Real-world walking cadence in people with COPD

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Real-world walking cadence should be further considered as a prognostic marker of COPD in observational research and in drug and non-drug clinical trials, as well as while developing pulmonary rehabilitation and physical activity interventions https://bit.ly/3TfJezh

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Abstract

Introduction The clinical validity of real-world walking cadence in people with COPD is unsettled. Our objective was to assess the levels, variability and association with clinically relevant COPD characteristics and outcomes of real-world walking cadence.

Methods We assessed walking cadence (steps per minute during walking bouts longer than 10 s) from 7 days' accelerometer data in 593 individuals with COPD from five European countries, and clinical and functional characteristics from validated questionnaires and standardised tests. Severe exacerbations during a 12-month follow-up were recorded from patient reports and medical registries.

Results Participants were mostly male (80%) and had mean±SD age of 68±8 years, post-bronchodilator forced expiratory volume in 1 s (FEV_1) of 57±19% predicted and walked 6880±3926 steps·day^{-1}. Mean walking cadence was 88±9 steps·min^{-1}, followed a normal distribution and was highly stable within-person (intraclass correlation coefficient 0.92, 95% CI 0.90–0.93). After adjusting for age, sex, height and number of walking bouts in fractional polynomial or linear regressions, walking cadence was positively associated with FEV_1, 6-min walk distance, physical activity (steps·day^{-1}, time in moderate-to-vigorous physical activity, vector magnitude units, walking time, intensity during locomotion), physical activity experience and health-related quality of life and negatively associated with breathlessness and depression (all $p<0.05$). These associations remained after further adjustment for daily steps. In negative binomial regression adjusted for multiple confounders, walking cadence related to lower number of severe exacerbations during follow-up (incidence rate ratio 0.94 per step·min^{-1}, 95% CI 0.91–0.99, p=0.009).

Conclusions Higher real-world walking cadence is associated with better COPD status and lower severe exacerbations risk, which makes it attractive as a future prognostic marker and clinical outcome.

Introduction

For people with COPD, physical activity limitation is of key importance [1–4]. Among the different types of physical activity they perform, walking stands out as an important contributor to wellbeing, survival and independence [5–7]. For this reason, abundant research has been conducted into the extent to which the amount that people walk is reduced in COPD [8]. However, few studies have pondered whether and how specific walking patterns are altered in terms of *e.g.* gait speed, step length or dynamic balance in these individuals [8, 9]. This is at odds with the increasing interest in characterising walking patterns in older people in general and also in people with other chronic diseases [8, 10].

Among a long list of spatiotemporal, kinematic and kinetic parameters that can be used to characterise walking patterns, walking cadence stands out for its simplicity of measurement and interpretation [11–13]. Walking cadence, also known as step frequency, step rate or walking tempo, is a temporal walking parameter defined as a step accumulation pattern over a period of time (*e.g.* number of steps in 1 min) [12] and can be interpreted as a proxy-indicator of walking intensity [11–14]. Increasing research has studied this parameter in healthy adults [11–14], and has shown that walking cadence decreases with age, with normative values for older adults ranging between <22 and >85 steps·min^{-1} (lower and uppermost quintiles, respectively) [13]. In COPD, individuals have reported "how fast they walk" as a meaningful aspect of their health [15, 16] and, thus, research has recently started to measure cadence. Regrettably, walking cadence in COPD has to date only been assessed during limited periods of time [17] and under controlled conditions, *i.e.* during clinical and laboratory tests of gait performance [8], thus providing information on individuals' walking capacity. No evidence is available yet on walking cadence in people with COPD under non-supervised daily-life conditions, *i.e.* real-world walking behaviour.

We aimed to characterise real-world walking cadence in COPD, assessing its level, within-person and between-person variability, relation with relevant clinical and functional COPD characteristics, and association with the risk of severe exacerbations. We hypothesise that given the reduced amount of walking performed by people with COPD and its association with a worse disease status [8], real-world walking cadence may also be impaired, and inversely associated with disease severity and exacerbations risk. Our results will provide further evidence for the clinical validity of walking cadence as a prognostic marker in COPD.

Methods

Study design and participants

We pooled individual participant data from two prospective cohort studies with a 12-month follow-up period: 1) the PROactive validation study (ClinicalTrials.gov: NCT01388218) [18, 19], which recruited people with COPD from primary care settings, rehabilitation centres and tertiary hospitals in five European cities (Athens, Edinburgh, Groningen, Leuven and London); and 2) the Urban Training study (ClinicalTrials.gov: NCT01897298) [20], which enrolled people with COPD from primary care and tertiary hospitals in five Catalan seaside municipalities (Badalona, Barcelona, Mataró, Viladecans and Gavà). Both studies diagnosed COPD according to the guidelines from the American Thoracic Society and European Respiratory Society (ERS) [21]. More details on eligibility criteria and characteristics of study participants are available in the supplementary methods and table S1. For this analysis, we excluded exacerbated participants at baseline (n=10) and participants who had no valid measure of walking cadence at baseline (n=40), resulting in a final sample of 593 clinically stable participants (92% of the original sample).

Both studies were approved by the ethics committees of all participating centres. Written informed consent, including re-utilisation of data for COPD-related research, was obtained from all participants.

Variables and instruments

The following data were collected at baseline, and pre-randomisation in the case of the Urban Training study, so that the intervention would not affect the characterisation of walking cadence. Walking was objectively measured in both studies using the DynaPort accelerometer (McRoberts, The Hague, the Netherlands) positioned on the lower back for 7 days. A valid measurement was defined as a minimum of 3 days with at least 8 h of wearing time within waking hours [4], and compliance with the device was considered good or excellent, as previously published [18–20]. The recording covered all types of activities including indoor and outdoor walking. The main walking parameter considered for this analysis was purposeful real-world walking cadence (steps·min^{-1}), computed as the number of steps·day^{-1} during walking bouts longer than 10 s, divided by the total duration of walking bouts longer than 10 s. We chose

a threshold of 10 s to identify purposeful walking in line with the Mobilise-D consensus (supplementary methods) [22]. Other parameters derived from the accelerometer included total number of walking bouts longer than 10 s, daily steps (number of steps·day^{-1} during wearing time), time spent on moderate-to-vigorous physical activity (MVPA) (recorded as min·day^{-1}, defined as activity of >3 metabolic equivalent tasks), mean vector magnitude units per minute (VMU·min^{-1}, measured as the total VMU during wearing time divided by wearing time), walking time (min·day^{-1} during wearing time) and intensity during locomotion (m·s^{-2}). Physical activity experience (amount, difficulty and total scores) was assessed using the validated Clinical visit – PROactive Physical Activity in COPD (C-PPAC) tool [18, 23].

In both studies, participants answered interviewer and self-administered validated questionnaires including data on age, sex, marital status, education level, working status, smoking history, number of people living at home, breathlessness (modified Medical Research Council (mMRC) dyspnoea scale), health-related quality of life (HRQoL) (using the COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ)) and anxiety and depression symptoms (Hospital Anxiety and Depression Scale (HADS)). We obtained the post-bronchodilator forced expiratory volume in 1 s (FEV_1), forced volume capacity (FVC) and FEV_1/FVC ratio from spirometry [24]. COPD severity was classified using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification (1=mild, 2=moderate, 3=severe and 4=very severe) and retrofitted to the ABE group assessment taking into consideration symptoms and history of exacerbations [25]. 6-min walk distance (6MWD) was determined following standardised methodology [26]. Height, weight and body mass index were obtained by physical examination. The presence and number of severe COPD exacerbations (leading to hospital or emergency-room admission) [25] were recorded over one full year of follow-up from patient reports and medical records, and considered as separate outcomes in the analyses because they provide relevant and complementary information for individuals with COPD, health professionals and healthcare providers.

Statistical analysis

A full version of the statistical analysis is available in the supplementary methods. All statistical analyses were performed pooling the PROactive and Urban Training datasets [18–20] given the lack of differences between studies, as previously published [27], and using a complete case strategy to deal with missing data. Sample size was given by the objectives of the main studies, and we calculated that the statistical power was >99% to address our study objectives.

Sample characteristics are presented as absolute frequencies and percentages for categorical variables, and as mean±SD or median and 25th percentile to 75th percentile for continuous variables, depending on their distribution. To assess the within-person variability of walking cadence, we calculated the intraclass correlation coefficient (ICC) between days of the same individual in the subset of participants with exactly seven measures (*i.e.* 7 days). To assess the between-person variability of walking cadence, we calculated the SD because the data were normally distributed.

We estimated the association between several sociodemographic, clinical and functional characteristics (sex, age, height, FEV_1, FVC, GOLD classification, ABE group assessment, mMRC dyspnoea levels, CAT score, CCQ total score, HADS anxiety and depression scores, 6MWD, daily steps, time spent in MVPA, VMU·min^{-1}, walking time, intensity during locomotion, and C-PPAC amount, difficulty and total scores) and walking cadence using linear or fractional polynomial regression models, one exposure variable at a time, and including age, sex, height, number of walking bouts and, where applicable, daily steps, as covariates. We additionally studied the possible effect modification by daily steps in the aforementioned relations, *via* stratification ($\leqslant$ or >5000 steps·day^{-1}).

To estimate the association between walking cadence (at baseline) and COPD exacerbations during follow-up, we built multivariable logistic regression (outcome: any severe exacerbation during follow-up (yes/no)) and negative binomial regression (outcome: number of severe exacerbations during follow-up) models. We used directed acyclic graphs to identify potential confounders (age, sex, education level, FEV_1, dyspnoea, exercise capacity (6MWD), HRQoL (CAT and CCQ scores), depression (HADS-D score), number of walking bouts, amount of physical activity (daily steps), physical activity's experience and history of exacerbations) and to determine the minimum set of covariates required to adjust our models (supplementary figure S1). We selected covariates based on previous research [8, 28, 29] and on subject matter knowledge. Final models were adjusted for age, sex, FEV_1, number of walking bouts, daily steps, 6MWD, depression and history of exacerbations. As a *post hoc* analysis, we standardised continuous variables in the model and estimated their association with exacerbations, adjusting for age and sex, in order to compare the magnitude of the associations between walking cadence and other predictors of severe exacerbations.

TABLE 1 Baseline characteristics and severe exacerbation events during 12-month follow-up of 593 individuals with COPD from nine cities in five European countries

Characteristic	
Participants (n)	593
Study of origin	
PROactive validation study	191 (32.2)
Urban Training study	402 (67.8)
City of origin	
Athens	43 (7.3)
Edinburgh	34 (5.7)
Groningen	30 (5.1)
Leuven	47 (7.9)
London	37 (6.2)
Badalona	28 (4.7)
Barcelona	182 (30.7)
Mataró	73 (12.3)
Viladecans	119 (20.1)
Male	476 (80.3)
Age (years)	68.3±8.5
Height (cm)	166.3±8.1
BMI (kg·m^{-2})	28.1±5.0
BMI category	
Underweight	26 (4.4)
Normal weight	136 (22.9)
Overweight	243 (41.0)
Obese	188 (31.7)
Current smoker	127 (21.4)
Smoking pack-years[#]	48 (30–80)
Oxygen at home	48 (8.1)
Marital status: married[#]	429 (72.6)
Living alone	142 (24.0)
Education level: high school/university[#]	280 (47.3)
Work status: retired	477 (80.4)
FEV_1 (% pred)	57.5±18.6
FVC (% pred)	83.4±19.9
Airflow limitation	
GOLD 1 mild (FEV_1⩾80% pred)	69 (11.6)
GOLD 2 moderate (50%⩽FEV_1<80% pred)	304 (51.3)
GOLD 3 severe (30%⩽FEV_1<50% pred)	176 (29.7)
GOLD 4 very severe (FEV_1<30% pred)	44 (7.4)
GOLD classification (ABE groups, 2023)[#]	
Group A (low symptom severity, low exacerbation risk)	165 (28.3)
Group B (high symptom severity, low exacerbation risk)	318 (54.6)
Group E (high exacerbation risk)	99 (17.0)
6-min walk distance (m)[#]	470.8±107.4
Dyspnoea (mMRC grade 0–4)	1 (1–2)
HRQoL (CAT score 0–40)[#]	12 (7–18)
HRQoL (CCQ scores 0–6)[#]	
Total score	1.3 (0.8–2.2)
Symptoms	1.5 (1–2.3)
Mental	1 (0–2)
Functional	1.3 (0.5–2.3)
HADS Anxiety (score 0–21)[#]	4 (2–8)
HADS Depression (score 0–21)[#]	3 (1–6)
Number of walking bouts >10 s	101.8±54.3
Steps (steps·day^{-1})[#]	6881±3926
Walking time (min·day^{-1})[#]	80.3±41.1
Time in MVPA (min·day^{-1})[#]	100.2±47.8
VMU (VMU·min^{-1})[#]	441.5±288.1
Intensity during locomotion (m·s^{-2})[#]	1.9±0.3
Sedentary time (min·day^{-1})[#]	629.2±110.8

Continued

TABLE 1 Continued

Characteristic	
Physical activity experience (C-PPAC scores, 0–100)	
Amount[#]	69.4±16.6
Difficulty[#]	78.6±15.5
Total score[#]	74.2±13.2
Any severe exacerbations in the 12 months prior to study inclusion[#]	51 (8.8)
Any severe exacerbations during 12-month follow-up (yes)[#]	44 (10.2)
Severe exacerbations during 12-month follow-up[#]	
None	387 (89.8)
1 exacerbation	35 (8.1)
2 exacerbations	5 (1.2)
⩾3 exacerbations	4 (0.9)

Data are presented as median (25th–75th percentile), mean±SD or n (%), unless otherwise stated. BMI: body mass index; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit – PROactive Physical Activity in COPD; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS: Hospital Anxiety and Depression scale; HRQoL: health-related quality of life; mMRC: modified Medical Research Council scale; MVPA: moderate-to-vigorous physical activity; VMU: vector magnitude units. [#]: missing values: two in pack-years; one in education level; one in marital status; 11 in GOLD ABE assessment scheme; one in 6-min walk distance; one in CAT score; three in CCQ variables; three in HADS Anxiety; five in HADS Depression; 13 in physical activity variables; 116 in C-PPAC amount; 100 in C-PPAC difficulty; 117 in C-PPAC total score; 11 in history of severe exacerbations in the prior 12 months; 162 in severe exacerbations (presence and number) during 12-month follow-up.

Sensitivity analyses were conducted: 1) excluding females, to indirectly check for any potential effect modification by sex; 2) using mixed-effects models to account for the potential correlation between subjects within the same city of origin as a random intercept.

We tested goodness of fit of final models. All analyses were conducted in Stata SE 14.0 (StataCorp, College Station, TX, USA).

Results

A total of 593 individuals with COPD were included in this analysis (32% from PROactive and 68% from Urban Training). A majority was male (80%) and the cohort had a mean±SD age of 68±8 years and height of 166±8 cm. On spirometry, 12% of participants had mild (GOLD 1), 51% moderate (GOLD 2), 30% severe (GOLD 3) and 7% very severe (GOLD 4) COPD. According to the ABE group assessment, 28% of participants were GOLD A, 55% were GOLD B and 17% were GOLD E. Participants walked 6880±3926 steps daily and spent a mean of almost 80 min per day walking (table 1).

Walking cadence was highly stable within participants (ICC 0.92, 95% CI 0.90–0.93) and followed a normal distribution with mean±SD of 88±9 steps·min^{-1}, with minimum and maximum values of 44 and 114 steps·min^{-1}, respectively (figure 1). Walking cadence was higher in females than in males (89±10 *versus* 88±9 steps·min^{-1}, p=0.183), and was inversely related with age, height and disease severity measured by the GOLD classification and ABE group assessment (supplementary figure S2, all p<0.05).

Walking cadence was associated in a monotonic nonlinear way with higher FEV_1, lower mMRC dyspnoea score, better CAT and CCQ scores, lower HADS-D score, higher 6MWD, higher daily steps, higher time in MVPA, higher VMU·min^{-1}, higher walking time, higher intensity during locomotion, and better experience of physical activity amount and difficulty (all p<0.05, figure 2). After adjustment for age, sex, height and number of walking bouts, all associations remained significant. After additional adjustment for steps, most associations remained significant except for those with CAT and CCQ. FVC and anxiety showed no association with walking cadence (figure 2 and supplementary table S2). Similar associations were observed after stratification according to daily steps, and when considering only the subset of males (supplementary table S2 and figure S3).

During 12-month follow-up, 44 participants (10%) had at least one severe exacerbation. After adjusting for age, sex, number of walking bouts, daily steps, FEV_1, 6MWD, depression and history of exacerbations, a higher walking cadence was not significantly associated with a lower risk of severe exacerbation (adjusted

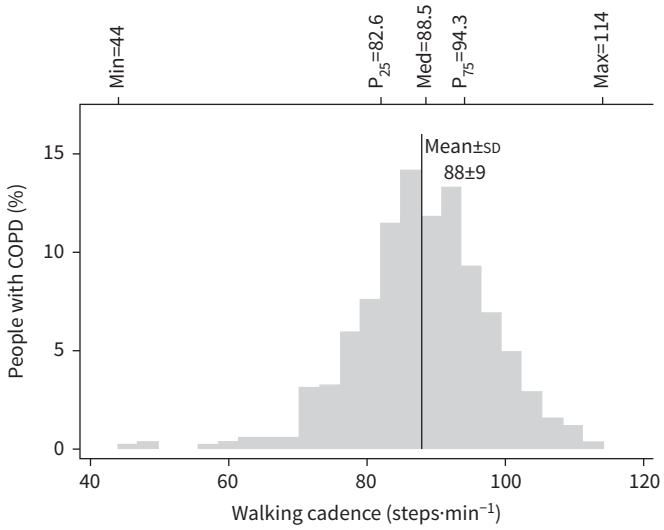

FIGURE 1 Real-world walking cadence in 593 individuals with COPD. Min: minimum; P_{25}: 25th percentile; Med: median; P_{75}: 75th percentile; Max: maximum.

OR 0.97 per step·min^{-1}, 95% CI 0.92–1.01 per step·min^{-1}, p=0.158) but was significantly associated with a lower number of severe exacerbations during follow-up (adjusted incidence rate ratio 0.94 per step·min^{-1}, 95% CI 0.91–0.99, p=0.009) (table 2 and supplementary tables S3 and S4). The *post hoc* analysis standardising walking cadence and other covariates showed that the ability to predict the risk or the number of severe exacerbations of walking cadence was higher than that of daily steps, although lower than that of FEV_1 and 6MWD (supplementary table S5 and S6). Sensitivity analyses considering only the subset of males (supplementary table S7) or using mixed-effect models (supplementary table S8) showed very similar estimates.

Discussion

The main findings of this study are as follows: 1) walking cadence is highly stable within person and normally distributed in people with COPD; 2) important clinical and functional characteristics of COPD, including the severity of airflow limitation, dyspnoea, exercise capacity, physical activity levels and physical activity experience are associated with real-world walking cadence in monotonic yet nonlinear relationships; and 3) a higher real-world walking cadence is associated with a lower number of severe exacerbations during 12 months in a multivariable analysis adjusted for confounders including disease severity and amount of physical activity.

The observed real-world walking cadence followed a normal distribution, with a mean walking cadence of 88±9 steps·min^{-1}, which, according to the literature, falls into the normative values (75th centile) for older adults [13] and would qualify as a medium pace of walking (80–99 steps·min^{-1}) [12, 13]. Our reported walking cadence values are lower than those shown under controlled conditions for people with COPD with similar clinical and demographic characteristics (between 99 and 119 steps·min^{-1}) [17, 28, 30, 31], but similar to those shown under simulated and guided free-living assessments (between 84 and 89 steps·min^{-1}) [17, 32]. This suggests a difference between the constrained behaviour during laboratory tests and the real-world walking behaviour in unsupervised settings. In addition, our observed values were lower than those reported for the real-world walking cadence of healthy younger adults [11], but similar to those reported among older adults [17] and individuals with heart failure, cardiac dysrhythmias [33] and obesity [34] or after a stroke [35]. This is in agreement with the notion that a real-world walking cadence of moderate intensity (*i.e.* ⩾100 steps·min^{-1}) [14] is difficult at older ages and in the presence of chronic conditions [11, 13, 36]. Of note, any comparisons of our findings with previous data should be interpreted with caution, given that former studies have estimated cadence levels from either peak performance values [13, 33], raw uncensored data (which includes incidental and sporadic movement) [12, 36] or constrained real-world data [17]. Our focus on the intentional component of walking (*i.e.* purposeful walking), by computing a daily average for walking bouts longer than 10 s [22], is a step beyond most previous studies, but requires replication in order to confirm its utility as a standardised metric to assess real-world walking cadence [12].

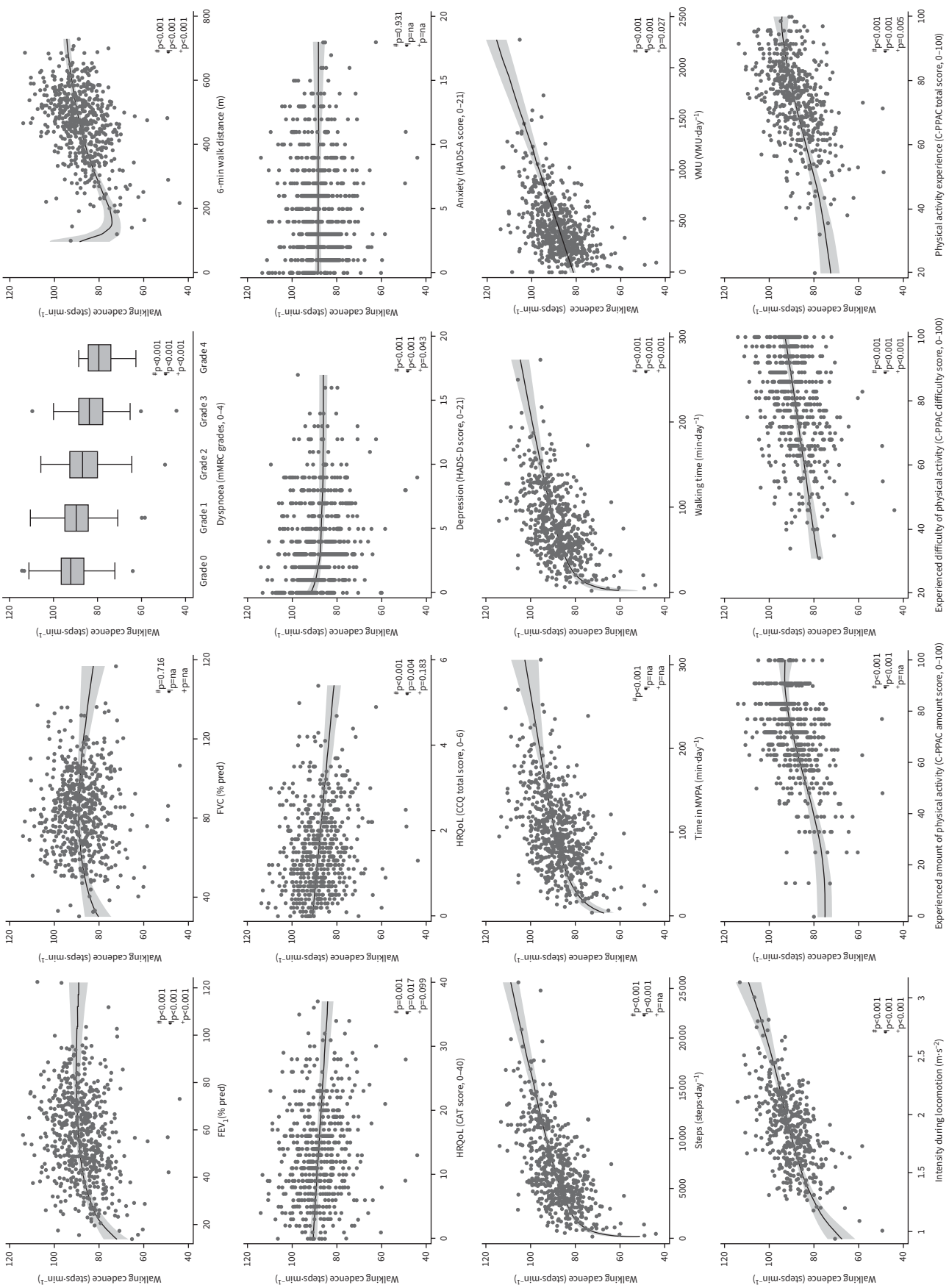
Walking cadence (steps·min⁻¹)
6-min walk distance (m)
Anxiety (HADS-A score, 0–21)
VMU (VMU·day⁻¹)
Physical activity experience (C-PPAC total score, 0–100)
Dyspnoea (mMRC grades, 0–4)
Grade 0
Grade 1
Grade 2
Grade 3
Grade 4
Depression (HADS-D score, 0–21)
Walking time (min·day⁻¹)
Experienced difficulty of physical activity (C-PPAC difficulty score, 0–100)
FVC (% pred)
HRQoL (CCQ total score, 0–6)
Time in MVPA (min·day⁻¹)
Experienced amount of physical activity (C-PPAC amount score, 0–100)
FEV1 (% pred)
HRQoL (CAT score, 0–40)
Steps (steps·day⁻¹)
Intensity during locomotion (m·s⁻²)

FIGURE 2 Unadjusted and adjusted associations between clinical measures of COPD and real-world walking cadence, with p-values reported from linear regressions or fractional polynomial regressions. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; mMRC: modified Medical Research Council scale; HRQoL: health-related quality of life; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; HADS-D/A: Hospital Anxiety and Depression scale – Depression/Anxiety; MVPA: moderate-to-vigorous physical activity; VMU: vector magnitude units; C-PPAC: Clinical visit – PROactive Physical Activity in COPD; na: not applicable. #: unadjusted p-value; ¶: p-value adjusted for age, sex, height and number of walking bouts; +: p-value adjusted for age, sex, height, number of walking bouts and steps.

We observed that COPD severity, assessed according to a range of parameters, was associated with a lower walking cadence after correcting for age, sex, height, number of walking bouts and, importantly, daily steps. More specifically, we found that lower FEV_1, higher dyspnoea levels, shorter 6MWD, more symptoms related to depression, lower physical activity and worse physical activity experience were significantly related to lower values of walking cadence. These results are consistent with previous studies showing that, under controlled conditions, patients with more severe COPD walk at a lower cadence compared to patients with milder disease severity [28, 29, 31]. Interestingly, the relations observed herein exhibited monotonic yet nonlinear trends with weaker (or a lack of) association in mild COPD. Our findings could be explained by the reduced functional capacity observed in people with COPD caused by different mechanisms, acting alone or in conjunction, including 1) airflow limitation and lack of systemic oxygen delivery [29, 31]; 2) the musculoskeletal effects of COPD (*e.g.* greater limb muscle weakness and dysfunction, neuromuscular fatigability) [31, 37, 38], more common in more severe stages of the disease [37, 39]; and 3) (mobility-impairing) comorbidities, whose number increase with disease severity [40]. Further investigation will provide a better understanding of the specific mechanisms connecting clinically relevant COPD characteristics with walking cadence.

To our knowledge, this is the first study to show that a higher real-world walking cadence is prospectively related to a lower number of severe exacerbations (up to 12 months), even after disease severity, amount of physical activity and exacerbation risk are taken into consideration. Moreover, after standardisation, walking cadence seemed to have a higher ability to predict the risk and number of severe exacerbations than daily steps. Although our novel finding requires replication, it suggests that more intense real-world walking (*i.e.* a higher walking cadence) may reduce the risk of future hospitalisations, irrespective of the number of daily steps walked. This interpretation, however, should be treated with caution in light of a previous study reporting that a higher number of daily steps related to lower risk of severe exacerbations only when the average intensity levels were low [41]. However, the use of different surrogate measures of intensity hinders direct comparison between studies for different reasons. First, by considering walking bouts lasting less than 1 min in the calculation of walking cadence, our measure is more granular and representative of real-world behaviour in patients with overall limited exercise capacity than the one used in the previous study. Second, our measure of walking intensity does not consider intensity during other types of physical activities (*e.g.* cycling, weight lifting), which were included in the previous study. Thus, the intensity categories identified by both studies may not match, which would explain their different findings. Future research using specific, precise characterisation of the intensity of different physical activities is needed to understand these apparently conflicting results and the role of physical activity intensity in COPD progression.

Our results are of interest for clinical research, medical practice and public health. In line with previous research highlighting the importance of walking changes for individuals living with mobility-impairing conditions, our results provide the first proof that real-world walking cadence is affected and affects the

TABLE 2 Association between walking cadence at baseline and severe exacerbations during 12-month follow-up (logistic and negative binomial regressions)

	Unadjusted		Adjusted#	
Outcome: any severe exacerbation during 12-month follow-up (logistic regression)	**OR¶ (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Walking cadence (steps·min^{-1})	0.95 (0.92–0.98)	0.001	0.97 (0.92–1.01)	0.158
Outcome: number of severe exacerbations during 12-month follow-up (negative binomial regression)	**IRR+ (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Walking cadence (steps·min^{-1})	0.94 (0.91–0.97)	<0.001	0.94 (0.91–0.99)	0.009

Full model is available in the supplementary material. #: adjusted for age, sex, forced expiratory volume in 1 s, depression, 6-min walk distance, daily steps, number of walking bouts and history of exacerbations at baseline; ¶: odds ratio (OR) can be interpreted as the change in the odds of having at least one severe exacerbation during one year per each increase of 1 step·min^{-1} in walking cadence; +: incidence rate ratio (IRR) can be interpreted as the change in the yearly rate of severe exacerbations per each increase of 1 step·min^{-1} in walking cadence.

clinical and functional status of people with COPD. We propose walking cadence as a parameter that could provide complementary information to that offered by traditional physical activity parameters, but further research is needed in the field. The association between COPD severity and higher risk of exacerbations with a lower walking cadence highlights the potential of real-world walking cadence as a prognostic marker in observational COPD research, and eventually as an outcome measure in pharmacological and nonpharmacological clinical trials [11, 12]. The simplicity of measurement and interpretation of walking cadence make it feasible for assessing in regular clinical practice, providing relevant information on disease status, and it should be considered while developing pulmonary rehabilitation and physical activity programmes. Last but not least, our findings could also be relevant in the development of public health interventions aimed at improving disease status through walking. For instance, interventions using rhythmic auditory cues or music to stimulate individuals to reach a higher walking cadence (*i.e.* higher walking intensity) [12, 42] may help people with COPD to unconsciously walk faster and reduce the risk of future severe exacerbations.

Strengths of our study are as follows: first, the novelty of our approach to characterise real-world walking cadence in people with COPD, using objective measures provided by accelerometer data and a purposeful walking approach; second, the recruitment of participants in primary care settings, rehabilitation centres and tertiary hospitals, thus providing a wide spectrum of COPD severity and increasing the external validity of our findings; and third, the inclusion of participants from diverse geographical locations, improving representation of the COPD population.

Our analysis also has a few shortcomings. First, our characterisation of real-world walking cadence is based on a sample of individuals with relatively stable COPD (only 10% had a severe exacerbation during follow-up) and may not be representative of more severe cases. Second, the low percentage of female participants in our study (19.7%) precluded us from performing sex-stratified analysis. However, when all analyses were repeated only in the male subsample, results were virtually identical to that of the full group. Third, the lack of quadricep strength measures in one of the studies prevented us from assessing a potential association between walking cadence and muscle weakness in COPD. Fourth, despite the well-known importance of moderate exacerbations for clinical outcomes in COPD, we could not use this variable in the present analysis because the information was not collected in the PROactive study, given the high heterogeneity in the reporting of moderate exacerbations across the different health systems in Europe, and the fact that moderate exacerbations were not considered in the original research questions of that study. Fifth, real-world walking cadence may be affected by environmental factors (*e.g.* housing characteristics, meteorological conditions), which were not assessed or controlled for in the present study, and ought to be the focus of future research. Finally, the lack of a control group could be seen as a limitation because we could not investigate differences in the walking cadence between people with COPD and healthy controls. However, this was not the objective of the current manuscript.

Conclusion

Higher real-world walking cadence is associated with better COPD status and a lower risk of severe exacerbations. This makes this parameter attractive as a prognostic marker and eventually as an outcome measure for clinical trials in COPD.

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Conflict of interest: N. Karlsson reports owning stock in AstraZeneca, of which they are an employee; discourse made outside the submitted work. L. Palmerini reports being the co-founder of mHealth Technologies srl and owns shares of mHealth Technologies srl; disclosures made outside the submitted work. M.I. Polkey reports receiving consulting fees from Philips Respironics, outside the submitted work. D.A. Rodríguez Chiaradia reports grants or contracts from Janssen and Ferrer; consulting fees from Ferrer; payments for lectures, presentations, speakers bureaus, manuscript writing or educational events from Ferrer and Janssen; support for attending meetings and/or travel from Ferrer, MSD and Janssen; and participation on a Data Safety Monitoring Board or Advisory Board for Janssen, all outside the submitted work. R. Rodriguez-Roisin reports grants or contracts from Chiesi and Beyond Air NO, outside the submitted work. I. Vogiatzis is an associate editor of this journal. T. Troosters reports grants or contracts from Mobilise-D IHI funding, outside the submitted work. The remaining authors have nothing to disclose.

Ethics statement: This study pools data from two individual studies. Both studies were approved by the ethics committees of all participating centres. Written informed consent, including re-utilisation of data for COPD-related research, was obtained from all participants.

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