Associated factors of fatigue in patients with COPD: results from the FAntasTIGUE study

Maarten Van Herck[1,2,3,4], Yvonne M.J. Goërtz[5], Zjala Ebadi[6,7], Chris Burtin[3], Jeannette B. Peters[7], Melissa S.Y. Thong[8], Rein Posthuma[1,2,4], Jean W.M. Muris[9], Erik W.M.A. Bischoff[10], Emiel F.M. Wouters[2,11], Mirjam A.G. Sprangers[8,12], Jan H. Vercoulen[6,7], Daisy J.A. Janssen[1,5,9] and Martijn A. Spruit[1,2]

[1]Department of Research and Education, Ciro, Horn, the Netherlands. [2]Department of Respiratory Medicine, School of Nutrition and Translational Research in Metabolism (NUTRIM), Faculty of Health, Medicine, and Life Sciences, Maastricht University Medical Centre+, Maastricht, the Netherlands. [3]REVAL – Rehabilitation Research Center, BIOMED – Biomedical Research Institute, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium. [4]Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands. [5]Department of Health Services Research, Care and Public Health Research Institute, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands. [6]Department of Medical Psychology, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands. [7]Department of Pulmonary Diseases, Radboud University Medical Center, Nijmegen, The Netherlands. [8]Department of Medical Psychology, Amsterdam UMC Location University of Amsterdam, Medical Psychology, Amsterdam, the Netherlands. [9]Department of Family Medicine, Care and Public Health Research Institute, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands. [10]Department of Primary and Community Care, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands. [11]Ludwig Boltzmann Institute for Lung Health, Vienna, Austria. [12]Mental Health, Amsterdam Public Health, Amsterdam, The Netherlands.

Corresponding author: Maarten Van Herck (maarten.vanherck@uhasselt.be)

Shareable abstract (@ERSpublications)
Worse dyspnoea, reduced sleep quality, worse fatigue catastrophising and worse pain are associated with worse fatigue in COPD. These findings provide a rationale for the screening for and treatment of these factors present in a fatigued COPD patient. https://bit.ly/4bNrcLK

Cite this article as: Van Herck M, Goërtz YMJ, Ebadi Z, *et al*. Associated factors of fatigue in patients with COPD: results from the FAntasTIGUE study. *ERJ Open Res* 2025; 11: 00857-2024 [DOI: 10.1183/23120541.00857-2024].

Received: 25 Aug 2024
Accepted: 26 Feb 2025

Abstract

Background Fatigue is present in about half of the patients with COPD. The associated factors of fatigue in COPD remain unclear and have not been studied in an integrated and holistic analysis. The aim of this study is to identify associated factors of fatigue in COPD.

Methods In this cross-sectional study, clinically stable patients with COPD from primary and secondary care were assessed for fatigue (Checklist Individual Strength Subjective Fatigue (CIS-Fatigue)), other symptoms, medication, and personal, COPD-related, physical, psychological and systemic factors. Multivariable stepwise regression analyses were performed for each domain, followed by a multivariable (enter) model with all identified factors.

Results In total, 247 patients with COPD (67±8 years, 60% male, forced expiratory volume in 1 s 57±21% predicted, 27% Global Initiative for Chronic Obstructive Lung Disease (GOLD) E) were included in the study of which 51% reported severe fatigue (CIS-Fatigue ⩾36 points). Distinct models for each group of factors identified the following factors associated with a higher level of fatigue: living alone, antidepressant use, anxiolytic use, systemic antihistamines use, higher Charlson comorbidity score, lower diffusion capacity, higher number of moderate exacerbations in the last year, higher dyspnoea, reduced sleep quality, higher pain, lower functional exercise capacity, higher fatigue-related catastrophising, more depressive symptoms, lower calcium and higher leukocyte count. The final model explained 46.6% of variance in fatigue with dyspnoea, sleep quality, fatigue-catastrophising and pain as significant associated factors ($F(17, 184)=11.312$, $p<0.001$).

Conclusion Pain, sleep quality, dyspnoea and fatigue-catastrophising were identified as associated factors of fatigue. These factors should not be overlooked when treating fatigue in patients with COPD.

Introduction

People diagnosed with COPD experience a range of pulmonary and extrapulmonary symptoms [1]. Fatigue, defined as "a subjective, unpleasant symptom which incorporates total body feelings ranging from

tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity" [2], affects around 30–70% of people with COPD [3]. Fatigue is, next to dyspnoea, the most common symptom in COPD [4]. These symptoms are related [5] and have a major impact on health status, quality of life and the ability to perform day-to-day activities [6, 7]. Despite being highly prevalent, fatigue is often underdiagnosed and undertreated in clinical practice [8, 9]. Importantly, treatment options for fatigue in COPD are scarce, partly because fatigue and its associated factors remain poorly understood. It is expected that multiple factors play a role in fatigue in COPD, further complicating its treatment [9]. Therefore, related factors of fatigue need to be identified to empower health professionals to design and tailor the optimal treatment for fatigue to the individual patient. A recent systematic review summarised the literature related to fatigue in COPD and found that the degree of airflow limitation is poorly related to fatigue in COPD and, therefore, does not appear to be the primary underlying cause of fatigue. Instead, the review identified a wide range of associated factors including dyspnoea, number of exacerbations, exercise capacity, peripheral muscle strength, quality of life, symptoms of anxiety and depression, and systemic factors such as the number of medications and comorbidities. However, the associations between these factors and fatigue have mostly been studied in isolation, making it difficult to understand the complex, multifactorial nature of fatigue in COPD [3].

A study that integrates variables from different domains that have been consistently shown to be associated with fatigue in an integrated and holistic analysis is lacking [3]. To address this, the objective of this study is to identify symptoms, medication, and personal, COPD-related, physical, psychological and systemic factors that are associated with fatigue in COPD.

Methods

Study design and recruitment

The present study is a cross-sectional analysis of baseline data from the multicentre, longitudinal, observational FAntasTIGUE study. A detailed description of the FAntasTIGUE study has been published elsewhere [10]. Briefly, patients with clinically stable COPD were recruited from April 2018 to June 2021 at the outpatient clinics of the Department of Respiratory Medicine in Maastricht and the Department of Pulmonary Diseases in Nijmegen, and *via* general practitioners (Research Network Family Medicine Maastricht, and the General Practice Research Network of the Radboud University Medical Center Nijmegen). Further, patients with COPD who attended a meeting for patients with chronic lung diseases (the so-called "longpunt") in Maastricht or Nijmegen, and patients recruited from primary and secondary care who previously participated in the Chance Study (NTR3416), inclusion period of the Chance Study was from 2012 to 2015, and who consented to be approached for follow-up research, were also invited to take part in the FAntasTIGUE study between April 2018 and June 2021. Written informed consent was obtained from all study participants.

Study participants

The eligibility criteria are published elsewhere [10]. In short, a doctor-diagnosis of COPD and stable COPD for at least 4 weeks preceding enrolment was required (*i.e.*, no exacerbation that required additional treatment with oral corticosteroids and/or antibiotics or exacerbation-related hospitalisation; a moderate or severe exacerbation, respectively). Further, participants were excluded from the current analyses if they had a forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio $\geqslant$0.7 at assessment [11], or data regarding sex, age or fatigue (*i.e.*, Checklist Individual Strength – subscale subjective fatigue (CIS-Fatigue)) were missing.

Outcomes

Participants came to the hospital for in-person assessments and an interview. At the end of the hospital visit a comprehensive questionnaire was distributed, which participants returned within 1 week after the in-person assessment. The choice of factors assessed in the FAntasTIGUE study was based on existing literature [3], expert opinion from the FAntasTIGUE partners, practical considerations and guidance from patient representatives, ensuring a comprehensive yet feasible approach.

Primary outcome

Subjective fatigue was measured by the CIS-Fatigue, consisting of eight items scored on a seven-point Likert scale. The total score ranges from 8 (No/normal fatigue) to 56 points (Most severe fatigue). A score of $\geqslant$36 points indicates severe fatigue [12]. The CIS-Fatigue is a standardised and validated questionnaire that has been used in healthy subjects and various patient populations, including COPD [6, 13].

Other measures

Demographical and clinical characteristics (age, sex, generic health status using the 5-level EuroQol 5-dimension and COPD-related health status using the COPD Assessment Test (CAT)) were assessed to characterise the study population. Further, potential associated factors of fatigue are grouped per domain as symptoms, medication, and personal, COPD-related, physical, psychological and systemic factors. Detailed information and explanation regarding the variables, cut-off scores, references, and a detailed description of the assessment procedures and outcome measures is reported in the online supplementary methods.

Personal factors

The personal factors assessed included living alone (yes/no), smoking status (yes/no current smoker) and smoking history (pack-years), Charlson comorbidity index, socioeconomic status, alcohol consumer (yes/no) and consumption, and caffeine consumer (yes/no) and consumption.

COPD-related factors

The COPD-related factors assessed included use of long-term oxygen therapy, number of moderate exacerbations and exacerbation-related hospitalisations in the previous 12 months, and pulmonary function testing (*i.e.*, spirometry, body plethysmography and diffusion capacity using single breath method).

Physical factors

The physical factors assessed included body composition (body mass index), fat-free mass index (*via* bioelectrical impedance analyses), functional exercise capacity (6-minute walking distance), physical activity and sedentary behaviour (Actigraph GT9X link), muscle function (quadriceps and handgrip strength), and physical frailty (Short Physical Performance Battery).

Psychological factors

The psychological factors assessed included symptoms of anxiety and depression (Hospital Anxiety and Depression Scale), social support (34-item Social Support List, Interaction version), fear of disease progression (Fear of Progression Questionnaire Short Form), and fatigue-catastrophising (*i.e.*, having a negative association with fatigue; Jacobsen Fatigue Catastrophising Scale).

Symptoms

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). The symptoms cough, insomnia, pain and dyspnoea were assessed using a visual analogue scale (VAS). In addition, dyspnoea during activities of daily living (ADL) was assessed using the modified Medical Research Council Dyspnoea Scale (mMRC dyspnoea).

Medication

Medication intake was recorded *via* interviewing. The amount of different medications taken by a patient was calculated. Further, medication related to COPD treatment and/or known because of fatigue as a potential side-effect were grouped based on their mechanism of action. The latter was determined by a health scientist (M. Van Herck) and physician (D.J.A. Janssen) involved in the study.

Systemic factors

A fasting venous blood sample was taken and analysed for inflammatory markers, haematology, clinical blood chemistry, cardiac diagnostics, endocrinology and antinuclear antibodies. Information on the systemic factors and the cut-off points used to define (ab)normal values can be found in supplementary table 1.

Statistical analysis

Descriptive statistics were presented for the total group. Data were reported as means and standard deviations, medians and interquartile ranges, or frequencies and proportions, as appropriate.

Stepwise multivariable regression analyses were performed to assess associated factors of fatigue. This was done per domain of variables (*i.e.*, medication, symptoms, and personal, COPD-related, physical, psychological and systemic factors) to restrict the number of variables per model [14]. Of note: the medication model only includes medication that has fatigue as a potential side-effect. Finally, all significant variables of the different separate models were entered in one multivariable regression model (enter method) to identify independent associated factors of fatigue. All models were adjusted for age and sex. Therefore, absolute values are used in the models. Variables with >40% missing were discarded. If multicollinearity was present (variance inflation factor >5), variables were identified and one of the related variables was removed from the model, as specified in supplementary table 2.

The level of significance was 0.05. Statistical analyses were performed using SPSS v28.0 (IBM Corp., Armonk, NY, USA). Visualisations were made using Graphpad Prism 9.3.1 (GraphPad Software, La Jolla, CA, USA).

Results

Initially, 557 persons showed interest in the FAntasTIGUE study. Main reasons for non-participation were lost interest (n=61) and finding the entire longitudinal study, including follow-up and assessments, too burdensome (n=132). In total, 260 doctor-diagnosed patients with COPD participated in the study. Patients were excluded from the current analysis as they had a FEV_1/FVC ⩾0.7 at assessment (n=3) or incomplete data regarding fatigue (n=10). Overall, 247 patients with COPD were included in the current analyses (figure 1).

Patients had a mean±SD age of 67±8 years and 40% (n=100) were women. The median (IQR) Charlson comorbidity score was 2 (1–3) points, and the median mMRC dyspnoea grade was 1 (0–2) with 41% (n=98) being highly dyspnoeic during ADL (mMRC dyspnoea grade ⩾2). The majority (n=184, 74%) had a moderate-to-severe airflow limitation, 9% (n=23) received long-term oxygen therapy and 27% (n=66) were classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) E. More specifically, 11% (n=27) of patients had ⩾1 exacerbation-related hospitalisation and 41% (n=100) ⩾1 moderate exacerbation within the past 12 months. Median patients' current perceived health (*i.e.*, EQVAS) was 70 (50–83) points, and they had an average CAT score of 17±8 points. A detailed description of all variables that were assessed can be found in table 1.

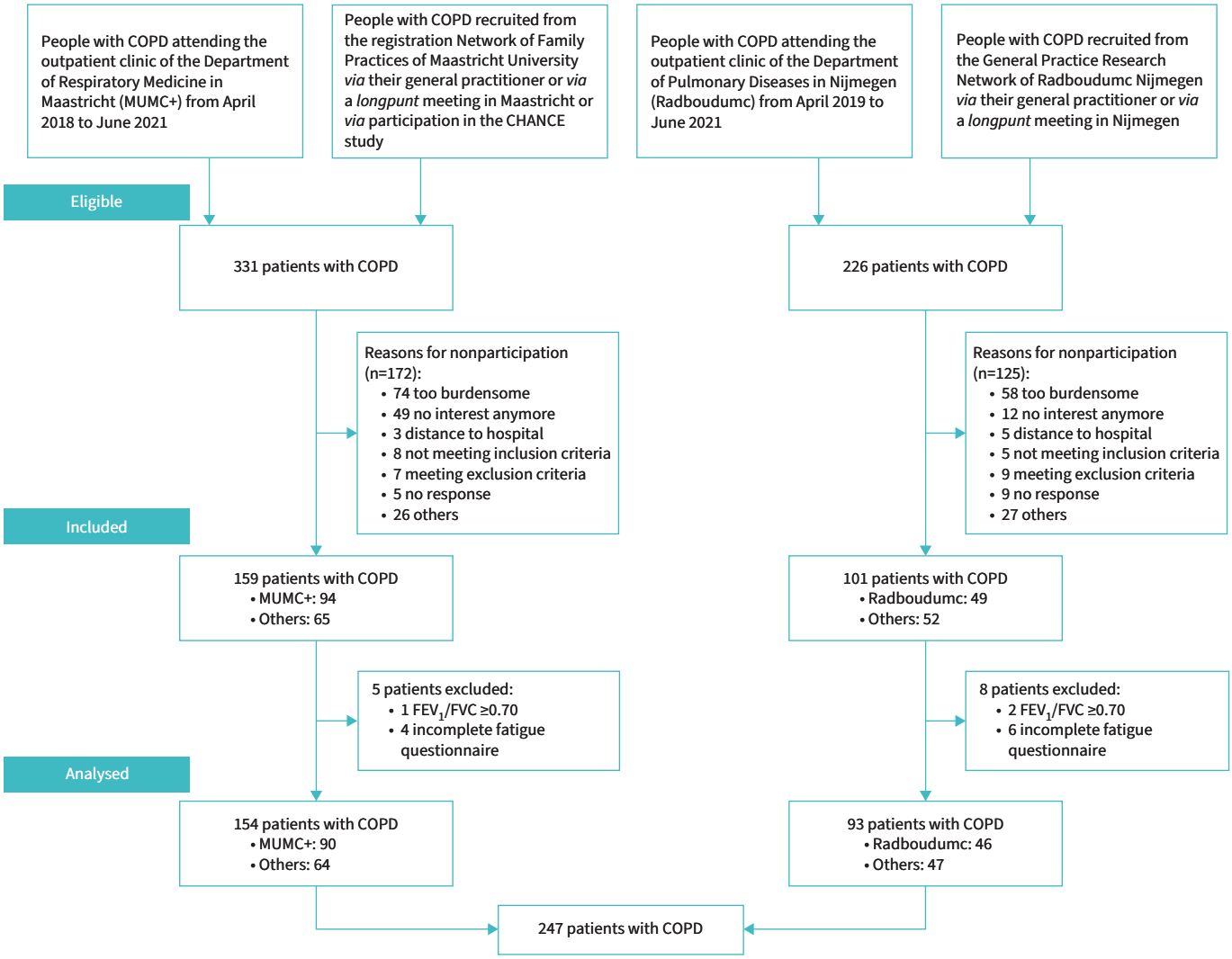

FIGURE 1 Flowchart of study population. FEV_1/FVC: forced expiratory volume in 1 s to forced vital capacity ratio.

Prevalence of severe fatigue

Patients with COPD had a mean CIS-Fatigue score of 36±13 points, and 51% (n=126) of patients were classified as having severe fatigue.

Associated factors of fatigue per domain

Distinct models for each domain of associated factors (supplementary table S2A–G) identified the following factors associated with a higher level of fatigue, 1) Personal factors: living alone and a higher Charlson comorbidity score (adjusted R^2 4.6%); 2) COPD related-factors: lower diffusion capacity and higher number of moderate exacerbations in the last year (adjusted R^2 14.7%); 3) Symptoms: higher dyspnoea, reduced sleep quality and higher pain (adjusted R^2 38.2%); 4) Physical factors: lower functional exercise capacity (*i.e.*, 6-min walking distance; adjusted R^2 20.0%); 5) Psychological factors: higher fatigue-related catastrophising and more depressive symptoms (adjusted R^2 37.1%); 6) Systemic factors: lower calcium and higher leukocyte count (adjusted R^2 4.8%); and 7) Medication: antidepressant use, anxiolytic use and systemic antihistamines use (adjusted R^2 6.3%).

Associated factors of fatigue in one integrated model

The overall model with statistically significant variables of the separate models had an adjusted R^2 of 46.6% ($F(17, 184)=11.312$, $p<0.001$; table 2). From all variables included in the model, higher dyspnoea, reduced sleep quality, higher pain and higher fatigue-related catastrophising were significantly associated with higher fatigue in COPD. Dyspnoea and fatigue-related catastrophising were responsible for the largest unique contribution with a standardised beta of 0.20 and 0.18, respectively. A visual presentation of identified associated factors of fatigue in COPD per domain and in the integrated model are shown in figure 2.

Discussion

The present study is the first integrative analysis that includes an array of potentially associated factors of fatigue in patients with COPD in a large Dutch multicentre sample. Our findings demonstrate that fatigue is present in about half of patients with COPD recruited from primary and secondary care. Several variables were identified as associated factors of fatigue in distinct models per domain of factors, of which higher dyspnoea, reduced sleep quality, higher fatigue-catastrophising and higher pain were significantly associated with higher fatigue in the final model.

The prevalence of fatigue in our sample (51%) is similar to that reported in the literature [3, 6]. The current study also confirms that airflow limitation is poorly related with fatigue in COPD [3], and highlights the importance of looking beyond lung function measurements when searching for associated factors of fatigue in COPD.

About half of the variance of fatigue in our COPD sample is explained by our final model. Other studies that are powered to perform this analysis reported explained variances in fatigue ranging from 30% to 42% [5–7]. Dyspnoea is often identified in these studies as a related factor of fatigue [6, 7, 15], while some studies also identified variables like depressive mood [7, 15], physical symptoms [16], exercise capacity [17], muscle strength [18], end-exercise oxygen saturation [18], physical activity [15] and number of exacerbations in the last year [6, 15]. Most of these studies only included a certain set of factors. Our study is the first integrative analysis that includes a wide range of factors potentially related to fatigue in COPD. Nevertheless, about half of the variance in fatigue remains unexplained. That said, it should be mentioned that fatigue is subjective by nature and involves personal opinions, perceptions and feelings. By that fatigue may inherently have a level of variability from person to person as it is a complex interaction between biological, psychological and social factors. Thereby it is impossible to explain 100% of the variance. Furthermore, our sample size is limited considering the amount of potential variables, which has implications in terms of the power to detect significant findings [19]. Indeed, it is possible that the current model lacks certain factors, like personality traits such as neuroticism and low extraversion, or the influence of specific comorbidities (*e.g.*, heart failure, rheumatoid arthritis) on fatigue in COPD [20, 21].

This study identified a number of potential treatable factors to be related to fatigue, including dyspnoea, sleep quality, pain and fatigue-related catastrophising. The link between fatigue and dyspnoea has been studied extensively, and both symptoms are highly interrelated [3]. Similarly, other multivariable analyses have identified dyspnoea as an associated factor of fatigue [6, 16, 17]. Dyspnoea, together with fatigue-related catastrophising, had the strongest association with fatigue in the final model. The association between fatigue-related catastrophising and fatigue is a novel finding which has never been researched before in COPD, but has been established in patients with interstitial lung diseases and other populations [22, 23]. A possible explanation for this relationship is that catastrophising can worsen the

TABLE 1 Characteristics of total group for all measured variables per domain (n=247)

	n	Reported data
Male, n (%)	247	147 (59.5)
Age years	247	67.3±8.1
Subjective fatigue		
Subjective fatigue (CIS-Fatigue) points	247	36±13
Severe fatigue (CIS-Fatigue ⩾36), n (%)		126 (51.0)
Quality of life		
Perceived health (EQ5D5L – health VAS) points	244	70 (50–83)
Health status (EQ5Dindex) points	243	0.810 (0.660–0.896)
COPD-related health (CAT) points	242	17±8
Impaired COPD-related health (CAT ⩾18), n (%)		111 (45.9)
Personal factors		
Current smoker, n (%)	247	53 (21.5)
Smoking history pack-years	245	31 (15–51)
Charlson Comorbidity Index score (incl. COPD)	247	2 (1–3)
Living alone, n (%)	247	78 (31.6)
Socioeconomic status points	243	−0.12 (−0.77–0.68)
Current alcohol consumer, n (%)	247	160 (64.8)
Alcohol consumption units·week^{-1}		2 (0–10)
Current caffeine consumer, n (%)	247	225 (91.1)
Caffeine consumption units·week^{-1}		21 (14–42)
COPD-related factors		
Forced expiratory volume in 1 s % pred	247	57.2±20.7
GOLD 1, n (%)		42 (17.0)
GOLD 2, n (%)		110 (44.5)
GOLD 3, n (%)		74 (30.0)
GOLD 4, n (%)		21 (8.5)
Total lung capacity % pred	243	116.3±16.3
RV % pred	243	153.4±44.6
Static hyperinflation (RV >140% pred), n (%)		137 (56.4)
Diffusion capacity (D_{LCOcSB}) % pred	245	59.8±22.8
Abnormal diffusion capacity (D_{LCOcSB} ⩽50% pred), n (%)		96 (39.2)
Oxygen therapy, n (%)	247	23 (9.3)
⩾1 moderate exacerbation (prior 12 months), n (%)		100 (40.5)
⩾1 AECOPD hospitalisation (prior 12 months), n (%)		27 (10.9)
GOLD E, n (%)	242	66 (27.3)
Symptoms		
mMRC dyspnoea grade	242	1 (0–2)
Severe dyspnoea (mMRC grade ⩾2), n (%)		98 (40.5)
Dyspnoea VAS points	243	32 (12–64)
Moderate-to-severe dyspnoea (dyspnoea VAS >30), n (%)		127 (52.3)
Sleep quality (PSQI) points	226	7 (4–11)
Poor sleep quality (PSQI ⩾6), n (%)		129 (57.1)
Cough VAS points	243	16 (4–46)
Moderate-to-severe cough (cough VAS >30), n (%)		83 (34.2)
Insomnia VAS points	242	13 (1–47)
Moderate-to-severe insomnia (insomnia VAS >30), n (%)		82 (33.9)
Pain VAS points	243	6 (1–27)
Moderate-to-severe pain (pain VAS >30), n (%)		59 (24.3)
Physical factors		
BMI kg·m^{-2}	247	26.8±5.1
Underweight (BMI <21), n (%)		28 (11.3)
Obese (BMI >30), n (%)		52 (21.1)
FFMI kg·m^{-2}	226	17.6±2.2
Low FFMI (FFMI <PC10), n (%)		83 (36.7)
Lower extremity functioning (SPPB) points	238	10 (9–11)
Impaired SPPB (SPPB ⩽9), n (%)		83 (34.9)
5-repetition sit-to-stand test s		14.5±4.6
Functional exercise capacity (6MWD) m	240	449.1±114.3
6MWD % pred		71.8±16.6
Impaired 6MWD (6MWD <70% pred), n (%)		98 (40.8)

Continued

TABLE 1 Continued

	n	Reported data
HGS kg	236	36.2±10.9
HGS % pred		115.9±23.7
Impaired HGS (HGS <PC10), n (%)		19 (8.1)
Quadriceps strength % pred	161	95.4±27.5
Impaired quadriceps strength (<70% pred), n (%)		28 (17.4)
Physical activity steps·day^{-1}	196	3776 (2423–5990)
Physically inactive (<5000 steps·day^{-1}), n (%)		131 (66.8)
Moderate-to-vigorous physical activity min·day^{-1}		16.1 (6.6–32.2)
Sedentary time min·day^{-1}		753 (696–817)
Psychological factors		
Depressive symptoms (HADS-D) points	244	4 (2–7)
Clinical symptoms of depression (HADS-D ⩾8), n (%)		57 (23.4)
Symptoms of anxiety (HADS-A) points	244	4 (2–8)
Clinical symptoms of anxiety (HADS-A ⩾8), n (%)		62 (25.4)
Fatigue-related catastrophising (J-FCS) points	244	18±7
Fear of disease progression (FoP-Q-SF) points	244	24±8
Abnormal fear of disease progression (FoP-Q-SF ⩾34), n (%)		32 (13.1)
Social support (SSLI-34) points		73±14
Systemic factors[#]		
HsCRP mg·L^{-1}	241	2.2 (1.1–5.0)
High HsCRP, n (%)		95 (39.4)
Fibrinogen g·L^{-1}	142	3.3 (2.7–3.9)
High fibrinogen, n (%)		20 (14.1)
Leukocyte count per nL	238	6.8 (5.6–8.0)
High leukocytes, n (%)		23 (9.7)
Cortisol nmol·L^{-1}	241	345.0 (262.0–441.6)
High cortisol, n (%)		19 (7.9)
Hb mmol·L^{-1}	238	9.1 (8.5–9.7)
Low Hb, n (%)		4 (1.7)
High Hb, n (%)		48 (20.2)
Glucose mmol·L^{-1}	241	5.2 (4.8–5.8)
Elevated, n (%)		48 (19.9)
Abnormally high, n (%)		26 (10.8)
TSH mU·L^{-1}	241	2.3 (1.6–3.1)
High TSH, n (%)		24 (10.0)
Creatinine µmol·L^{-1}	242	83.0 (73.0–96.3)
High creatinine, n (%)		18 (7.4)
Sodium mmol·L^{-1}	240	142.0 (140.0–143.0)
Low sodium, n (%)		6 (2.5)
High sodium, n (%)		20 (8.3)
Potassium mmol·L^{-1}	192	4.8 (4.5–5.1)
Low potassium, n (%)		1 (0.5)
High potassium, n (%)		3 (1.6)
Calcium mmol·L^{-1}	240	2.4 (2.3–2.5)
Low calcium, n (%)		4 (1.7)
High calcium, n (%)		18 (7.5)
Magnesium mmol·L^{-1}	239	0.90 (0.86–0.94)
High magnesium, n (%)		11 (4.6)
Vitamin B12 pmol·L^{-1}	242	292.5 (220.8–387.3)
Low vitamin B12, n (%)		11 (4.5)
High vitamin B12, n (%)		19 (7.9)
Vitamin 25(OH)D3 nmol·L^{-1}	242	60.3 (42.2–75.3)
Deficiency vitamin 25(OH)D3, n (%)		8 (3.3)
Low vitamin 25(OH)D3, n (%)		173 (71.5)
ASAT U·L^{-1}	242	24.0 (20.8–28.0)
High ASAT, n (%)		7 (2.9)
ALAT U·L^{-1}	242	21.0 (17.0–27.0)
High ALAT, n (%)		9 (3.7)
NT-proBNP ng·L^{-1}	243	98.0 (51.4–209.0)
High NT-proBNP, n (%)		34 (14.0)

Continued

TABLE 1 Continued

	n	Reported data
ESR mm·h^{-1}	236	7.0 (5.0–12.8)
High ESR, n (%)		29 (12.3)
Antinuclear antibodies titre positive, n (%)	240	68 (28.3)
Medication		
Number of medications	247	6 (3–9)
Short-acting β-agonists, n (%)		100 (40.5)
Short-acting muscarinic antagonist, n (%)		33 (13.4)
Long-acting β-agonists, n (%)		158 (64.0)
Long-acting muscarinic antagonist, n (%)		165 (66.8)
Inhaled corticosteroids, n (%)		101 (40.9)
Systemic corticosteroids, n (%)		23 (9.3)
Systemic antihistamines, n (%)		11 (4.5)
Anxiolytics, n (%)		29 (11.7)
Antidepressants, n (%)		34 (13.8)
Opioids, n (%)		17 (6.9)
β-blockers, n (%)		64 (25.9)

Data are presented as mean±SD and median (IQR) unless indicated otherwise. CIS-Fatigue: Checklist Individuals Strength – subscale fatigue; EQ5D5L: 5-level EuroQol 5 dimensions; CAT: COPD Assessment Test; GOLD: Global Initiative for Chronic Obstructive Lung Disease; RV: residual volume; D_{LCOcSB}: single breath diffusing capacity of lung for carbon monoxide corrected for haemoglobin; AECOPD: acute exacerbation of COPD; mMRC: modified Medical Research Council; VAS: Visual Analogue Scale; PSQI: Pittsburgh Sleep Quality Index; BMI: body mass index; FFMI: fat-free mass index; SPPB: Short Physical Performance Battery; 6MWD: 6-minute walking distance; HGS: handgrip strength; HADS-D: Hospital Anxiety and Depression Scale – subscale depression; HADS-A: Hospital Anxiety and Depression Scale – subscale anxiety; J-FCS: Jacobsen Fatigue Catastrophising Scale; FoP-Q-SF: Fear of Progression Questionnaire – Short Form; SSLI-34: 34-item Social Support List, Interaction Version; HsCRP: high sensitivity C-reactive protein; Hb: haemoglobin; TSH: thyroid-stimulating hormone; vitamin 25(OH)D3: vitamin 25-hydroxyvitamin D3; ASAT: aspartate amino transferase; ALAT: alanine amino transferase; NT-proBNP: N-terminal pro-brain natriuretic peptide; ERS: erythrocyte sedimentation rate. #: the cut-off values used to define abnormal high/low value for systemic factor are described in supplementary table 1.

TABLE 2 Final multivariable regression model for fatigue (CIS-Fatigue) with significant variables from separate models as independent variables (enter method)

Variables	Unstandardised coefficient β (95% CI)	Standardised β	p-value
(Constant)	55.21 (17.84–92.58)	NA	**0.004**
Age years	−0.13 (−0.32–0.05)	−0.08	0.162
Sex, female	−3.53 (−7.14–0.09)	−0.13	0.056
Living alone (yes)	1.46 (−1.57–4.49)	0.05	0.342
Charlson comorbidity score points	0.65 (−0.32–1.63)	0.08	0.187
D_{LCO} corrected for haemoglobin mL·min^{-1}·mmHg^{-1}	−0.18 (−1.04–0.68)	−0.03	0.675
Exacerbations in the last 12 months, n	0.25 (−0.83–1.34)	0.03	0.643
Dyspnoea VAS points	0.09 (0.03–0.15)	0.20	**0.005**
Sleep quality (PSQI) points	0.47 (0.08–0.85)	0.16	**0.017**
Pain VAS points	0.07 (0.01–0.13)	0.14	**0.024**
Functional exercise capacity (6MWD) m	−0.01 (−0.03–0.01)	−0.10	0.202
Fatigue-related catastrophising (J-FCS) points	0.33 (0.07–0.59)	0.18	**0.012**
Depressive symptoms (HADS-D) points	0.45 (−0.05–0.94)	0.13	0.075
Calcium mmol·L^{-1}	−10.94 (−25.25–3.39)	−0.08	0.134
Leukocyte count per nL	0.53 (−0.25–1.30)	0.08	0.183
Systemic antihistamines (yes)	4.28 (−2.84–11.41)	0.07	0.237
Antidepressants (yes)	3.13 (−1.28–7.53)	0.08	0.163
Anxiolytics (yes)	0.63 (−4.19–5.45)	0.02	0.797

$F(17, 184)=11.312$, $p<0.001$; $R^2=0.511$, adjusted $R^2=0.466$. Bold type for p-values denotes statistical significance. CIS-Fatigue: Checklist Individuals Strength – subscale fatigue; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; VAS: Visual Analogue Scale; PSQI: Pittsburgh Sleep Quality Index; 6MWD: 6-minute walking distance; J-FCS: Jacobsen Fatigue Catastrophising Scale; HADS-D: Hospital Anxiety and Depression Scale – subscale depression.

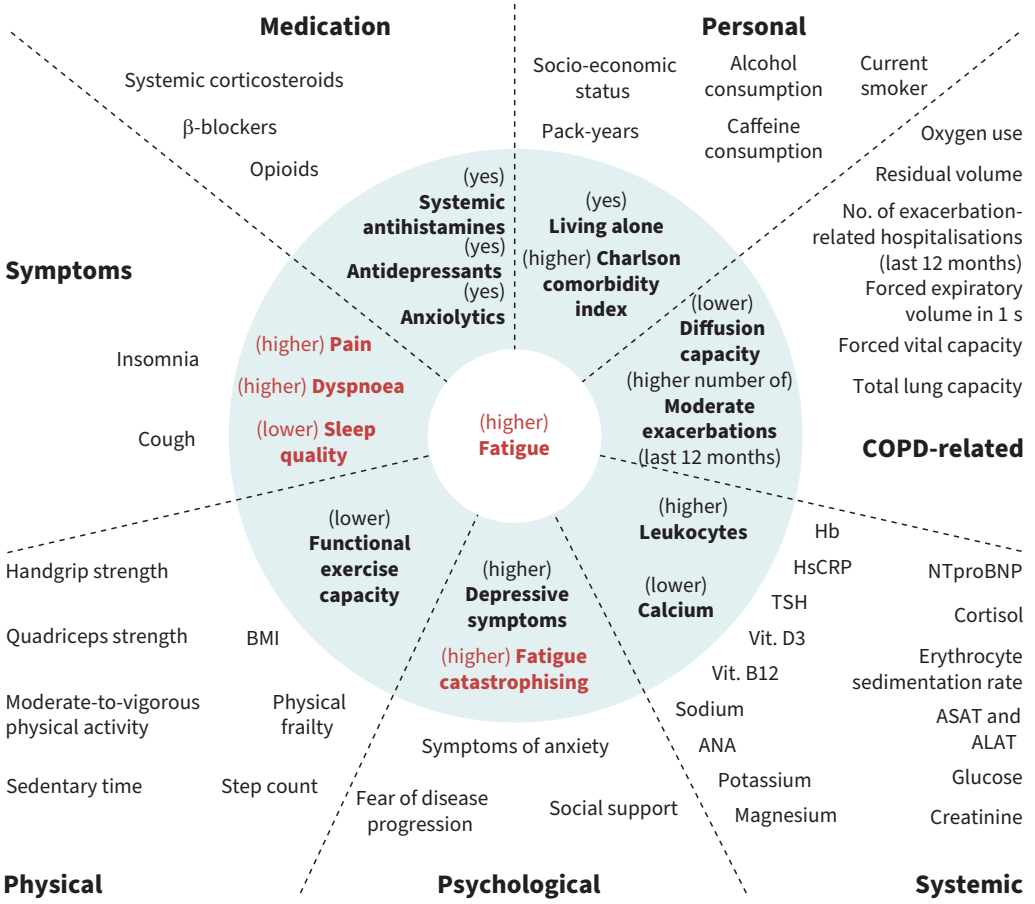

FIGURE 2 Visual presentation of all potential factors of fatigue considered per domain and identified associated factors of fatigue in COPD per model (in pale blue circle). Pain, dyspnoea, sleep quality and fatigue-related catastrophising (in red) were found to be significant associated factors of fatigue in COPD in the final model that included all identified factors per domain. BMI: body mass index; HsCRP: high sensitivity C-reactive protein; TSH: thyroid-stimulating hormone; ANA: antinuclear antibody test; NT-proBNP: N-terminal pro-brain natriuretic peptide; ASAT: aspartate amino transferase; ALAT: alanine amino transferase; Hb: haemoglobin; vit. D3: vitamin 25-hydroxyvitamin D3; vit. B12: vitamin B12.

perception of fatigue, potentially leading to avoidance of, for example, physical activity, which in turn worsens fatigue [23].

Further, sleep quality was identified as a related factor of fatigue. Sleep disturbances and disorders are common in COPD [24]. Also, night-time symptoms like dyspnoea and cough may contribute to poor sleep quality in patients with COPD, which subsequently can contribute to fatigue in COPD [25]. One other study identified poor sleep quality as a predictor of fatigue in COPD [5]. The reasons for this poor sleep quality were not explored in the current study but require a detailed assessment including a nocturnal polysomnography.

Lastly, pain was associated with fatigue. In previous studies, moderately strong bivariate positive relations between fatigue and pain were observed in COPD (*i.e.*, r=0.48 and 0.58) [26, 27]. COPD is often associated with chronic pain [28]. Several (non-)pharmacological and noninvasive interventions for pain exist [29]. Understanding the physiology of pain will help healthcare professionals to select the most effective intervention(s).

A number of variables did not reach the threshold for statistical significance in the final integrated model but should not be disregarded when considering their role in fatigue of patients with COPD. These variables (and similar directions) are found to be related with fatigue in COPD and other populations [3, 15, 18, 30–32]. A higher number of severe exacerbations was not identified in the current study, although there

is evidence suggesting that an exacerbation-related hospitalisation is related to an increase in fatigue severity and prevalence [15]. Only 10% of the individuals in our sample experienced an exacerbation-related hospitalisation in the past 12 months, this could have contributed to this finding. In addition, comparing the associated factors identified in the current study with those highlighted in the systematic review by Ebadi and colleagues [3], both similarities and differences can be found. Ebadi and colleagues reviewed a broad range of factors and found multiple associations with fatigue in COPD. However, factors such as age, sex, socioeconomic status, degree of airflow limitation, exercise capacity and body composition showed inconclusive and sometimes contradictory results. Only dyspnoea, depression, anxiety, quality of life and peripheral muscle strength were found to be conclusive and have moderate-to-strong associations with fatigue. Interestingly, symptoms of depression and anxiety, and peripheral muscle strength were not identified as significant factors in the current integrated model, whereas the key factors sleep quality, pain and fatigue-related catastrophising were not identified in the systematic review. These differences may be due to sample characteristics and assessment methods for fatigue.

Clinical implications

The current findings can help shape fatigue-specific screening for associated factors of fatigue in patients with COPD and subsequently link this to management strategies that target these specific factors. Up to now, a holistic approach, such as a comprehensive pulmonary rehabilitation (PR) programme, may be the most appropriate choice to reduce fatigue in a patient with COPD [33], although not all patients with COPD report a clinical improvement of fatigue following a PR programme despite room for improvement [34]. Further, referral to PR is poor and access is limited [35]. Other accessible treatment strategies such as exercise training or self-management programmes have been shown to reduce fatigue in people with COPD on a group level [36, 37]. However, on their own, these strategies may benefit a limited number of fatigued patients. This is probably due to the multifactorial nature of fatigue, because these treatment strategies tend to target a specific underlying factor of fatigue.

A more personalised approach when treating fatigue is needed, based on a comprehensive assessment of possible contributing factors of fatigue. Patients with COPD and fatigue should be screened for associated factors of fatigue like dyspnoea, sleep quality, pain and fatigue-catastrophising. Subsequently, personalised and tailored treatment strategies should be initiated for these identified factors instead of providing a one-size-fits-all treatment. Hence, patients with COPD with fatigue and dyspnoea, for example, could benefit from an inhaler drug education programme to reduce dyspnoea, and thereby also fatigue [38]. Also, other treatment strategies proven to be effective in the management of dyspnoea, such as exercise training, inspiratory muscle training and others, can be proposed to treat dyspnoea and consequently fatigue [36]. Another example is the screening, identification and management of sleep-related problems in patients with COPD with fatigue. By minimising sleep disturbances, sleep quality can be improved [39]. Further, psychological interventions could be effective in addressing fatigue-related catastrophising [40]. Therefore, it is crucial we start screening our patients with COPD and fatigue for all possible associated factors of fatigue, and subsequently treating these factors when present in an integrated way with tailored and evidence-based treatment strategies.

Strengths and limitations

To date, only few studies have investigated associated factors that contribute to increased fatigue in patients with COPD in a multivariable model [5–7, 15, 16, 18]. This study is the first in its kind that integrates an extensive list of factors from different domains that have been consistently shown to be associated with fatigue in one multivariable analysis and evaluates the unique contribution of each factor in explaining fatigue. Furthermore, patients were involved in setting the agenda and prioritising this fatigue research in COPD. The current study has some limitations. Firstly, the data are cross-sectional, therefore we are unable to assess causality. Secondly, a large share of interested individuals declined participation as they found the study too burdensome. This can imply a potential selection bias in our study. Thirdly, a large number of participants were recruited for this study, but a higher sample size would have created greater power to detect associated factors of fatigue in the regression model. Fourthly, although we have data on an extensive range of factors, there may be factors associated with fatigue we did not assess. Fifth, a limitation of questionnaires, including the CIS-Fatigue scale to measure subjective fatigue, is recall bias, as participants may have difficulty to accurately report their fatigue levels over the last 2 weeks. The use of Ecological Momentary Assessment (EMA) could be considered for future studies, as it evaluates day-to-day variability and diurnal changes of fatigue.

Conclusion

Severe fatigue occurs in half of patients with COPD. Key factors associated with fatigue include dyspnoea, sleep quality, fatigue-related catastrophising and pain. These findings provide a rationale for the screening

for and tailored treatment of associated factors present in a patient with COPD and fatigue. Further, longitudinal assessment of fatigue is needed in future studies to establish causal relationships.

Acknowledgements: We gratefully acknowledge the patient representatives Jacqueline Otker, Arnold Coors and Yvonne Meertens-Kerris who contributed to the FAntasTIGUE project. Furthermore, we would like to thank the staff of the outpatient clinics of the Department of Respiratory Medicine in Maastricht (Maastricht University Medical Centre+) and the Department of Pulmonary Diseases in Nijmegen (Radboud University Medical Center), and the staff of Medische Laboratoria Dr Stein & Collegae, in particular Jacques Janssen and Michel Laaper, for facilitating the study.

Provenance: Submitted article, peer reviewed.

Data availability: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics statement: The study was approved by Medical Research Ethics Committees United (Nieuwegein, the Netherlands; R17.036/NL60484.100.17) and was registered in the Dutch Trial Register (NTR6933).

Author contributions: M. Van Herck, Y.M.J. Goërtz, C. Burtin, D.J.A. Janssen and M.A. Spruit conceptualised the current manuscript. M. Van Herck performed the statistical analysis and wrote the first draft of the manuscript. All authors revised the manuscript critically for important intellectual content, approved the definitive version, and agreed to be accountable for all aspects of the manuscript.

Conflict of interest: M. Van Herck, Y.M.J. Goërtz, Z. Ebadi, C. Burtin, J.B. Peters, M.S.Y. Thong, R. Posthuma, J.W.M. Muris, E.W.M.A. Bischoff, E.F.M. Wouters, M.A.G. Sprangers and J.H. Vercoulen have nothing to disclose. D.J.A. Janssen reports grants from the Stichting Astmabestrijding and the Netherlands Respiratory Society, and speaker fees from Chiesi, Abbott and AstraZeneca in the past 36 months outside the submitted work and all paid to her institution. M.A. Spruit reports grants from Lung Foundation Netherlands, Stichting Astma Bestrijding, Boehringer Ingelheim and AstraZeneca to support the FAntasTIGUE project, grants from Boehringer Ingelheim, AstraZeneca, TEVA, Chiesi and Sanofi outside the submitted work, consulting fees from Boehringer Ingelheim and GSK, and speaker fees from Boehringer Ingelheim in the past 36 months outside the submitted work. All payments were made to his institution.

Support statement: This project is supported by grant 4.1.16.085 of Lung Foundation Netherlands (Leusden, The Netherlands), AstraZeneca Netherlands, Boehringer Ingelheim Netherlands and Stichting Astma Bestrijding (Amsterdam, The Netherlands). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Machado A, Marques A, Burtin C. Extra-pulmonary manifestations of COPD and the role of pulmonary rehabilitation: a symptom-centered approach. *Expert Rev Respir Med* 2021; 15: 131–142.
2 Ream E, Richardson A. Fatigue: a concept analysis. *Int J Nurs Stud* 1996; 33: 519–529.
3 Ebadi Z, Goërtz YMJ, Van Herck M, *et al.* The prevalence and related factors of fatigue in patients with COPD: a systematic review. *Eur Respir Rev* 2021; 30: 200298.
4 Blinderman CD, Homel P, Billings JA, *et al.* Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. *J Pain Symptom Manage* 2009; 38: 115–123.
5 Kapella MC, Larson JL, Patel MK, *et al.* Subjective fatigue, influencing variables, and consequences in chronic obstructive pulmonary disease. *Nurs Res* 2006; 55: 10–17.
6 Goërtz YMJ, Spruit MA, Van't Hul AJ, *et al.* Fatigue is highly prevalent in patients with COPD and correlates poorly with the degree of airflow limitation. *Ther Adv Respir Dis* 2019; 13: 1753466619878128.
7 Kentson M, Tödt K, Skargren E, *et al.* Factors associated with experience of fatigue, and functional limitations due to fatigue in patients with stable COPD. *Ther Adv Respir Dis* 2016; 10: 410–424.
8 Vaes AW, Goërtz YMJ, van Herck M, *et al.* Physical and mental fatigue in people with non-communicable chronic diseases. *Ann Med* 2022; 54: 2522–2534.
9 Spruit MA, Vercoulen JH, Sprangers MAG, *et al.* Fatigue in COPD: an important yet ignored symptom. *Lancet Respir Med* 2017; 5: 542–544.
10 Goërtz YMJ, Looijmans M, Prins JB, *et al.* Fatigue in patients with chronic obstructive pulmonary disease: protocol of the Dutch multicentre, longitudinal, observational FAntasTIGUE study. *BMJ Open* 2018; 8: e021745.
11 Agustí A, Celli BR, Criner GJ, *et al.* Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. *Eur Respir J* 2023; 61: 2300239.

12 Vercoulen JH, Swanink CM, Fennis JF, *et al.* Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994; 38: 383–392.
13 Worm-Smeitink M, Gielissen M, Bloot L, *et al.* The assessment of fatigue: psychometric qualities and norms for the Checklist individual strength. *J Psychosom Res* 2017; 98: 40–46.
14 Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. *Fam Med Community Health* 2020; 8: e000262.
15 Baghai-Ravary R, Quint JK, Goldring JJ, *et al.* Determinants and impact of fatigue in patients with chronic obstructive pulmonary disease. *Respir Med* 2009; 103: 216–223.
16 Gift AG, Shepard CE. Fatigue and other symptoms in patients with chronic obstructive pulmonary disease: do women and men differ? *J Obstet Gynecol Neonatal Nurs* 1999; 28: 201–208.
17 Woo K. Physical activity as a mediator between dyspnea and fatigue in patients with chronic obstructive pulmonary disease. *Can J Nurs Res* 2000; 32: 85–98.
18 Lewko A, Bidgood PL, Garrod R. Evaluation of psychological and physiological predictors of fatigue in patients with COPD. *BMC Pulm Med* 2009; 9: 47.
19 VanVoorhis CW, Morgan BL. Understanding power and rules of thumb for determining sample sizes. *Tutorials in quantitative methods for psychology* 2007; 3: 43–50.
20 Stephan Y, Sutin AR, Luchetti M, *et al.* Personality and fatigue: meta-analysis of seven prospective studies. *Sci Rep* 2022; 12: 9156.
21 Goërtz YMJ, Braamse AMJ, Spruit MA, *et al.* Fatigue in patients with chronic disease: results from the population-based Lifelines Cohort Study. *Sci Rep* 2021; 11: 20977.
22 Lukkahatai N, Saligan LN. Association of catastrophizing and fatigue: a systematic review. *J Psychosom Res* 2013; 74: 100–109.
23 Bloem AEM, Mostard RLM, Stoot N, *et al.* Severe fatigue is highly prevalent in patients with IPF or sarcoidosis. *J Clin Med* 2020; 9: 1178.
24 McNicholas WT, Verbraecken J, Marin JM. Sleep disorders in COPD: the forgotten dimension. *Eur Respir Rev* 2013; 22: 365–375.
25 Price D, Small M, Milligan G, *et al.* Impact of night-time symptoms in COPD: a real-world study in five European countries. *Int J Chron Obstruct Pulmon Dis* 2013; 8: 595–603.
26 Borge CR, Wahl AK, Moum T. Association of breathlessness with multiple symptoms in chronic obstructive pulmonary disease. *J Adv Nurs* 2010; 66: 2688–2700.
27 Chen YW, Camp PG, Coxson HO, *et al.* A comparison of pain, fatigue, dyspnea and their impact on quality of life in pulmonary rehabilitation participants with chronic obstructive pulmonary disease. *COPD* 2018; 15: 65–72.
28 Roberts MH, Mapel DW, Hartry A, *et al.* Chronic pain and pain medication use in chronic obstructive pulmonary disease. A cross-sectional study. *Ann Am Thorac Soc* 2013; 10: 290–298.
29 Morris JR, Harrison SL, Robinson J, *et al.* Non-pharmacological and non-invasive interventions for chronic pain in people with chronic obstructive pulmonary disease: a systematic review without meta-analysis. *Respir Med* 2023; 211: 107191.
30 Anagha K, Shihabudheen P, Uvais NA. Side effect profiles of selective serotonin reuptake inhibitors: a cross-sectional study in a naturalistic setting. *Prim Care Companion CNS Disord* 2021; 23: 20m02747.
31 Nishitani N, Sakakibara H. Association of psychological stress response of fatigue with white blood cell count in male daytime workers. *Ind Health* 2014; 52: 531–534.
32 Ozdemir PG, Karadag AS, Selvi Y, *et al.* Assessment of the effects of antihistamine drugs on mood, sleep quality, sleepiness, and dream anxiety. *Int J Psychiatry Clin Pract* 2014; 18: 161–168.
33 McCarthy B, Casey D, Devane D, *et al.* Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; 2: CD003793.
34 Souto-Miranda S, Rocha V, Mendes MA, *et al.* The presence of extra-pulmonary treatable traits increases the likelihood of responding to pulmonary rehabilitation. *Respir Med* 2023; 206: 107086.
35 Rochester CL, Spruit MA, Holland AE. Pulmonary rehabilitation in 2021. *JAMA* 2021; 326: 969–970.
36 Couto N, Cid L, Alves S, *et al.* Analysing the effects of different types of exercise on dyspnoea and fatigue in adults through COPD-systematic review and meta-analysis of randomised clinical trials. *Healthcare (Basel)* 2023; 11: 1449.
37 Mitchell KE, Johnson-Warrington V, Apps LD, *et al.* A self-management programme for COPD: a randomised controlled trial. *Eur Respir J* 2014; 44: 1538–1547.
38 Ozoglu Aytac S, Kilic SP, Ovayolu N. Effect of inhaler drug education on fatigue, dyspnea severity, and respiratory function tests in patients with COPD. *Patient Educ Couns* 2020; 103: 709–716.
39 Budhiraja R, Siddiqi TA, Quan SF. Sleep disorders in chronic obstructive pulmonary disease: etiology, impact, and management. *J Clin Sleep Med* 2015; 11: 259–270.
40 Schellekens MPJ, Bruggeman-Everts FZ, Wolvers MDJ, *et al.* What web-based intervention for chronic cancer-related fatigue works best for whom? Explorative moderation analyses of a randomized controlled trial. *Support Care Cancer* 2022; 30: 7885–7892.