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TITLE

Fatigue in patients with Chronic Obstructive Pulmonary Disease: protocol of the longitudinal, observational *FAntasTIGUE* study

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ABSTRACT

Introduction: Fatigue is the second most common symptom in patients with Chronic Obstructive Pulmonary Disease (COPD), and has most likely a multi-causal origin. Approximately 50% of clinically stable patients with COPD experience abnormal fatigue. Despite its high prevalence, fatigue is often ignored in daily practice. For this reason, little is known about the underlying determinants of fatigue in patients with COPD. Therefore, the primary aim of this study is to identify the physical, systemic, psychological, and behavioural factors that precipitate and perpetuate fatigue in patients with COPD. Moreover, the secondary aim is to evaluate the impact of exacerbation-related hospitalizations on fatigue and to better understand the association between fatigue and 2-year all-cause hospitalization and mortality in patients with COPD. This manuscript describes the protocol of the *FAntasTIGUE* study and gives an overview of the possible strengths, weaknesses and clinical implications.

Methods and analysis: A two-year longitudinal, observational study, enrolling 400 patients with clinically stable COPD has been designed. Fatigue, the primary outcome, will be measured by the subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue). The secondary outcome is the day-to-day/diurnal fatigue, registered in a subsample (n=60) by Ecological Momentary Assessment (EMA). CIS-Fatigue and EMA will be evaluated at baseline, and at 4, 8 and 12 months. The precipitating and perpetuating factors of fatigue (physical, psychological, behavioural, and systemic factors), will be assessed at baseline and at 12 months. Additional assessments will be conducted following hospitalization due to an exacerbation of COPD that occurs between baseline and 12 months. Finally, at 18 and 24 months the participants will be followed-up on their fatigue, number of exacerbations, exacerbation-related hospitalization, and survival.

Ethics and dissemination: This protocol was approved by the Medical research Ethics Committees United (MEC-U), Nieuwegein, the Netherlands (NL60484.100.17). It has been registered at the Dutch Trial Register (NTR6933).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The present study is a large, longitudinal, multicenter study evaluating a wide range of possible precipitating and perpetuating factors of moderate to severe fatigue in patients with COPD.
- The Ecological Momentary Assessment data will give us more insight in the diurnal variations of fatigue.
- The longitudinal design enables to examine the association between fatigue, exacerbation-related hospitalizations and mortality.
- The perpetuating- and precipitating factors have been carefully selected, it is –however- possible that there are other factors that contribute to fatigue in COPD that will be missed.

INTRODUCTION

Fatigue, the subjective feeling of tiredness or exhaustion, is next to dyspnoea the most common and distressing symptom in patients with Chronic Obstructive Pulmonary Disease (COPD).[1] It affects the ability to perform activities of daily living and impacts the patient's quality of life (QoL).[2, 3] Among patients with stable moderate to severe COPD, around fifty percent experiences moderate to severe fatigue,[4] which is significantly higher compared to elderly, non-COPD subjects.[5] Nevertheless, despite its high prevalence and significant negative health consequences, fatigue remains often undiagnosed and, in turn, untreated.[6] This might be due to the underrepresentation of fatigue questions in commonly used health status assessment tools.[7, 8] Moreover, relatively few studies have focused on the symptom fatigue and, therefore, little is known about the precipitating and perpetuating factors of moderate to severe fatigue in patients with COPD. Consequently, specific interventions aimed at reducing COPD-related fatigue are lacking. A better insight into the underlying determinants, will provide guidance for the development of personalized interventions for this important yet disregarded symptom in patients with COPD.[9]

Multiple precipitating factors are expected to play a role in the cause of COPD-related fatigue.[9] It has been suggested that COPD-specific features are associated with fatigue, since the prevalence of fatigue is higher in patients with COPD compared to elderly control subjects.[5] However, evidence suggests that fatigue is not related to the degree of airflow limitation.[4] This indicates that the degree of airflow limitation may not be the primary underlying cause of moderate to severe fatigue in patients with COPD. On the other hand, a COPD exacerbation precipitates moderate to severe fatigue.[5, 10] However, the size of the impact of an exacerbation-related hospitalization on fatigue remains to be clarified.

Next to precipitating factors, various physical, systemic, psychological, and behavioural factors are assumed to perpetuate moderate to severe fatigue in patients with COPD. Generally, studies report significant, weak-to-moderate associations between fatigue and health status, exercise performance, physical activity, functional impairments, sleep quality, symptoms of anxiety or depression, and mood status.[2, 5, 11-15] Moreover, research indicates that COPD is associated with low-grade systemic inflammation.[16] Nonetheless, whether and to what extent low-grade systemic inflammation is related to fatigue needs to be further explored.

Thus, fatigue in COPD is a complex symptom, due to a combination of precipitating and perpetuating factors. To date, the abovementioned factors have rarely been assessed comprehensively in one

study in patients with COPD.[17] Moreover, the role of sleep apnoea, comorbidities, medication, and exacerbation-related hospitalizations are unknown. Therefore, we have designed a longitudinal, observational study, which evaluates a wide range of possible underlying factors of moderate to severe fatigue in patients with COPD. This manuscript describes the protocol of the *FAntasTIGUE* study and gives an overview of its possible strengths, weaknesses and clinical implications.

Objectives of this study

The primary objectives of the *FAntasTIGUE* study are:

1.1 To chart the course of fatigue in patients with COPD.

1.2 To identify physical, systemic, psychological, and behavioural factors that precipitate and/or perpetuate fatigue in patients with COPD.

1.3 To identify the impact of exacerbation-related hospitalizations on fatigue and its perpetuating factors.

1.4 To better understand the association between baseline fatigue and 2-year all-cause hospitalization and mortality in patients with COPD.

The secondary objective of this study is:

2. To identify diurnal differences in fatigue by augmenting traditional questionnaire data with Ecological Momentary Assessment (EMA).

METHODS

The *FAntasTIGUE* study is a collaboration between CIRO (Horn, The Netherlands), Radboud university medical centre (Nijmegen, The Netherlands), Academic Medical Centre (Amsterdam, The Netherlands), Maastricht University Medical Centre (Maastricht, The Netherlands), and Hasselt University (Diepenbeek, Belgium). The consortium consists of members from various disciplines and backgrounds (e.g. chest physicians, clinical psychologists, an elderly care specialist, a cardiologist, a general practitioner, and researchers), to ensure necessary know-how to enable the successful completion of the project. Moreover, a patient advisory board is closely involved to advice and monitor the *FAntasTIGUE* project, by providing valuable insight from the patient perspective.

STUDY DESIGN

A two-year longitudinal, observational study, enrolling patients with clinically stable COPD has been designed (Figure 1). The assessments at baseline, 12 months, and during the first days of a possible

exacerbation-related hospitalization will be performed in a hospital setting. The remaining measurements at 4, 8, 18, and 24 months will take place at the patients' homes.

The primary outcome fatigue severity will be assessed with a questionnaire at baseline, and at 4, 8, 12, 18 and 24 months, as well as during exacerbation-related hospitalizations and two weeks after discharge. The secondary outcome, day-to-day/diurnal variation in fatigue, will be registered using Ecological Momentary Assessment (EMA) in a subsample (n=60) at baseline, and at 4, 8 and 12 months. Selection is based on convenient sampling, a "first-come, first-serve" approach. The precipitating and perpetuating factors of moderate to severe fatigue in patients with COPD (physical, psychological, behavioural, and systemic factors), will be assessed at baseline and at 12 months. Also, when patients are admitted to the hospital between baseline and 12 months due to an exacerbation of COPD, some tests will be repeated during the first days of hospitalization, and two weeks after discharge. At last, at 18 and 24 months the participants will be followed-up on their fatigue, number of exacerbations, exacerbation-related hospitalization and survival.

ELIGIBILITY CRITERIA

To be eligible, a subject must meet the following criteria:

1. A diagnosis of COPD according to the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD, grade 1A to 4D);[18]
2. No exacerbation-related hospitalization less than 4 weeks preceding enrolment;
3. No use of oral corticosteroids and/or antibiotics less than 4 weeks preceding enrolment;
4. Provided written informed consent.

Patients lacking a sufficient understanding of the Dutch language and/or participating in concurrent intervention studies will be excluded.

Extra eligibility criteria for the EMA sub-study are:

1. Access to the internet at home (Wi-Fi);
2. Able to operate a smartphone/iPod.

RECRUITMENT

Participants will be recruited at the outpatient clinics of the Department of Respiratory Medicine in Maastricht and the Department of Pulmonary Diseases in Nijmegen, and from the registration Network of Family Practices (RNH) of Maastricht University.[19] Eligible patients from the outpatient clinics will be informed about the research by their physician during their pulmonary consultation and are asked if the investigator may contact them to provide detailed information. Patients

recruited via the RNH network will receive a letter on behalf of their general practitioner introducing the research project. In case the patient agrees to participate, an appointment for the baseline assessment at the hospital will be made. Written informed consent will be obtained at the beginning of this visit.

OUTCOMES

Primary outcome

Fatigue severity will be measured by the subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue).[20] The CIS-Fatigue consists of eight items scored on a seven-point Likert scale. The scores range from 8 (normal fatigue) to 56 (most severe fatigue). A score of 26 or lower indicates normal fatigue, scores between 27 to 35 indicate moderate fatigue and a score of 36 or higher indicates severe fatigue. The CIS-Fatigue is a standardized and validated questionnaire that has been used in healthy subjects,[21-23] and among various patient populations including COPD.[20, 24-26] The CIS-Fatigue will be administered at baseline, and at 4, 8, 12, 18 and 24 months, as well as during exacerbation-related hospitalizations and two weeks after discharge.

Secondary outcome

Day-to-day/diurnal variations of fatigue will be measured in a subsample (n=60) with Ecological Momentary Assessment (EMA).[27, 28] EMA involves repeated measurements of the participant's behaviour and context in vivo and in real time. In the current study, the participants will be given an iPod for the duration of the study with the EMA application (www.psymate.eu) installed. The participants will be prompted to answer questions about their fatigue, context and surroundings, 8 times per day at random moments between 7:30 a.m. and 10:30 p.m. for 5 consecutive days at baseline, and at 4, 8 and 12 months. Patients will be given instructions to carry the device with them at all times for 5 consecutive days. Furthermore, they will be requested to fill out the questions immediately after the alert and to keep a normal day/night routine.

Explanatory factors

Table 1 provides an overview of the precipitating and perpetuating factors of moderate to severe fatigue that will be assessed at baseline, and at months 4, 8, 12, 18 and 24, as well as during non-elective, exacerbation-related hospitalizations and two weeks after discharge.

Table 1 Overview outcome measurements

		Number (n)	0 months	4 months	8 months	12 months	18 months	24 months	Exacerbation-related hospitalizations*
Fatigue	Subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue) [20]	400	•	•	•	•	•	•	•
	Ecological Momentary Assessment (EMA) [27 28]	60	•	•	•	•			
Socio-demographic factors	Gender	400	•						
	Age	400	•						
	Social-economic status (SES) [33]	400	•						
	Marital status	400	•			•			
	Survival status	400	•	•	•	•	•	•	
Physical factors	Current medication	400	•			•			
	Charlson Comorbidity Index (CCI) [34]	400	•			•			
	Symptoms checklist [35]	400	•			•			
	mMRC dyspnoea scale [36]	400	•	•	•	•			•
	Exacerbations last 4 or 6 months (as appropriate)	400	•	•	•	•	•	•	
	All-cause hospitalizations	400	•	•	•	•	•	•	
	Body Mass Index (BMI)	400	•			•			
	Waist circumference	400	•			•			
	Bioelectrical impedance analyses [37]	400	•			•			
	6 Minute Walk Test (6MWT) [38]	400	•			•			
	Short Physical Performance Battery (SPPB) [39]	400	•			•			
	Lower-limb muscle function (MicroFet2 Wireless Hand-held Dynamometer) [40]	400	•			•			
	Hand grip strength [41]	400	•			•			
	Lung function (post-bronchodilator spirometry, whole-body plethysmography, and transfer factor for carbon monoxide)	400	•						
	Peripheral arterial disease (Dopplex D900, Huntleigh Healthcare Ltd, Cardiff, UK) [42 43]	400	•			•			
	Resting cardiac echocardiography (Maastricht only)	200	•						
	Resting electrocardiogram (Maastricht only)	200	•						
	Retinal microcirculation [44] (Maastricht only)	200	•						
	Polysomnography (PSG) (Maastricht only)	50	•						
Psychological factors	Nijmegen Clinical Screening Instrument (NCSI) [45]	400	•			•			
	COPD Assessment Test (CAT) [8]	400	•	•	•	•			•
	Euroqol-5d-5L (EQ-5D-5L) [46]	400	•			•			
	Hospital Anxiety Depression Scale (HADS) [47]	400	•	•	•	•			•

	Montreal Cognitive Assessment (MOCA) [48]	400	•			•			
	Qualitative experience of fatigue (KWAMOE) [49]	400	•			•			
	Acceptance of Disease and Impairments Questionnaire (ADIQ) [50]	400	•			•			
	Fatigue-related self-efficacy (Self-Efficacy-5) [51]	400	•			•			
	Jacobsen Fatigue Catastrophizing Scale (FCS) [52]	400	•			•			
	Fear of Progression Questionnaire (FOPQ) [53]	400	•			•			
	Patient Activations Measure (PAM) [54]	400	•			•			
	Activity Cognitions Instrument (ACI) (self-developed questionnaire)	400	•			•			
Behavioural factors	Smoking status	400	•			•			
	Alcohol consumption	400	•			•			
	Caffeine consumption	400	•			•			
	Objectified physical activity (Actigraph GT9X Link, 3-axis activity monitor, sample frequency 30 Hz) [55]	400	•			•			
	Pittsburgh Sleep Quality Index (PSQI) [56]	400	•			•			
	Epworth Sleepiness Scale (ESS) [57]	400	•			•			
	Causal Attribution List (CAL) [58]	400	•			•			
	Sickness Impact Profile (SIP) [59]	400	•			•			
	Social Support List, Interactions and Discrepancies (SSL-I and SSL-D) [60]	400	•			•			
Systemic factors	Venous blood samples	400	•						

** Non-elective hospitalizations due to an exacerbation of COPD may occur at any moment after the start of the study. Those which occur between baseline and 12 months will result in additional measurements. Those which may occur between 12 and 24 months will not result in additional measurement.*

Questionnaires will be completed via RadQuest in the home-environment. RadQuest allows very simple online questionnaire completion. If, for any reason (e.g. no PC or internet connection), it is not possible to fill out the questionnaires via RadQuest, the participant will receive a paper version. Regarding the systemic factors, we will collect blood at baseline to assess systemic high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumornecrosisfactor-α (TNF-α), interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-1-RA (IL-1-RA), interleukin-10 (IL-10), fibrinogen, leukocytes, cortisol, haemoglobin, glucose, thyroid function (TSH), renal function (creatinine), sodium, potassium, calcium, magnesium, vitamin B12, vitamin 25(OH)D3, liver function (aspartate-aminotransferase (ASAT) and alanine-aminotransferase (ALAT)), N-Terminal pro-Brain Natriuretic Peptide (NT-pro-BNP), blood sediment (BSE), antinuclear antibodies (ANA) and deoxyribonucleic acid (DNA).

SAMPLE SIZE CALCULATION

A total of 260 patients is needed to detect a medium to small effect size of 0.175 between factors (218 (2 groups with or without an exacerbation) or 264 (3 groups normal, mild or severe fatigue)) and a small effect within-between factors (222 (3 groups normal, mild or severe fatigue)), with a power of 90%, a significance level of 5% and an expected drop-out rate of 20%.[29] Nevertheless, as a rather large number of possible perpetuating and precipitating factors will be evaluated, it is decided to augment the sample size to 400 inclusions.

For EMA, a sample of 60 patients with each 160 observations (5 days with 8 measurements, collected over 4 time points) ensures that the EMA analyses are adequately powered to detect differences in fatigue, based on a power of 0.8 and two-tailed significance of 0.05.[30]

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Missing data of questionnaires will be minimized using RadQuest, since items cannot be skipped. In case of missing data for other variables, the likeliness of this being missing at random will be assessed. If missing data is random, we will use appropriate imputation methods.[31]

All statistical analyses will be performed using statistics software (SPSS V.25.0 for Windows, Chicago, Illinois, USA). First, to characterize transitions over time in fatigue, we will use latent transition analysis.[32] Second, to identify the factors that precipitate and/or perpetuate fatigue in patients with COPD, mixed model analyses will be applied for continuous outcomes measures and generalized estimating equations for dichotomous outcomes measures. Third, to study the impact of

exacerbation-related hospitalizations on fatigue and its perpetuating factors we will use mixed model analyses. Fourth, to better understand the extent to which baseline fatigue is related to 2-year all-cause hospitalization and mortality, Cox proportional hazard models will be applied. At last, to identify whether there are diurnal differences in fatigue and what factors are associated with these variations, we will use hierarchical linear modelling as items are nested within moments and moments are nested within individuals. The responsiveness and sensitivity of the fatigue questionnaire versus EMA data are compared with effect sizes (Cohen's d) for the component of observed change derived from model parameters. *A priori*, a two-tailed p-value of <0.05 is considered significant.

ETHICS AND DISSEMINATION

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subject Act (WMO). MEC United approved the study on December 22, 2017 (R17.036/NL60484.100.17). The study was registered on www.trialregister.nl on January 8, 2018. The results will be submitted for publication in peer-reviewed journals and will be presented at (inter)national conferences.

DISCUSSION

The *FAntasTIGUE* study has been designed to identify the factors that perpetuate and/or precipitate moderate to severe fatigue in patients with COPD. The novel findings will hopefully further guide the development of tailored interventions, which –in turn- will help to diminish the impact on daily life of this important yet ignored symptom.

STRENGTHS

A major strength of the *FAntasTIGUE* study is that a wide range of possible precipitating and perpetuating factors will be tested concurrently in one model of stable patients with COPD. Moreover, the *FAntasTIGUE* study also examines the impact of an exacerbation-related hospitalization on fatigue. This way, we aim to identify relevant factors that explain variance in fatigue. Another strength of this study is the use of EMA to capture diurnal variations of fatigue in patients with COPD. In comparison with the usual web-based or paper-and-pencil questionnaires, data gathered via EMA are not subject to recall bias and provide us with a film of variations in the patient's fatigue in their natural environment rather than a snapshot. To our knowledge, this is the

first study that uses EMA to evaluate fatigue in a population of patients with COPD. The information about the diurnal variations of fatigue will further help us to tailor interventions for reducing fatigue in patients with COPD. Moreover, EMA provides us with contextual information of factors that could precipitate or perpetuate fatigue. A methodological strength of this study is the longitudinal design. It enables us to examine the association between fatigue, exacerbation-related hospitalizations and mortality. And last, the structure of the *FAntasTIGUE* consortium, including a steering committee and a patient's advisory board, allows us to improve the research capacity, to share (academic) resources, to disseminate study results and to speed up future research.

LIMITATIONS

The present study may encounter the following limitations: *first,* despite the benefits of repeated measurements in longitudinal studies, higher drop-out rates are expected as disease progresses. This attrition could result in a biased sample, which may compromise the study's generalizability. To limit the loss to follow-up, we will minimize the burden as much as possible and keep close contact with the patients. The patient advisory board has been intimately involved in the design of the *FAntasTIGUE* project to balance patient burden and number of variables that needed to be assessed to identify the factors that perpetuate and/or precipitate moderate to severe fatigue in patients with COPD. *Second,* the current study selection is based on convenience sampling. This may cause selection bias, since participants with a lack of motivation and a higher disease burden are less likely to respond. We will try to prevent selection bias, by inviting all patients who are diagnosed with COPD either via their physician during consultation hour or via their own general practitioner. *Third,* together with the steering committee and patient advisory board the perpetuating- and precipitating factors that will be evaluated have been carefully selected. However, we still may miss other factors that potentially contribute to fatigue in COPD.

CLINICAL IMPLICATIONS

The results of the *FAntasTIGUE* study will contribute to a better understanding of the physical, psychological, behavioural, and systemic factors that precipitate and/or perpetuate fatigue in patients with COPD when studied concurrently. Furthermore, it will give us more insight in the diurnal variations of fatigue and the impact of exacerbations on fatigue. These findings will provide further guidance for the development of fatigue-reducing and coping interventions to improve the daily functioning of patients with COPD. This will be an important first step in the management of COPD-related fatigue.

CONCLUSION

Fatigue is an important yet ignored symptom. A better understanding in the underlying factors of moderate to severe fatigue in patients with COPD, is essential for the development of personalized fatigue-related therapies. This manuscript describes the protocol of the *FAntasTIGUE* study and gives an overview of the possible strengths, weaknesses and clinical implications.

AUTHORS' CONTRIBUTIONS

YMJG and ML are responsible for the recruitment, data collection and data analysis. JHV is the principal investigator of Radboud university medical centre, EFWM is the principal investigator of Maastricht University Medical Centre, and MAS is the project leader. Together with DJAJ, MSYT, JBPe, CB, JWMM, MAGS, and JBPr they form the FAntasTIGUE consortium, and are responsible for the design, recruitment, and interpretation of the results. YM and AC are members of the patient advisory board. All authors contributed to the writing of this manuscript, read and approved the final version of the manuscript.

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COMPETING INTEREST STATEMENTS

Prof. Spruit discloses receiving personal remuneration for consultancy and/or lectures from Boehringer Ingelheim, GSK, Novartis, and AstraZeneca outside the scope of this work.

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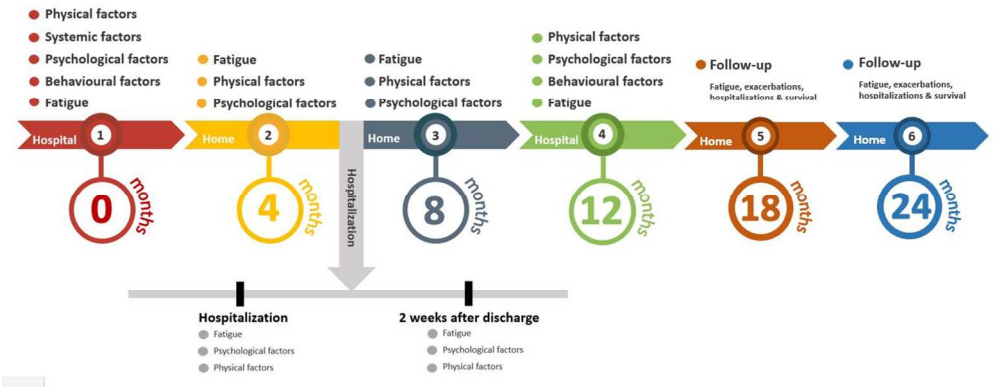
FIGURE LEGENDS

Figure 1 Timeline: measurements will be performed at baseline, and at months 4, 8 and 12. Additional measurements will be carried out when a non-elective, exacerbation-related hospitalization occurs. Patients will be followed-up at month 18 and 24.



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Fatigue in patients with Chronic Obstructive Pulmonary Disease: protocol of the Dutch multicentre, longitudinal, observational *FAntasTIGUE* study

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TITLE

Fatigue in patients with Chronic Obstructive Pulmonary Disease: protocol of the Dutch multicentre, longitudinal, observational *FAntasTIGUE* study

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ABSTRACT

Introduction: Fatigue is the second most common symptom in patients with Chronic Obstructive Pulmonary Disease (COPD). Despite its high prevalence, fatigue is often ignored in daily practice. For this reason, little is known about the underlying determinants of fatigue in patients with COPD. The primary objectives of this study are to chart the course of fatigue in patients with COPD, to identify the physical, systemic, psychological, and behavioural factors that precipitate and perpetuate fatigue in patients with COPD, to evaluate the impact of exacerbation-related hospitalizations on fatigue, and to better understand the association between fatigue and 2-year all-cause hospitalization and mortality in patients with COPD. The secondary aim is to identify diurnal differences in fatigue by using Ecological Momentary Assessment (EMA). This manuscript describes the protocol of the *FAntasTIGUE* study and gives an overview of the possible strengths, weaknesses and clinical implications.

Methods and analysis: A two-year longitudinal, observational study, enrolling 400 patients with clinically stable COPD has been designed. Fatigue, the primary outcome, will be measured by the subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue). The secondary outcome is the day-to-day/diurnal fatigue, registered in a subsample (n=60) by EMA. CIS-Fatigue and EMA will be evaluated at baseline, and at 4, 8 and 12 months. The precipitating and perpetuating factors of fatigue (physical, psychological, behavioural, and systemic), will be assessed at baseline and at 12 months. Additional assessments will be conducted following hospitalization due to an exacerbation of COPD that occurs between baseline and 12 months. Finally, at 18 and 24 months the participants will be followed-up on their fatigue, number of exacerbations, exacerbation-related hospitalization, and survival.

Ethics and dissemination: This protocol was approved by the Medical research Ethics Committees United (MEC-U), Nieuwegein, the Netherlands (NL60484.100.17). It has been registered at the Dutch Trial Register (NTR6933).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The present study is a large, longitudinal, multicenter study evaluating a wide range of possible precipitating and perpetuating factors of mild to severe fatigue in patients with COPD.
- The Ecological Momentary Assessment data will give us more insight in the diurnal variations of fatigue.
- The longitudinal design enables to examine the association between fatigue, exacerbation-related hospitalizations and mortality and allows us to investigate whether the associations between fatigue and the explaining factors are temporarily or fluctuate over time.
- The perpetuating- and precipitating factors have been carefully selected, it is –however- possible that there are other factors that contribute to fatigue in COPD that will be missed.

INTRODUCTION

Fatigue, the subjective feeling of tiredness or exhaustion, is next to dyspnoea the most common and distressing symptom in patients with Chronic Obstructive Pulmonary Disease (COPD).[1] It affects the ability to perform activities of daily living and impacts the patient's quality of life (QoL).[2, 3] Among patients with stable moderate to severe COPD, around fifty percent experiences mild to severe fatigue,[4] which is significantly higher compared to elderly, non-COPD subjects.[5] Nevertheless, despite its high prevalence and significant negative health consequences, fatigue remains often undiagnosed and, in turn, untreated.[6] This might be due to the underrepresentation of fatigue questions in commonly used health status assessment tools.[7, 8] Moreover, relatively few studies have focused on the symptom fatigue and, therefore, little is known about the precipitating and perpetuating factors of mild to severe fatigue in patients with COPD. Consequently, specific interventions aimed at reducing COPD-related fatigue are lacking. A better insight into the underlying determinants, will provide guidance for the development of personalized interventions for this important yet disregarded symptom in patients with COPD.[9]

Multiple precipitating factors are expected to play a role in the cause of COPD-related fatigue.[9] It has been suggested that COPD-specific features are associated with fatigue, since the prevalence of fatigue is higher in patients with COPD compared to elderly control subjects.[5] However, evidence suggests that fatigue is not related to the degree of airflow limitation.[4] This indicates that the degree of airflow limitation may not be the primary underlying cause of mild to severe fatigue in patients with COPD. On the other hand, a COPD exacerbation precipitates mild to severe fatigue.[5, 10] However, the size of the impact of an exacerbation-related hospitalization on fatigue remains to be clarified.

Next to precipitating factors, various physical, systemic, psychological, and behavioural factors are assumed to perpetuate mild to severe fatigue in patients with COPD. Generally, studies report significant, weak-to-moderate associations between fatigue and health status, exercise performance, physical activity, functional impairments, sleep quality, symptoms of anxiety or depression, and mood status.[2, 5, 11-15] Moreover, research indicates that COPD is associated with low-grade systemic inflammation.[16] Nonetheless, whether and to what extent low-grade systemic inflammation is related to fatigue needs to be further explored.

Thus, fatigue in COPD is a complex symptom, due to a combination of precipitating and perpetuating factors. To date, the abovementioned factors have rarely been assessed comprehensively in one

study in patients with COPD.[17] Moreover, the role of sleep apnoea, comorbidities, medication, and exacerbation-related hospitalizations are unknown. Therefore, we have designed a longitudinal, observational study, which evaluates a wide range of possible underlying factors of mild to severe fatigue in patients with COPD. This manuscript describes the protocol of the *FAntasTIGUE* study and gives an overview of its possible strengths, weaknesses and clinical implications.

Objectives of this study

The primary objectives of the *FAntasTIGUE* study are:

1.1 To chart the course of fatigue in patients with COPD.

1.2 To identify physical, systemic, psychological, and behavioural factors that precipitate and/or perpetuate fatigue in patients with COPD.

1.3 To identify the impact of exacerbation-related hospitalizations on fatigue and its perpetuating factors.

1.4 To better understand the association between baseline fatigue and 2-year all-cause hospitalization and mortality in patients with COPD.

The secondary objective of this study is:

2. To identify diurnal differences in fatigue by augmenting traditional questionnaire data with Ecological Momentary Assessment (EMA).

METHODS

The *FAntasTIGUE* study is a collaboration between CIRO (Horn, The Netherlands), Radboud university medical centre (Nijmegen, The Netherlands), Academic Medical Centre (Amsterdam, The Netherlands), Maastricht University Medical Centre (Maastricht, The Netherlands), and Hasselt University (Diepenbeek, Belgium). The consortium consists of members from various disciplines and backgrounds (e.g. chest physicians, clinical psychologists, an elderly care specialist, a cardiologist, a general practitioner, and researchers), to ensure necessary know-how to enable the successful completion of the project. Moreover, a patient advisory board is closely involved to advice and monitor the *FAntasTIGUE* project, by providing valuable insight from the patient perspective.

PATIENT AND PUBLIC INVOLVEMENT

Based on the input of patients with chronic lung disease, fatigue was prioritized as a research topic during the Netherlands Respiratory Society (NRS) meeting

(www.nationaalprogrammalongonderzoek.nl).[18] As stated, patient representatives are full members of the *FAntasTIGUE* consortium, and have an active role in the decision process. The patient advisory board has been involved in setting up the proposal, in reviewing the study design before submission to the ethical committee, and in discussing the schedules of assessment. After completion of the study, the patient advisory board will also be asked to be involved in the development of post-trial communication.

STUDY DESIGN

A two-year longitudinal, observational study, enrolling patients with clinically stable COPD has been designed (Figure 1). The assessments at baseline, 12 months, and during the first four days of a possible exacerbation-related hospitalization will be performed in a hospital setting. The remaining measurements at 4, 8, 18, and 24 months will take place at the patients' homes.

The primary outcome fatigue severity will be assessed with a questionnaire at baseline, and at 4, 8, 12, 18 and 24 months, as well as during exacerbation-related hospitalizations and two weeks after discharge. The secondary outcome, day-to-day/diurnal variation in fatigue, will be registered using Ecological Momentary Assessment (EMA) in a subsample (n=60) at baseline, and at 4, 8 and 12 months. Selection is based on convenient sampling, a "first-come, first-serve" approach. The precipitating and perpetuating factors of mild to severe fatigue in patients with COPD (physical, psychological, behavioural, and systemic factors), will be assessed at baseline and at 12 months. Also, when patients are admitted to the hospital between baseline and 12 months due to an exacerbation of COPD, some tests will be repeated during the first four days of hospitalization, and two weeks after discharge. At last, at 18 and 24 months the participants will be followed-up on their fatigue, number of exacerbations, exacerbation-related hospitalizations and survival.

ELIGIBILITY CRITERIA

To be eligible, a subject must meet the following criteria:

1. A diagnosis of COPD according to the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD, grade 1A to 4D), with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio, $FEV_1/FVC < 0.7$;[19]
2. No exacerbation-related hospitalization less than 4 weeks preceding enrolment;
3. No use of oral corticosteroids and/or antibiotics less than 4 weeks preceding enrolment;
4. Provided written informed consent.

Patients lacking a sufficient understanding of the Dutch language and/or participating in concurrent intervention studies will be excluded. There are no age or smoking status restrictions, as well as no exclusion based on comorbidities or the use of long term oxygen therapy.

Extra eligibility criteria for the EMA sub-study are:

1. Access to the internet at home (Wi-Fi);
2. Able to operate a smartphone/iPod.

RECRUITMENT

Participants will be recruited at the outpatient clinics of the Department of Respiratory Medicine in Maastricht and the Department of Pulmonary Diseases in Nijmegen, and from the registration Network of Family Practices (RNH) of Maastricht University.[20] Eligible patients from the outpatient clinics will be informed about the research by their physician during their pulmonary consultation and are asked if the investigator may contact them to provide detailed information. Patients recruited via the RNH network will receive a letter on behalf of their general practitioner introducing the research project. In case the patient agrees to participate, an appointment for the baseline assessment at the hospital will be made. Written informed consent will be obtained at the beginning of this visit.

OUTCOMES

Primary outcome

Fatigue severity will be measured by the subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue).[21] The CIS-Fatigue consists of eight items scored on a seven-point Likert scale. The scores range from 8 (normal fatigue) to 56 (most severe fatigue). A score of 26 or lower indicates normal fatigue, scores between 27 to 35 indicate mild fatigue and a score of 36 or higher indicates severe fatigue. The CIS-Fatigue is a standardized and validated questionnaire that has been used in healthy subjects,[22-24] and among various patient populations including COPD.[21, 25-27] The CIS-Fatigue will be administered at baseline, and at 4, 8, 12, 18 and 24 months, as well as during exacerbation-related hospitalizations and two weeks after discharge.

Secondary outcome

Day-to-day/diurnal variations of fatigue will be measured in a subsample (n=60) with Ecological Momentary Assessment (EMA).[28, 29] EMA involves repeated measurements of the participant's behaviour and context in vivo and in real time. In the current study, the participants will be given an iPod for the duration of the study with the EMA application (www.psymate.eu) installed. The

participants will be prompted to answer questions about their fatigue, context and surroundings, 8 times per day at random moments between 7:30 a.m. and 10:30 p.m. for 5 consecutive days at baseline, and at 4, 8 and 12 months. Patients will be given instructions to carry the device with them at all times for 5 consecutive days. Furthermore, they will be requested to fill out the questions immediately after the alert and to keep a normal day/night routine.

Explanatory factors

Table 1 provides an overview of the precipitating and perpetuating factors of mild to severe fatigue that will be assessed at baseline, and at months 4, 8, 12, 18 and 24, as well as during non-elective, exacerbation-related hospitalizations and two weeks after discharge.

Table 1 Overview outcome measurements

		Number (n)	0 months	4 months	8 months	12 months	18 months	24 months	Exacerbation-related hospitalizations*
Fatigue	Subjective fatigue subscale of the Checklist Individual Strength (CIS-Fatigue) [21]	400	•	•	•	•	•	•	•
	Ecological Momentary Assessment (EMA) [28, 29]	60	•	•	•	•			
Socio-demographic factors	Gender	400	•						
	Age	400	•						
	Social-economic status (SES) [30]	400	•						
	Marital status	400	•			•			
	Survival status	400	•	•	•	•	•	•	
Physical factors	Current medication	400	•			•			
	Charlson Comorbidity Index (CCI) [31]	400	•			•			
	Symptoms checklist [32]	400	•			•			
	mMRC dyspnoea scale [33]	400	•	•	•	•			•
	Exacerbations last 4 or 6 months (as appropriate)	400	•	•	•	•	•	•	
	All-cause hospitalizations	400	•	•	•	•	•	•	
	Body Mass Index (BMI)	400	•			•			
	Waist circumference	400	•			•			
	Bioelectrical impedance analyses [34]	400	•			•			
	6 Minute Walk Test (6MWT) [35]	400	•			•			
	Short Physical Performance Battery (SPPB) [36]	400	•			•			
	Lower-limb muscle function (MicroFet2 Wireless Hand-held Dynamometer) [37]	400	•			•			
	Hand grip strength [38]	400	•			•			
	Lung function (post-bronchodilator spirometry, whole-body plethysmography, and transfer factor for carbon monoxide)	400	•						
	Peripheral arterial disease (Dopplex D900, Huntleigh Healthcare Ltd, Cardiff, UK) [39, 40]	400	•			•			
	Resting cardiac echocardiography (Maastricht only)	200	•						
	Resting electrocardiogram (Maastricht only)	200	•						
	Retinal microcirculation [41] (Maastricht only)	200	•						
	Polysomnography (PSG) (Maastricht only)	50	•						
Psychological factors	Nijmegen Clinical Screening Instrument (NCSI) [42]	400	•			•			
	COPD Assessment Test (CAT) [8]	400	•	•	•	•			•
	Euroqol-5d-5L (EQ-5D-5L) [43]	400	•			•			
	Hospital Anxiety Depression Scale (HADS) [44]	400	•	•	•	•			•

	Montreal Cognitive Assessment (MOCA) [45]	400	•			•			
	Qualitative experience of fatigue (KWAMOE) [46]	400	•			•			
	Acceptance of Disease and Impairments Questionnaire (ADIQ) [47]	400	•			•			
	Fatigue-related self-efficacy (Self-Efficacy-5) [48]	400	•			•			
	Jacobsen Fatigue Catastrophizing Scale (FCS) [49]	400	•			•			
	Fear of Progression Questionnaire (FOPQ) [50]	400	•			•			
	Patient Activations Measure (PAM) [51]	400	•			•			
	Activity Cognitions Instrument (ACI) (self-developed questionnaire)	400	•			•			
Behavioural factors	Smoking status	400	•			•			
	Alcohol consumption	400	•			•			
	Caffeine consumption	400	•			•			
	Objectified physical activity (Actigraph GT9X Link, 3-axis activity monitor, sample frequency 30 Hz) [52]	400	•			•			
	Pittsburgh Sleep Quality Index (PSQI) [53]	400	•			•			
	Epworth Sleepiness Scale (ESS) [54]	400	•			•			
	Causal Attribution List (CAL) [55]	400	•			•			
	Sickness Impact Profile (SIP) [56]	400	•			•			
	Social Support List, Interactions and Discrepancies (SSL-I and SSL-D) [57]	400	•			•			
Systemic factors	Venous blood samples	400	•						

** Non-elective hospitalizations due to an exacerbation of COPD may occur at any moment after the start of the study. Those which occur between baseline and 12 months will result in additional measurements. Those which may occur between 12 and 24 months will not result in additional measurement.*

Questionnaires will be completed via RadQuest in the home-environment. RadQuest allows very simple online questionnaire completion. If, for any reason (e.g. no PC or internet connection), it is not possible to fill out the questionnaires via RadQuest, the participant will receive a paper version. Regarding the systemic factors, we will collect blood at baseline to assess systemic high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumornecrosisfactor-α (TNF-α), interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-1-RA (IL-1-RA), interleukin-10 (IL-10), fibrinogen, leukocytes, cortisol, haemoglobin, glucose, thyroid function (TSH), renal function (creatinine), sodium, potassium, calcium, magnesium, vitamin B12, vitamin 25(OH)D3, liver function (aspartate-aminotransferase (ASAT) and alanine-aminotransferase (ALAT)), N-Terminal pro-Brain Natriuretic Peptide (NT-pro-BNP), blood sediment (BSE), antinuclear antibodies (ANA) and deoxyribonucleic acid (DNA).

SAMPLE SIZE CALCULATION

A total of 260 patients is needed to detect a medium to small effect size of 0.175 between factors (218 (2 groups with or without an exacerbation) or 264 (3 groups normal, mild or severe fatigue)) and a small effect within-between factors (222 (3 groups normal, mild or severe fatigue)), with a power of 90%, a significance level of 5% and an expected drop-out rate of 20%.[58] Nevertheless, as a rather large number of possible perpetuating and precipitating factors will be evaluated, it is decided to augment the sample size to 400 inclusions.

For EMA, a sample of 60 patients with each 160 observations (5 days with 8 measurements, collected over 4 time points) ensures that the EMA analyses are adequately powered to detect differences in fatigue, based on a power of 0.8 and two-tailed significance of 0.05.[59]

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Missing data of questionnaires will be minimized using RadQuest, since items cannot be skipped. In case of missing data for other variables, the likeliness of this being missing at random will be assessed. If missing data is random, we will use appropriate imputation methods.[60]

All statistical analyses will be performed using statistics software (SPSS V.25.0 for Windows, Chicago, Illinois, USA). First, to characterize transitions over time in fatigue, we will use latent transition analysis.[61] Second, to identify the factors that precipitate and/or perpetuate fatigue in patients with COPD, mixed model analyses will be applied for continuous outcomes measures and generalized estimating equations for dichotomous outcomes measures. Third, to study the impact of

exacerbation-related hospitalizations on fatigue and its perpetuating factors we will use mixed model analyses. Fourth, to better understand the extent to which baseline fatigue is related to 2-year all-cause hospitalization and mortality, Cox proportional hazard models will be applied. At last, to identify whether there are diurnal differences in fatigue and what factors are associated with these variations, we will use hierarchical linear modelling as items are nested within moments and moments are nested within individuals. The responsiveness and sensitivity of the fatigue questionnaire versus EMA data are compared with effect sizes (Cohen's d) for the component of observed change derived from model parameters. *A priori*, a two-tailed p-value of <0.05 is considered significant.

ETHICS AND DISSEMINATION

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subject Act (WMO). MEC United approved the study on December 22, 2017 (R17.036/NL60484.100.17). The study was registered on www.trialregister.nl on January 8, 2018. The results will be submitted for publication in peer-reviewed journals and will be presented at (inter)national conferences.

DISCUSSION

The *FAntasTIGUE* study has been designed to identify the factors that perpetuate and/or precipitate mild to severe fatigue in patients with COPD. The novel findings will hopefully further guide the development of tailored interventions, which –in turn- will help to diminish the impact on daily life of this important yet ignored symptom.

STRENGTHS

A major strength of the *FAntasTIGUE* study is that a wide range of possible precipitating and perpetuating factors will be tested concurrently in one model of stable patients with COPD. Moreover, the *FAntasTIGUE* study also examines the impact of an exacerbation-related hospitalization on fatigue. This way, we aim to identify relevant factors that explain variance in fatigue. Another strength of this study is the use of EMA to capture diurnal variations of fatigue in patients with COPD. In comparison with the usual web-based or paper-and-pencil questionnaires, data gathered via EMA are not subject to recall bias and provide us with a film of variations in the patient's fatigue in their natural environment rather than a snapshot. To our knowledge, this is the

first study that uses EMA to evaluate fatigue in a population of patients with COPD. The information about the diurnal variations of fatigue will further help us to tailor interventions for reducing fatigue in patients with COPD. Moreover, EMA provides us with contextual information of factors that could precipitate or perpetuate fatigue. A methodological strength of this study is the longitudinal design. It enables us to examine the association between fatigue, exacerbation-related hospitalizations and mortality. Moreover, it allows us to investigate if the associations between fatigue and the precipitating and perpetuating factors are temporarily or can change over time. And last, the structure of the *FAntasTIGUE* consortium, including a steering committee and a patient's advisory board, allows us to improve the research capacity, to share (academic) resources, to disseminate study results and to speed up future research.

LIMITATIONS

The present study may encounter the following limitations: *first,* despite the benefits of repeated measurements in longitudinal studies, higher drop-out rates are expected as disease progresses. This attrition could result in a biased sample, which may compromise the study's generalizability. To limit the loss to follow-up, we will minimize the burden as much as possible and keep close contact with the patients. The patient advisory board has been intimately involved in the design of the *FAntasTIGUE* project to balance patient burden and number of variables that needed to be assessed to identify the factors that perpetuate and/or precipitate mild to severe fatigue in patients with COPD. *Second,* the current study selection is based on convenience sampling. This may cause selection bias, since participants with a lack of motivation and a higher disease burden are less likely to respond. We will try to prevent selection bias, by inviting all patients who are diagnosed with COPD either via their physician during consultation hour or via their own general practitioner. *Third,* together with the steering committee and patient advisory board the perpetuating- and precipitating factors that will be evaluated have been carefully selected. However, we still may miss other factors that potentially contribute to fatigue in COPD.

CLINICAL IMPLICATIONS

The results of the *FAntasTIGUE* study will contribute to a better understanding of the physical, psychological, behavioural, and systemic factors that precipitate and/or perpetuate fatigue in patients with COPD when studied concurrently. Furthermore, it will give us more insight in the diurnal variations of fatigue and the impact of exacerbations on fatigue. These findings will provide further guidance for the development of fatigue-reducing and coping interventions to improve the

daily functioning of patients with COPD. This will be an important first step in the management of COPD-related fatigue.

AUTHORS' CONTRIBUTIONS

YMJG and ML are responsible for the recruitment, data collection and data analysis. JHV is the principal investigator of Radboud university medical centre, EFWM is the principal investigator of Maastricht University Medical Centre, and MAS is the project leader. Together with DJAJ, MSYT, JBPe, CB, JWMM, MAGS, and JBPr they form the FAntasTIGUE consortium, and are responsible for the design, recruitment, and interpretation of the results. YM and AC are members of the patient advisory board. All authors contributed to the writing of this manuscript, read and approved the final version of the manuscript.

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COMPETING INTEREST STATEMENTS

Prof. Spruit discloses receiving personal remuneration for consultancy and/or lectures from Boehringer Ingelheim, GSK, Novartis, and AstraZeneca outside the scope of this work.

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FIGURE LEGENDS

Figure 1 Timeline: measurements will be performed at baseline, and at months 4, 8 and 12. Additional measurements will be carried out when a non-elective, exacerbation-related hospitalization occurs. Patients will be followed-up at month 18 and 24.

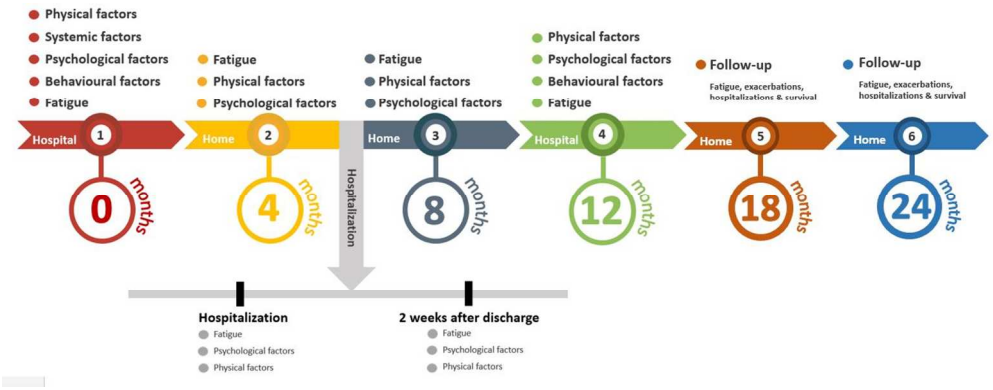

Figure 1 Timeline: measurements will be performed at baseline, and at months 4, 8 and 12. Additional measurements will be carried out when a non-elective, exacerbation-related hospitalization occurs. Patients will be followed-up at month 18 and 24.

114x43mm (300 x 300 DPI)