

# BMJ Open Factors associated with severity and persistence of fatigue in patients with primary biliary cholangitis: study protocol of a prospective cohort study with a mixed-methods approach (SOMA.LIV)

Anne Toussaint <sup>1</sup>, Laura Buck,<sup>1</sup> Johannes Hartl,<sup>2</sup> Bernd Löwe <sup>1</sup>, Christoph Schramm<sup>2,3</sup>

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<sup>1</sup>Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

<sup>2</sup>i. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

<sup>3</sup>i. Department of Medicine and Martin Zeitz Centre for Rare Diseases, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

**Correspondence to**  
Dr Anne Toussaint;  
[a.toussaint@uke.de](mailto:a.toussaint@uke.de)

## ABSTRACT

**Introduction** Fatigue is a common symptom and the major ‘unmet need’ in the management of patients with primary biliary cholangitis (PBC). To date, only few prospective studies have addressed the development of PBC-associated fatigue over time. At the same time, few biological and psychosocial risk factors and mechanisms have been identified that could explain the development and maintenance of fatigue in PBC. It is the overall aim of this study to identify factors that determine the course and severity of fatigue in PBC, and to target these factors within deliverable interventions in order to improve patients’ quality of life.

**Methods and analysis** To identify biological and psychosocial risk factors for severe fatigue, a prospective 12-month cohort study with one baseline and two follow-up measurements will be conducted. In a cross-sectional part, we will simultaneously examine clinically relevant biomedical and psychosocial factors and systematically assess and compare associations and interactions between these factors and fatigue in n=240 patients with PBC (a patient group severely affected by fatigue) and n=240 patients with primary sclerosing cholangitis, a control cholestatic liver disease group much less affected by fatigue. In a prospective part, we will longitudinally monitor these variables and assess their predictive value at 12-month follow-up. Within an embedded mixed-methods design, we will conduct an experimental study and qualitative interviews in patients with newly diagnosed PBC.

**Ethics and dissemination** The study was approved by the Ethics Committee of the Hamburg Medical Association (2020–10196-BO-ff). The study will shed light onto the mechanisms underlying the evolvement and maintenance of fatigue in patients with PBC and enable the development of evidence-based intervention strategies. Findings will be disseminated through peer-reviewed publications, scientific conferences and the involvement of relevant stakeholders, patients and the lay public.

**Trial registration number** ISRCTN14379650.

## INTRODUCTION

### Background

SOMA.LIV is one of seven individual projects that are realised by the research unit

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study simultaneously examines biomedical and psychosocial risk factors for fatigue in patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).
- ⇒ The prospective study design allows to examine the predictive value of predefined risk factors for the evolvement and persistence of fatigue in patients with PBC and PSC.
- ⇒ The embedded experimental study focuses on the role of expectations by examining whether anticipated fatigue correlates with actual performance and perceived fatigue after physical activity.
- ⇒ The qualitative study explores patients’ subjective perception, causal attributions and experience of fatigue and gives insight into their specific needs for support and treatment.
- ⇒ Although measures to control for covariates will be taken, the risk of confounding variables associated with an observational study design cannot be completely ruled out.

on Persistent SOMatic Symptoms ACROSS Disease (SOMACROSS, RU5211), led by the University Medical Center Hamburg-Eppendorf (UKE). The overall aim of this interdisciplinary research unit is the identification of risk factors and mechanisms for the persistence of somatic symptoms across diseases and the development of a disease-overarching multivariable prediction model for persistent somatic symptoms (PSS).<sup>1</sup> SOMA.LIV specifically focuses on patients with primary biliary cholangitis (PBC) and has the primary objective to identify biomedical and psychosocial risk factors that determine the course and severity of fatigue as the main unmet clinical need in PBC.<sup>2</sup> As a multidimensional construct, fatigue affects patients on a physical, psychological and

cognitive level and is a major determinant of patients' quality of life (QoL).<sup>3</sup> However, fatigue is largely resistant to current treatment modalities and the mechanisms leading to its development and persistence are mostly unknown.<sup>4</sup> This study is based on an integrated biopsychosocial approach that will allow us to simultaneously explore a broad range of potential influences on fatigue in PBC. Thereby, we will include 'innovative' risk factors such as intestinal microbiota alterations and apprehensive expectations, which have received little attention in fatigued patients with PBC before. Results will improve our understanding of the mechanisms underlying fatigue in PBC and form the basis for future interventions and treatment approaches.

### Primary Biliary Cholangitis

#### *Clinical presentation, prevalence and aetiology*

PBC is an autoimmune, chronic inflammatory disease of the intrahepatic bile ducts, which can lead to cholestasis, fibrosis progression and liver cirrhosis in patients with inadequate treatment response.<sup>5</sup> The incidence ranges from 0.33 to 5.8 per 100 000 persons/year with a prevalence from 1.91 to 40.2 per 100 000 persons.<sup>6</sup> About 9 out of 10 persons affected by PBC are women. Elevated markers of cholestasis, presence of circulating anti-mitochondrial antibodies or other specific antinuclear autoantibodies, and in selected cases, typical liver histology is used for diagnosis.<sup>7</sup> The course of PBC is most often accompanied by the occurrence of non-specific symptoms such as fatigue, sicca or pruritus with up to 70% of patients reporting such symptoms.<sup>8</sup> The pathogenesis of PBC is incompletely understood, but genetic predisposition combined with external triggers such as environmental exposure, bacterial metabolism of xenobiotics or gut microbiota probably initiates the disease.<sup>3,9</sup>

#### *Fatigue in PBC*

Fatigue is the most commonly reported symptom of PBC, with more than 40% of patients reporting moderate to severe levels.<sup>10</sup> Being a major determinant of patients' QoL, it severely impairs daily activities in 20%–30% of patients and is the most prominent factor limiting the ability to work.<sup>11</sup> In the other cholestatic autoimmune bile duct disease, primary sclerosing cholangitis (PSC), fatigue is less frequent and affects patients' QoL to a much lesser extent.<sup>12</sup> Unrelated to the severity of liver disease, fatigue may occur even in early stages of PBC, and it is largely unclear how it evolves and maintains over time,<sup>13</sup> whereas ursodeoxycholic acid as standard treatment of PBC improves biochemical abnormalities and liver transplantation-free survival, there is no evidence for an effect on fatigue. Fatigue in PBC tends to remain stable over time and is often irreversible after liver transplantation. Its presence is independently associated with increased mortality, particularly from cardiovascular disease.<sup>13</sup>

#### *Biomedical factors*

The pathogenesis of fatigue is complex and presumably multifactorial, with associated peripheral and central nervous system (CNS) features. Cholestasis-related CNS changes, which may drive autonomic dysfunction, abnormalities in sleep patterns and bioenergetic function of skeletal and cardiac muscle have been reported in patients with fatigue.<sup>10</sup> Moreover, elevation of inflammatory cytokines or progesterone metabolites has been postulated as underlying mechanisms of fatigue in PBC and other chronic inflammatory conditions such as rheumatoid arthritis (RA).<sup>3,14</sup> More recently, data demonstrated that inflammatory cytokine levels were elevated but unrelated to fatigue severity in patients with PBC,<sup>15</sup> suggesting that further non-inflammatory factors mediate and predispose certain patients to fatigue. Intestinal microbiota are now well-recognised modulators of central nervous function ('brain-gut axis').<sup>16</sup> Stool microbiota alterations have been reported for patients with PBC,<sup>17</sup> and there is evidence of gut microbiota dysbiosis contributing to the pathomechanism of chronic fatigue syndrome (CFS).<sup>18</sup>

#### *Psychological factors*

There is a growing body of literature suggesting that psychological factors, such as patients' beliefs, play a significant role in the persistence of somatic symptoms.<sup>19</sup> For example, patients with RA usually attribute fatigue to disease activity, side effects of medication or unrefreshing sleep, while they consider effects on physical activities, emotions or relationships as consequences of fatigue.<sup>20</sup> Current conceptual models of PSS encompass multiple and mutually interacting biomedical, psychological and social factors. These include, but are not limited to, disease process-related factors, physical activity, psychological functioning, comorbidities, biographical variables and others.<sup>19</sup> In terms of psychological putative causes, 'general' psychosocial variables, such as higher levels of psychological distress, childhood trauma or life stressors, have been reported in patients with PBC, but the link to fatigue is still poorly understood.<sup>21</sup> More specific factors such as high catastrophising, low perceived self-efficacy and dysfunctional coping have been identified as triggering, maintaining and aggravating factors in conceptual models of PSS<sup>19</sup> but have not been explicitly studied in patients with PBC and fatigue yet. Integrated biopsychosocial research in patients with multiple sclerosis (MS) and poststroke found a fatigue-enhancing cycle of avoidance behaviour towards physical activity and depression,<sup>22,23</sup> whereas cognitive behavioural therapy reduced fatigue in patients with MS,<sup>22</sup> and graded exercise therapy moderately improved outcomes for patients with CFS.<sup>24</sup> The effectiveness of a home-based exercise programme to reduce refractory fatigue in patients with PBC is currently being studied.<sup>25</sup> A recent systematic review on fatigue in RA stated that multivariate and longitudinal associations were too seldom assessed to draw firm conclusions on biopsychosocial pathways.<sup>26</sup> The same appears true for fatigue in PBC.

### Research needs

Being the most commonly reported symptom of PBC, fatigue is a major burden on patients and severely impairs their functioning in various spheres of life.<sup>3</sup> There is a lack of evidence regarding its underlying biomedical and psychosocial mechanisms and current treatment modalities rarely alleviate symptoms of fatigue in patients with PBC. Only few prospective studies have addressed the evolution of PBC-associated fatigue over time and biological and psychosocial risk factors have scarcely been examined simultaneously. Therefore, prospective studies that apply a comprehensive approach and integrate potential biomedical and psychological risk factors of fatigue are needed to answer the question of who is at risk for severe and chronic fatigue, and whom to target for treatment.

### Objectives and hypotheses

#### Objective 1

To identify group differences in frequency and severity of fatigue and its underlying biomedical and psychosocial determinants in patients with PBC and PSC.

#### Objective 2

To determine the relative role and interaction of the prespecified biomedical and psychosocial predictors for severity of fatigue in patients with PBC at 12-month follow-up.

#### Objective 3

To explore the role of intestinal microbiota composition and symptom expectations as hypothesised predictors of fatigue severity.

In order to complement our quantitative data by evidence other than self-report, we will embed an *experimental study* (objective 4) and *qualitative interviews* (objective 5) in subsamples of patients. The qualitative study will be restricted to patients with newly diagnosed PBC. Both approaches represent a valuable opportunity for an in-depth exploration of mechanisms of fatigue perception, development and maintenance.

#### Objective 4

To test associations of expectation, exercise performance and experienced fatigue.

#### Objective 5

To understand processes of fatigue development after new diagnosis of PBC by longitudinally investigating individual symptom perceptions, causal attributions and expectations. As this is an exploratory objective, no specific hypothesis will be tested.

Four hypotheses are assigned to the respective research objectives:

#### Hypothesis 1

Biomedical and psychosocial factors account for differences in fatigue experience between patients with PBC and PSC.

#### Hypothesis 2

Biomedical risk factors (eg, inflammatory cytokines, autonomic dysfunction) and psychological risk factors (eg, depression, avoidance) predict the severity of fatigue among patients with PBC at 12-month follow-up, and their interplay determines its course over time.

#### Hypothesis 3a

Intestinal microbiota alterations are independently or conjointly with other biomedical and psychosocial factors associated to the severity of fatigue in patients with PBC.

#### Hypothesis 3b

Expectation of fatigue severity independently or conjointly with biomedical and psychosocial factors determines the severity of fatigue in patients with PBC.

#### Hypothesis 4

Higher anticipated fatigue prior to a stair climbing task will correlate with worse performance and more severe post fatigue.

## METHODS AND ANALYSIS

### Study design

#### Study design and rationale

This is a prospective single-centre cohort study with one baseline and two follow-up measurements during a 4-year period (1 October 2021—30 September 2025) (figure 1). Follow-up measurements will take place after 6 and 12 months. Information will be collected through self-report questionnaires, blood and stool samples. The experimental study will be conducted at 6-month follow-up with 20 patients that reported high fatigue scores, and 20 patients with low fatigue scores at baseline, respectively. Our embedded qualitative study will be conducted in a subsample of n=48 patients with newly diagnosed PBC. The experimental approach aims to explore the interaction between symptom expectations and self-perceived fatigue while the qualitative approach may capture the context and complexity of participants' illness representations and management strategies.

#### Setting

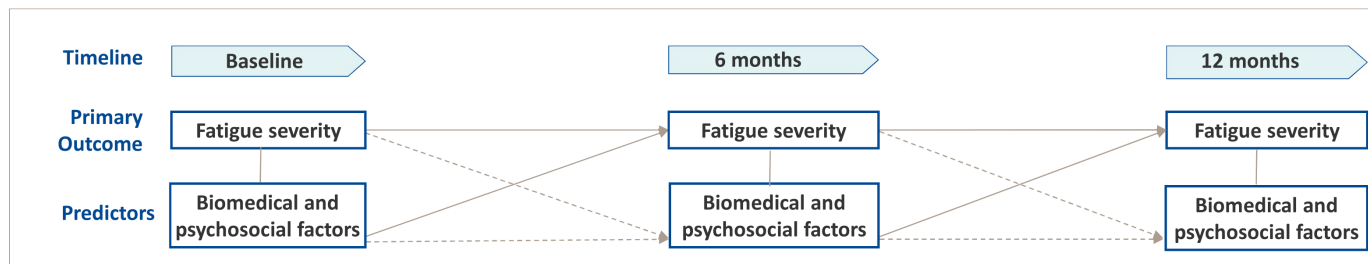
The study will be carried out at the YAEL-Center for Auto-immune Liver Disease of the UKE. After having received written information on the study, eligible patients will receive details on the study procedure at their semi-annual appointment at the YAEL Center. Enrolment for the cohort study is planned to be carried out over 12 months. Patients with newly diagnosed PBC will be informed about the study before their first appointment at the outpatient department. Once they agree to participate, they will take part in the qualitative study before receiving a confirmed diagnosis of PBC. Enrolment of this subgroup is planned to take 24 months.

#### Inclusion criteria

Our study population will consist of adult patients with a clinical diagnosis of PBC according to the most recent

### Observational prospective cohort study

- Study population: n=240 patients with Primary Biliary Cholangitis (PBC)
- Control: n=240 patients with Primary Sclerosing Cholangitis (PSC)



### Longitudinal qualitative study ➤ Patients with newly diagnosed PBC

#### Experimental study

- Patients with lowest and highest fatigue scores

#### Microbiome analyses

**Figure 1** Study design of the prospective cohort study.

European practice guidelines.<sup>8</sup> Furthermore, prerequisites are sufficient oral and written German language proficiency to complete self-report questionnaires and interviews and provision of written informed consent.

#### Exclusion criteria

Advanced cirrhosis (defined as Child Pugh score of  $\geq 8$ ), decompensated liver disease or liver transplantation; history or presence of other concomitant liver disease (autoimmune hepatitis or chronic viral hepatitis B or C); presence of clinically significant untreated intercurrent medical condition itself associated with fatigue (ie, hypothyroidism, anaemia, fibromyalgia, RA, systemic lupus erythematosus and manifest depression); antibiotic treatment during the past 6 weeks will preclude participation in microbiome study; ongoing participation in other clinical trials investigating fatigue; intercurrent active or latent infection; florid psychosis, substance abuse disorder, and acute suicidality.

#### Treatments

The study investigates the natural course of fatigue in PBC and there will be no causal treatment of fatigue within the scope of this study. However, patients might be treated by another healthcare provider and other therapies may influence the course of fatigue. We will consider received treatments as a covariate in the statistical analysis.

The *comparison group* will consist of patients with a clinical diagnosis of PSC, established according to generally accepted criteria.<sup>27</sup> Because of the unbalanced sex distribution of PBC and PSC patients at diagnosis, one-on-one matching will not be fully possible. Matched controls will be selected wherever possible, and sex differences will be accounted for in the multivariable regression analysis.

#### Patient involvement

The YAEL Center has a pre-existing patient advisory board. During the preparation stage of the study, board members will advise the study team on the display of the study material, and the qualitative interview questions pertinent to patients with PBC.

#### Experimental study (objective 4)

Symptom expectations and related psychological processes influence the performance of physical activities.<sup>28</sup> In a subgroup of patients who reported low and high fatigue scores at baseline, we will measure performance (duration and increase in heart rate) during self-paced climbing and descending of stairs at 6-month follow-up. Increase in heart rate is defined as the difference between the heart rate after descending the last step of stairs and the baseline heart rate. Heart rate will be measured using a mobile device (ie, electrocardiographic sensors by movisens GmbH). Baseline heart rate will be measured right before stair climbing in standing position at the base of the stairs after a 5 min rest. Before this task, patients will rate momentary fatigue and anticipated fatigue after stair climbing. After the task, they will rereate experienced fatigue. We will test whether performance during stair climbing and postexperienced fatigue can be explained by pre-experienced and anticipated fatigue and further psychological factors (eg, kinesiophobia, catastrophising).

#### Qualitative interviews (objective 5)

Since the subsample of patients with newly diagnosed PBC is of special interest in terms of development and maintenance of fatigue, we will evaluate them in detail. In order to complement the quantitative data, patients will undergo semistructured interviews before their first medical consultation at the YAEL Center, and at

6-month and 12-month follow-up. The interviews provide an opportunity for an in-depth examination of expectations on fatigue, that is, on the perception and course of fatigue, causal attributions, effects of treatment and on the ability to cope with the disease and symptoms.

## Assessment and study outcomes

### Measurement points

Assessments are carried out at baseline and after 6 and 12 months. All questionnaires are selected based on their validity, previous use in this specific population, availability of reference values and length. [Table 1](#) provides an overview of all constructs, self-report instruments and laboratory test parameters, number of items and measurement times.

*Patients' socioeconomic characteristics* will be assessed via self-report. Clinical data such as histologic grade, duration of disease and medication will be extracted from medical records.

### Primary outcome

The Fatigue Visual Analogue Scale (Fatigue-VAS) score and the Primary Biliary Cirrhosis-40 (PBC-40) fatigue domain score will be used as primary outcome measures for the severity of fatigue. The Fatigue-VAS assesses fatigue severity over the past week with the anchors: no fatigue (0 mm) and extremely fatigued (100 mm). We will differentially assess global, physical and mental fatigue severity via three individual VAS. The PBC-40 is a fully validated patient-derived QoL measure that includes a fatigue domain with a potential value range of 11–55 and higher values denoting worse fatigue. Although PBC-specific, the PBC-40 has also been used as a patient-reported outcome measure in patients with PSC.<sup>29</sup>

*Secondary outcomes* include total somatic symptom severity (PHQ-15),<sup>30</sup> symptom intensity (Numeric Rating Scale (NRS)), symptom interference with daily activities (NRS),<sup>31</sup> symptom-related disability (adapted Pain Disability Index (PDI)),<sup>32</sup> pruritus intensity (NRS)<sup>31</sup> and general mental and physical QoL (Short Form 12 (SF-12)).<sup>33</sup> Furthermore, we will assess disease-specific QoL using the respective domains of the PBC-40.<sup>34</sup>

### Biomedical and psychosocial predictors

Blood samples will be drawn to assess serum levels of C reactive protein, interleukin 6 and tumour necrosis factor as systemic biomarkers of central sensitisation to shed light on the controversial role of central sensitisation in the persistence of somatic symptoms across all projects of RU SOMACROSS.<sup>35</sup> Faecal samples will be collected for microbiome analysis.

Daytime somnolence, vasomotor autonomic dysfunction, physical inactivity, depression, anxiety, health anxiety, illness cognitions, causal attributions, coping, illness behaviour, somatosensory amplification, expectations, nutrition and stool condition will be assessed via self-report.

Additionally, we will apply joint RU SOMACROSS core instruments to identify risk factors and mechanisms for the persistence of somatic symptoms across diseases. Supplements from the core set include adverse childhood experiences, neuroticism, negative affectivity, emotion regulation, alexithymia, life stressors, perceived stigmatisation and diagnosis of somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders.<sup>36</sup>

### Sample size

Sample size calculation is based on the prediction model we aim to develop for the course of fatigue. A rule of thumb states that the number of 'events' should be  $\geq 10$  for every variable in a multivariate prediction model.<sup>37</sup> We plan to develop a model with approximately eight variables. A sample size of  $n=240$  patients per group (prevalent PBC and PSC) is needed to estimate a model based on an expected event rate (severe persistent fatigue) of at least 40%. This includes an assumption of 10% attrition at 6-month and 12-month follow-up, respectively (based on experience in clinical trials on PBC<sup>13</sup>). A sample of approximately 40 patients with PBC will be included in the qualitative study. The exact sample size will depend on the theoretical saturation of the research question, that is, reaching the point of information redundancy.<sup>38</sup> Shotgun metagenomic sequencing in order to identify bacterial species and functional annotations in the stool samples will be performed in the last year of the project in  $2 \times 50$  patients with PBC,  $2 \times 30$  patients with PSC and  $2 \times 10$  patients with newly diagnosed PBC, grouped in patients with lowest and highest fatigue scores, respectively. As this is an exploratory analysis of associations between microbiota and fatigue, an exact sample size calculation cannot be performed, but based on previous experiences, the intended group sizes will be sufficient.<sup>39–41</sup> [Figure 2](#) shows the anticipated flow of participants throughout the trial.

### Feasibility of recruitment

Eligible patients will be recruited at the YAEL—Center for Autoimmune Liver Disease of the UKE. The Center provides care for approximately 700 patients with PBC, 500 patients with PSC each year and around 40 newly diagnosed PBC patients.

### Statistical methods

The prevalence and distribution of fatigue and covariables at the respective time points will be examined by descriptive analyses in the two study groups and interaction tests will be performed to investigate whether the cohorts differ systematically (*objective 1*). In case of a significant interaction, a multivariate model consisting of approximately eight determinants (mixed-effects models (logistic and linear)) will be used to examine predictors for the severity of fatigue (*objectives 2 and 3*). For validation of models, a random-fold cross-validation will be used. Analyses will be repeated for secondary outcomes and within the subsample of newly diagnosed patients.

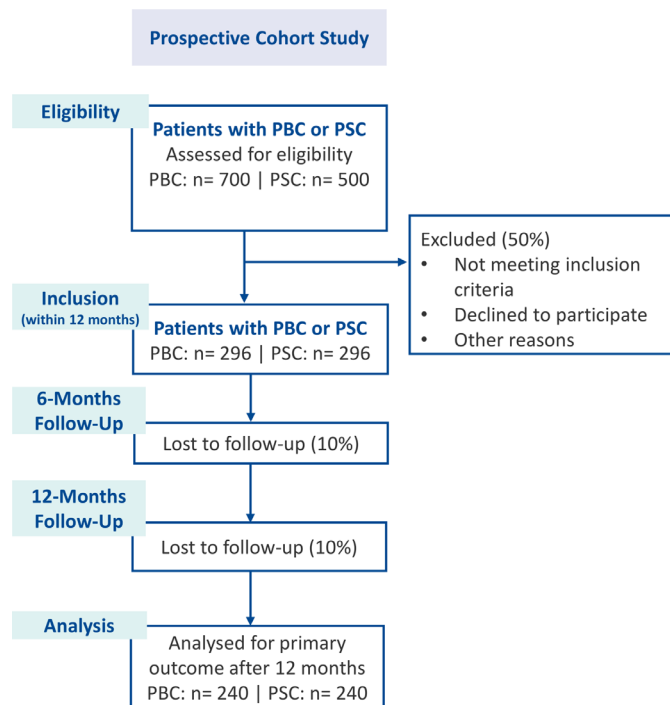
**Table 1** Joint core instruments of RU SOMACROSS and specific instruments additionally used by SOMA.LIV\* (assessed via patient self-report/laboratory test)

Predisposing, triggering and maintaining/aggravating factors	Single constructs	Instrument	Months			
			Items	0	6	12
Sociodemographic factors	Gender, age, nationality, heights, weights, marital status, migration status, current housing situation, insurance, education, occupational status, smoking behaviour, use of antibiotics	Single items	18	X		
	Healthcare utilisation	Multiple questions	3	X	X	X
Psychosocial factors	COVID-19 questions	Multiple questions	7	X	X	X
	Adverse childhood experiences	Adverse Childhood Experiences Questionnaire (ACE-D)	10	X		
	Personality: neuroticism	Big Five Inventory-10 (BFI-10)	10	X		
	Negative affectivity	Positive and Negative Affectivity Schedule (PANAS)	20	X		
	Life stressors	Perceived Stress Scale (PSS-10)	10	X		
	Perceived stigmatisation	Single items	2	X		
	Somatosensory amplification	Somatosensory Amplification Scale (SSAS)	10	X	X	X
Cognitive perceptual and emotional mechanisms	Catastrophising	Coping Strategies Questionnaire—Catastrophizing Subscale (CSQ-CAT)	6	X	X	X
	Treatment expectations	Treatment Expectation Questionnaire (TEX-Q)	15	X	X	X
	Expectation of symptom severity	Numeric Rating Scale	1	X	X	X
	Expectation of symptom burden	Numeric Rating Scale	1	X	X	X
Expectation of coping with symptoms	Expectation of coping with symptoms	Numeric Rating Scale	1	X	X	X
	Psychological burden related to somatic symptoms or associated health concerns	Somatic Symptom Disorder-B Criteria Scale (SSD-12)	12	X	X	X
	Illness-related worries	Whiteley-Index Short Version (WI-7)	7	X	X	X
Symptom perception	Symptom perception	Illness Perception Questionnaire (B-IPQ)	8	X	X	X
	Anxiety	Generalized Anxiety Disorder-7 (GAD-7)	7	X	X	X
Depression	Depression	Patient Health Questionnaire-9 (PHQ-9)	9	X	X	X
	Alexithymia	Toronto Alexithymia Scale (TAS-20)	20	X		
Emotion regulation	Emotion regulation	Emotion Regulation Questionnaire (ERQ)	10	X		
	Fear of movement*	Tampa Scale for Kinesiophobia (TSK)	11	X	X	X
Behavioural factors	Physical inactivity/avoidance	International Physical Activity Questionnaire (IPAQ-SF)	7	X	X	X
	Nutrition*	Food Frequency Questionnaire	57	X		
	Illness behaviour	Somatic Symptom Disorder-B Criteria Scale (SSD-12)	listed above			

Continued

**Table 1** Continued

Predisposing, triggering and maintaining/aggravating factors	Single constructs	Instrument	Months			
			Items	0	6	12
Biomedical factors	Duration of disease	Single interview questions	2	X		X
	Medication	Single interview question	1	X		X
	Medication adherence	Medication Adherence Report Scale (MARS-D)	5	X	X	X
	(Prior) organic disease/comorbidity	Self-Administered Comorbidity Questionnaire (SCQ-D)	28	X	X	X
	Daytime somnolence*	Epworth Sleeping Scale (ESS)	8	X	X	X
	Autonomic dysfunction*	Orthostatic Grading Scale (OGS)	5	X	X	X
	Treatment experiences	Numeric Rating Scale	2	X	X	X
	Side effects	Numeric Rating Scale	1	X	X	X
	Systemic inflammation, markers of central sensitisation (projects 1–6)	C reactive protein (CRP) Interleukin 6 (IL-6) Tumour necrosis factor alpha (TNF $\alpha$ )			X	
	Intestinal inflammation	Faecal calprotectin		X		
	Stool microbiota alterations*	Shotgun metagenomics sequencing		X		
	Stool texture*	Bristol Stool Form Scale (BSFS)	1	X		
	Outcome variables (assessed via self-report/diagnostic interview)					
	Somatic symptoms	Somatic symptom burden	Patient Health Questionnaire-15 (PHQ-15)	15	X	X
Symptom intensity		EURONET-SOMA Numeric Rating Scale	1	X	X	X
Severity of fatigue*		VAS PBC-40 fatigue domain	3 11	X X	X X	X X
Functioning/health-related quality of life	Pruritus and other somatic symptoms*	Pruritus scale, PBC-40 somatic symptoms	13	X	X	X
	Symptom interference	EURONET-SOMA Numeric Rating Scale	1	X	X	X
	Symptom-related disability	Pain Disability Index-adapted (PDI)	7	X	X	X
	Health-related quality of life	Short Form Health Survey (SF-12)	12	X	X	X
Diagnosis of somatic symptom disorder (DSM-5)	Disease-specific QoL*	PBC-40 cognitive, emotional, social domains	22	X	X	X
	Diagnostic classification	Structured Clinical Interview for the DSM-5 (SCID)	18	X		X
	Total (self-report items)		418			
PBC-40, Primary Biliary Cirrhosis-40; QoL, quality of life; SOMACROSS, Somatic Symptoms ACROSS Disease; VAS, Visual Analogue Scale.						



**Figure 2** Anticipated flow of participants through the course of the study. PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

Data will be imputed if more than 5% are missing. In accordance with White *et al.*,<sup>42</sup> the number of imputations will be chosen depending on the proportion of missing data. *Objective 4*: Spearman correlations will be calculated for the duration of stair climbing and anticipated fatigue, the difference between anticipated and experienced fatigue and the additional psychological variables. Significant correlations will be corrected for sex, age, body mass index and symptoms before stair climbing using multiple regression analysis. Software packages SPSS, SAS and R will be used for all analyses. *Objective 5*: interviews will be digitally recorded, fully transcribed and evaluated by means of reflexive thematic analysis.<sup>38</sup> In a two-step approach, we will shed light on known risk factors and their interplay (top-down), and in addition, explore new putative risk factors.

#### Methods against bias

Outcome assessment will be either self-reported or performed by a trained interviewer. Data will be directly entered into electronic databases, avoiding error-prone transfer from paper to electronic databases. Hypothetically, the prevalence of severe fatigue may be higher among patients who refuse to participate. To minimise selection bias, we will stimulate all eligible patients to participate, even if they have severe symptoms. A non-response analysis will be performed. It is conceivable that patients with severe fatigue may prematurely discontinue study participation (attrition bias), as participation costs energy, but has no apparent personal advantages. To stimulate continuation of participation, small incentives will be provided. In case of discontinuation, efforts will

be made to continue to obtain follow-up data. In addition, baseline characteristics, including severity of fatigue, will be compared between participants and dropouts. Data will be reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for reporting observational studies.<sup>43</sup> The study was prospectively registered at the ISRCTN registry.

## ETHICS AND DISSEMINATION

### Ethical approval

The study protocol was approved by the Ethics Committee of the Hamburg Medical Association on 25 January 2021 (processing number: 2020–10196-BO-ff). The trial will be conducted in accordance with the WMA Declaration of Helsinki, guidelines for Good Clinical Practice, national and local laws. The study includes the smallest necessary number of patients to test for significant effects. Before inclusion, eligible participants are informed about the course of the study verbally and in written form and they will provide written informed consent. All patients will receive financial compensation of 15 €/hour for time expenditure at each assessment point. The data will be stored in pseudonymised form. Any changes to the study protocol will be listed in the study registry and publications.

### Adverse events

This is a non-interventional cohort study with minimal adverse event risk due to study participation. Nevertheless, adverse events not related to the study may occur. Patients may develop severe somatic or psychiatric complications. In case of an emergency, immediate medical treatment will be initiated. All participants will be given a study emergency number to contact the study team.

### Suicide risk

Patients at risk to commit suicide may be detected, either by the PHQ-9 questionnaire or during the course of the study. If patients endorse suicidal ideation, additional questions will be presented to judge severity and clinical relevance of the suicidal thoughts. A proven algorithm on how to process cases of suicidal ideation is already available as it was used in prior studies (eg, GETFEEDBACK. GP trial<sup>44</sup>).

### Documentation and stopping rules

Adverse events will be monitored and reported to the supervisory board. For the individual patient, the study procedure will end in case of an adverse event, that is, acute suicidality or acute emergency condition, or withdrawal of informed consent. The study will be discontinued in case the applicants or supervisory board detect significant associations between study participation and adverse events. They will thoroughly evaluate whether study continuation complies with ethical considerations.



The study will also be terminated if procedures to handle adverse events are non-compliant with ethical standards.

### Possible disadvantages of participating in the study

Since the study procedure does not influence patients' regular medical treatment and both patient groups receive 'care as usual', there are no disadvantages for participants compared with non-participants.

### Data sharing

In accordance with the approval of the ethics committee, deidentified individual patient data will be made publicly available. Times and the conditions of the availability of data will be in accordance with the 'Recommendations for Sharing Clinical Trial Data' of the Institute of Medicine. The full data package (ie, analysable data set, protocol, statistical analysis plan and statistical programming code) will be freely available through a clinical data repository (eg, Dryad Digital Repository) and saved for at least 10 years. Data sharing will follow FAIR Data Principles (Findable, Accessible, Interoperable and Reusable) and international naming conventions (eg, Systematized Nomenclature of Medicine) to maximise transparency and scientific reproducibility. According to the WHO Statement on Public Disclosure of Clinical Trials ([www.who.int/ictrp/results/reporting/en/](http://www.who.int/ictrp/results/reporting/en/)), the main findings will be submitted for publication in a peer-reviewed journal with open access within 12 months of study completion. Results will be presented at national and international scientific conferences, and disseminated through the RU SOMACROSS website. Scientific results will be communicated in lay language via press releases and patient forums.

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### ORCID iDs

Anne Toussaint <http://orcid.org/0000-0002-5189-6615>

Bernd Löwe <http://orcid.org/0000-0003-4220-3378>

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