, Lewis GD. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation* 2019;**140**:353–365.
- Shoemaker MJ, Roper SE, Calkins TN. Seasonal variation of daily physical activity in individuals with heart failure. *Heart Int* 2016;11:e25–e31.
- Rosenberger ME, Haskell WL, Albinali F, Mota S, Nawyn J, Intille S. Estimating activity and sedentary behavior from an accelerometer on the hip or wrist. *Med Sci* Sports Exerc 2013;45:964–975.
- Montoye AHK, Moore RW, Bowles HR, Korycinski R, Pfeiffer KA. Reporting accelerometer methods in physical activity intervention studies: a systematic review and recommendations for authors. Br J Sports Med 2018;52:1507–1516.