


# BMJ Open Prognostic factors for work disability in patients with chronic widespread pain and fibromyalgia: protocol for a cohort study

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## ABSTRACT

**Introduction** The association between chronic widespread pain (CWP) and disability is well established. Although research support large interindividual differences in functional outcomes, limited studies are available on the socio-economic consequences of offering stratified treatment based on prognostic factors. Identification of predictors of long-term functional outcomes such as work disability as a critical consequence, could assist early and targeted personalised interventions. The primary objective of this cohort study is to identify prognostic factors for the primary endpoint work status (employed and working vs not working) in patients with CWP assessed 3 years from baseline, that is, at referral for specialist care.

**Methods and analyses** Data are collected at the diagnostic unit at Department of Rheumatology, Frederiksberg Hospital. The first 1000 patients ≥18 years of age registered in a clinical research database (DANFIB registry) with CWP either 'employed and working' or 'not working' will be enrolled. Participants must meet the American College of Rheumatology 1990 definition of CWP, that is, pain in all four body quadrants and axially for more than 3 months and are additionally screened for fulfilment of criteria for fibromyalgia. Clinical data and patient-reported outcomes are collected at referral (baseline) through clinical assessment and electronic questionnaires. Data on the primary endpoint work status at baseline and 3 years from baseline will be extracted from the Integrated Labour Market Database, Statistics Denmark and the nationwide Danish DREAM database. Prognostic factor analysis will be based on multivariable logistic regression modelling with the dichotomous work status as dependent variable.

**Ethics and dissemination** Sensitive personal data will be anonymised according to regulations by the Danish Data Protection Agency, and informed consent are obtained from all participants. Understanding and improving the prognosis of a health condition like CWP should be a priority in clinical research and practice. Results will be published in international peer-reviewed journals.

**Trial registration number** NCT04862520.

## INTRODUCTION

Chronic pain is associated with substantial economic burden for the healthcare system

## Strengths and limitations of this study

- Potential prognostic factors for developing pain-related work disability can be identified in patients with chronic widespread pain (CWP).
- This study describes a large clinical cohort of patients with CWP.
- The study will add knowledge to the risk profiling of patients with CWP.
- Recruitment from a specialised tertiary care setting may limit generalisability of study findings.

and work force and it has been demonstrated that the costs tend to increase as the pain condition gradually limits the patient's functional ability.<sup>1</sup> Chronic widespread pain (CWP) is prevalent in the background population with an estimated prevalence of about 10% and represents a major clinical challenge due to the complexity of the disease.<sup>2,3</sup> Apart from pain and other centrally mediated symptoms, CWP is strongly associated with disability affecting activities of daily living (ADLs), incapacity for normal employment and poor social participation, and incurs high direct medical costs as well as significant indirect costs, for example, sick leave and disability compensation.<sup>4-6</sup> Fibromyalgia (FM) is the best characterised subset of patients presenting with CWP and is by many considered to represent the upper end of a pain severity spectrum, that is, associated with greater disease burden and higher levels of disability, in comparison to patients with CWP not fulfilling FM disease criteria or more localised pain conditions.<sup>7,8</sup> Only few studies have explored predictors of long-term functional outcomes including work disability in the CWP population and only few data are available on the socioeconomic benefits of intervention.<sup>9-11</sup> In a study performed by

our study group, participants' baseline intake of analgesics and pain phenotype were shown to predict observed functional ability as an outcome of a standardised rehabilitation programme 6 months postintervention.<sup>10</sup> The following predictors of work disability in patients with FM have been identified in a longitudinal multicentre survey published in 1997: pain, self-reported functional ability, and unmarried status.<sup>12</sup> Furthermore, in a Finish twin cohort study, the burden of FM-associated symptoms was shown to strongly predict early disability retirement.<sup>13</sup> Work-related factors like heavy workload or low decision authority, previously identified as general risk factors for early disability retirement, had only marginal effect in this study.<sup>13</sup> A systematic review discovered that treatment studies evaluating work disability as outcome in FM were scarce.<sup>14</sup> The conclusion was that more studies of treatment effects on outcomes related to work disability and longitudinal studies to explore long-term effects of symptoms on work disability were needed.<sup>14</sup> By quantifying a significant health-related at-work productivity loss as a critical outcome it is anticipated that major stakeholders—such as policy-makers—will get insights as to the resource use and thus the economic impact of CWP on both society and individual.

### Rationale and hypothesis

Prognostic factor research aims to discover and evaluate factors that might be useful as modifiable targets for interventions or predictors of differential treatment responses.<sup>15 16</sup> It is a fundamental component of 'stratified medicine', which refers to the targeting of pharmacological and non-pharmacological interventions according to the biological or clinical risk characteristics shared by subgroups of patients and generally contextual factors in rheumatology.<sup>17–19</sup> By using prognostic factor research, the purpose is to understand and improve future outcomes in patients with CWP. Identification of prognostic factors for long-term functional outcomes, including work disability, could assist tailoring and timing the therapeutic decision for specific patients based on risk profiling and potentially optimise functional outcomes compared with offering standardised (ie, ignorant) intervention programmes to patients with CWP.

### Objectives

Our aim is to understand and improve future outcomes in people with CWP. Thus, this study has three objectives:

- I. To reveal prognostic factors, among the cohort of CWP patients, that are associated with the primary endpoint work status (employed and working vs not working) assessed after 3 years.
- II. Identification of prognostic factors for work status (employed and working vs not working) after 3 years in patients with CWP, who are employed and working at baseline.
- III. Identification of prognostic factors for work status (employed and working vs not working) after 3

years in patients with CWP, who are not working at baseline.

The potential prognostic factors for variation in work status will be explored among the following covariates:

1. Age.
2. Sex.
3. Level of education.
4. Marital status.
5. Symptom duration.
6. Primary CWP (no other established rheumatic disease).
7. Secondary CWP (as comorbidity to other established rheumatic disease).
8. Number of weeks outside the labour market the preceeding 5 years.
9. Labour market affiliation and work status
  - Employed and working.
  - Not working.
  - Interdisciplinary rehabilitation programme.
10. Baseline use of analgesics
11. Self-reported functional ability and overall symptom burden assessed by the functioning and symptom subscales of the Revised Fibromyalgia Impact Questionnaire (FIQR).
12. Self-reported ability to cope with pain assessed by the Pain Self Efficacy Questionnaire (PSEQ).
13. Pain phenotype: tender point (TP) count, total score on the Pain Detect Questionnaire (PDQ), total score on the Widespread Pain Index (WPI).
14. Fulfilment of criteria for FM in addition to CWP.

The reason for considering these covariates is based on previous studies, as mentioned in the introduction section; work disability in FM has been associated with level of pain, self-reported functional ability and unmarried status.<sup>12 14</sup> Intake of analgesics and pain phenotype has been shown to predict observed functional ability.<sup>10</sup> The overall burden of FM-associated symptoms has been found to be a predictor of loss of employment and early disability retirement.<sup>13 14 20</sup> FM patients who are employed and working report better health, and patients with a pending social welfare application perform worse than the ones without.<sup>20 21</sup> Finally, the social and motivational support from family seem to enable the maintenance of work for women with FM.<sup>14</sup>

### METHODS AND ANALYSIS

#### Study design

The study is designed as a clinical cohort study enabling multivariable logistic regression modelling of data from the large Danish Fibromyalgia registry (DANFIB) cohort of CWP patients with the primary aim assessed after 3 years.

#### Patient and public involvement

This project follows the European League Against Rheumatism recommendations for the inclusion of patient representatives in contemporary scientific projects.<sup>22</sup>

The cohort study is designed with assistance from two Danish patient representatives, Trine Leth (TL) and Elena Andersen (EA). Both TL and EA are diagnosed with FM and were invited while participating in a 2-week group-based rehabilitation programme at Department of Rheumatology, Frederiksberg Hospital. They have participated in discussions of relevance to the cohort study, but not the recruitment of participants. The author group will disseminate results to the participants through The Danish Fibromyalgia Association, in which there is a good collaboration.

## Setting

Data collection takes place in a specialised clinical care setting at the diagnostic unit at Department of Rheumatology, Frederiksberg Hospital. Here patients presenting with CWP, either as their primary pain problem or secondary to other established rheumatic disease, have been offered clinical assessment and screening for CWP since 1 January 2018.

The diagnostic work-up includes manual TP examination and an electronic questionnaire based multidimensional assessment (table 1). The electronic data collection is accessed via touchscreens and data are exported to a designated clinical research database (the DANFIB registry). The use of computerised health status questionnaires in FM populations has prior been validated by the Parker Institute.<sup>23</sup> Data extracted from electronic patient files, including findings at clinical examination (manual TP count), are also integrated into the DANFIB registry. A protocol outlining the content and objectives of the DANFIB registry can be accessed online.<sup>24</sup> The DANFIB registry will serve as point of departure for the current cohort study.

## Participants

The first 1000 patients consecutively registered in the DANFIB registry with CWP independent of working status (figure 1). Participant inclusion is expected to be completed by December 2021. Informed consent will be obtained for all participants when registered in the DANFIB registry. To be eligible for enrolment, participants must be over 18 years of age, able to understand and read Danish, and have retrievable data in the DANFIB registry. Participants at baseline receiving pension, that is, public or early retirement pension, disability pension or retirement will be excluded, because their work status is resolved. Thus, participants will be excluded from the study if the following criteria are present: (1) no consent, (2) do not read and understand Danish, (3) non-retrievable data in the DANFIB registry and (4) pension.

## Variables and outcome measures

### Data sources

Baseline demographics, clinical characteristics and individual labour market status assessed at baseline will be extracted from the DANFIB registry (table 1). Data on the primary endpoint work status ('employed

**Table 1** Summary of data to be collected

	Baseline	3 years
<b>Baseline demographic</b>		
Sex (M/F)	X	–
Age (years)	X	–
Labour market affiliation	X	–
Duration of pain (weeks)	X	–
Level of education (primary or high school, medium-term or long higher education)	X	–
Marital status (married, cohabiting, separated/divorced, widowed, single)	X	–
Outcome of clinical assessment (pain diagnosis)	X	–
Other inflammatory or degenerative rheumatic diseases (y/n)	X	–
<b>Baseline analgesics:</b>		
Use of mild analgesics, including NSAIDs (y/n)	X	–
Use of anti-rheumatics (y/n)	X	–
Use of antidepressant for example, Amitriptyline (y/n)	X	–
Use of antiepileptics, for example, Gabapentin (y/n)	X	–
Use of muscle relaxants for example, Chlorzoxazone (y/n)	X	–
Low dose naltrexone (y/n)	X	–
Use of Cannabinoids (y/n)	X	–
<b>Clinical examination:</b>		
Tender point count (0–18)	X	–
<b>Patient-reported outcomes:</b>		
FIQR	X	–
PSEQ	X	–
PDQ	X	–
SSS	X	–
WPI	X	–
<b>Official registry extraction:</b>		
DREAM database	X	X
Integrated Labour Market Database	X	X

FIQR, Fibromyalgia Impact Questionnaire; M/F, Male/Female; PDQ, Pain Detect Questionnaire; PSEQ, Pain Self Efficacy Questionnaire; SSS, Symptom Severity Scale; y/n, yes/no; WPI, Widespread Pain Index.

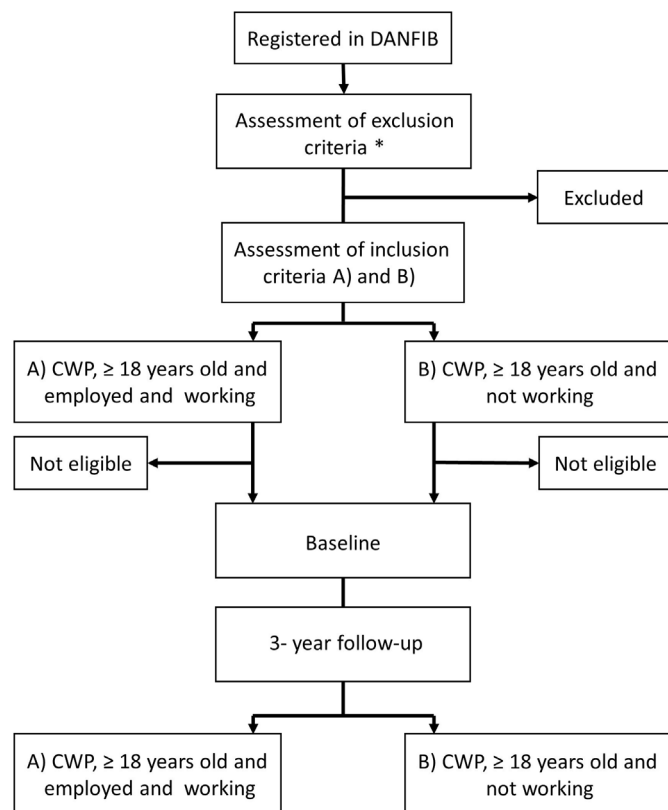
and working' or 'not working') at baseline and again 3 years from baseline will be extracted from the Integrated Labour Market Database at Statistics Denmark and the nationwide Danish DREAM database.

## Measurements

### Baseline demographics and clinical characteristics

Data on age and sex are based on the Danish Civil Registration (CPR) number, given at birth and unique to every Danish citizen. Data concerning labour market status (ensuring sufficient enrolment), level of education, marital status, primary or secondary CWP, symptom





**Figure 1** Overview of participant flow. \*Exclusion criteria: (1) no consent, (2) do not read and understand Danish, (3) non-retrievable data in the DANFIB and (4) pension. CWP, chronic widespread pain.

duration, baseline use of analgesics, and scores obtained by the FIQR, PSEQ, PDQ, Symptom Severity Scale (SSS) and WPI are self-reported by the patient, based on the following patient-reported outcome measurements (PROMs):

1. The FIQR, which is the recommended self-rating tool in evaluating disease burden and impact of disease on ADLs in patients with FM.<sup>25</sup> The FIQR consists of 21 individual questions categorised in three different domains termed; function (ADL), overall impact and symptoms.<sup>26</sup> The domain 'function' includes nine items, 'overall impact' two items and 'symptoms' ten items.<sup>26</sup> All items are rated on an 11-category numeric rating scale (0–10), with 10 representing the 'worst' scenario (eg, very difficult, no energy, very tender).<sup>26</sup> All questions refer to the context of the past 7 days.<sup>26</sup> The scoring of the FIQR is a summed score for 'function' (range 0–90) divided by three with a max score of 30, a summed score for 'impact' (range 0–20) with a max score of 20 and a summed score for 'symptoms' (range 0–100) divided by two with a max score of 50.<sup>26</sup> The three domain scores are summed into a FIQR total score.<sup>26</sup>
2. The PSEQ, originally developed and validated in a heterogeneous group of patients with chronic pain and patients with low back pain.<sup>27</sup> The PSEQ has been translated, culturally adapted and validated in a Dan-

ish population of FM patients.<sup>28</sup> The PSEQ consists of ten items reflecting a variety of ADL tasks and life situations, including paid work. Patients are asked to rate their perceived confidence in performing tasks while in pain on a 0–6 Numeric Rating Scale with a max score of 60. The higher the score, the greater self-efficacy.<sup>27 28</sup>

3. The PDQ, originally developed and validated in 2006 for the purpose of establishing a screening questionnaire to detect the likelihood of a neuropathic pain component in patients with low back pain.<sup>29</sup> Since then the PDQ has proved to be a useful instrument in identification of neuropathic pain features in various clinical conditions including CWP.<sup>30–32</sup> The PDQ consists of seven items which are somatosensory descriptor items rated on a 0–5 Numeric Rating Scale: never, hardly noticed, slightly, moderately, strongly and very strongly. Questions regarding pain intensity on a VAS scale), the radiating quality of the pain (yes/no) and the course of pain (selection between four pain course patterns). For screening purposes, the PDQ has a score ranging from –1 to 38 with cut-off scores ≤12 (a neuropathic pain component is unlikely) and ≥19 (a neuropathic pain component is likely), respectively.<sup>29</sup>
4. The SSS and WPI, which constitutes part of the 2016 American College of Rheumatology (ACR) diagnostic criteria for FM.<sup>33</sup> The SSS sums the 0–3 scores of major defining symptoms, including waking unrefreshed, dyscognition and fatigue with a resulting sum score ranging from 0 to 12. The WPI divides the body into 19 body sites and five regions and the WPI score indicates in which of the 19 predefined pain sites there have been pain during the last week, corresponding to a WPI score ranging between 0 and 19. The ACR 2016 diagnostic criteria for FM are met if: (WPI ≥7 and SSS ≥5) or (WPI 4–6 and SSS ≥9). Furthermore, a generalised pain criterion must be satisfied, defined as pain in minimum four of five regions.<sup>33</sup>

#### Clinical examination

The manual TP count and fulfilment of criteria for FM is assessed at baseline. The clinical examination comprises a manual TP examination according to 1990 ACR guidelines<sup>34</sup> (table 1). The 1990 ACR definition of CWP are considered met if the patient present with persistent or recurrent pain during the last 3 months located both axially plus in all four body quadrants, whereas FM patients present with CWP according to the 1990 ACR definition and a minimum of 11/18 TP, that is, fulfils the dual 1990 ACR classification criteria and/or fulfil the ACR 2016 diagnostic criteria.<sup>33 34</sup>

#### Register-based data on participants' work status

Data collection regarding the primary endpoint on participants' work status at baseline and 3 years from baseline will be based on the CPR number, which makes it possible to link the DANFIB registry with other official registry data on employment, occupation and income. Data on

**Box 1 Primary endpoint and labour market affiliation****Work status****Working**

Employed  
Self-employed  
Flexjob\*  
Under education  
Part-time sick leave†

**Not working**

Unemployed  
Social assistance, activated and non-activated‡  
Interdisciplinary rehabilitation programme§  
Sick leave  
Supported by a spouse, home maker

\*Subsidised job scheme, created for persons with limited work capacity.

†People who are employed and working part time.

‡Transfer income administered by the municipal social service department.

§Rehabilitation programme offered to people with realistic return to work prospective.

employment status will be extracted from the Integrated Labour Market Database, Statistics Denmark. Employers report data on their employees to Statistics Denmark each year in November.<sup>35</sup> Work status will be collected from all participants the preceeding 5 years before baseline, at baseline and again 3 years from baseline to ensure the accuracy of data as opposed to PROMs.

Data on participants receiving social transfer payment will be extracted through the nationwide Danish DREAM database.<sup>36</sup> The DREAM database is based on data from the Danish Ministry of Employment, Ministry of Social Affairs, Ministry of Education, Ministry of Integration, Statistics Denmark and the 98 municipalities. DREAM contains data on all the Danish citizens receiving social benefits or any other transfer income. Information is obtained prospectively each week. Furthermore, Statistics Denmark has a database that compares every person's job with their job the previous year and defines the work status on that basis, which includes a change of job position and workplace, as well as mobility in or out of unemployment. Labour market affiliation at baseline and 3 years after baseline will be categorised as 'working' and 'not working' as illustrated in **box 1**. Those 'working' will include participants that are employed, self-employed or in a 'flexjob' and working. A rehabilitation team in each municipality assigns people to a 'flexjob', interdisciplinary rehabilitation programme, disability pension or another plan. 'Flexjob' is a subsidised job scheme, created for persons with limited work capacity, consequently the person receives ordinary wage paid by the employer and a supplemental social benefit which is paid by municipality. Participants undergoing a formal education or training will be presumed able to work and considered as employed. Whereas 'not working' will cover participants receiving transfer payment benefits including unemployment benefits, social assistance, full sick leave,

an interdisciplinary rehabilitation programme, support by a spouse and home makers. If a person is on sick leave, a municipally administered benefit is paid to the person or transferred to the employer, if the employer pays the ordinary wage to the sick-listed employee. In Denmark, getting sick-leave payment benefits, might refer to persons which are still employed or unemployed. A person can have a part-time sick leave and thereby still be employed and working part-time. In this cohort study, those on part-time sick leave will be considered as 'working'. The interdisciplinary rehabilitation programme refers to people, who are not able to work and comprises activities based on recommendations from the rehabilitation team. The programme consists of health education and employment opportunities and last from 1 to 5 years. The interdisciplinary rehabilitation programme is offered to people, whom the rehabilitation team evaluated with realistic return to work prospective and are therefore of particular interest in the context of patients with CWP.

**Bias and confounding**

Selection of the participants reflects recruitment from a specialised tertiary care setting, but participants selected for the primary endpoint work status (employed and working vs not working) was done using rigorous criteria to avoid ambiguous results. Recall bias could occur for the participants that is, regarding current medication and other patient-reported data. Attrition bias can occur if there is an unequal lost to follow-up between the prognostic factor groups. In clinical trials, participants might withdraw due to unsatisfactory treatment efficacy, intolerable adverse events or even death.

The 14 different covariates will all be considered as potential prognostic factors for variation in work status and could also be regarded as confounders. The challenge with observational data is that prognostic 'exposure groups' are not applied randomly, possibly leading to selection bias and confounding variables. Consequently, it is sensible to try to estimate the 'causal effects' of prognostic factors. Propensity score methods are reliable tools for addressing such objectives because the assumptions needed to make their answers appropriate are more assessable and transparent to the investigator.<sup>37</sup> Improved confounding variable balance between groups will be achieved by matching observations from each prognostic group based on the propensity score.<sup>38</sup> Thus, by use of propensity score methods attempt will be made to correct for the 'assignment mechanism' by finding unexposed units similar to exposure units ( $Y_0|X_E \approx Y_0|X_U$ ). The following pragmatic definition of what makes a confounding variable (*C*) will be used:

- ▶ The covariate (*C*) is an ancestor (cause) of the outcome (*Y*).
- ▶ The covariate (*C*) probably cause the exposure (*X*; for example, group).
- ▶ The covariate (*C*) is not a descendant (effect) of the exposure (*X*) or outcome (*Y*).

## Statistical analyses

### Sample size considerations

The clinical cohort in this study will comprise the first 1000 consecutively enrolled patients in the DANFIB registry either 'employed and working' or 'not working', given the PROMs on labour market status. For a comparison of two independent binomial proportions (comparing prognostic factor exposed *vs* unexposed) using Pearson's  $\chi^2$  statistic with a  $\chi^2$  approximation with a two-sided significance level of 0.05, a sample size of 388 per group (776 in total) achieves a power of at least 80%; when comparing 50% *vs* 40%.

### Descriptive statistics and main analyses

All descriptive statistics and tests will be reported in concurrence with the recommendations of the 'Enhancing the QUALity and Transparency Of health Research' network: the Strengthening the Reporting of Observational Studies in Epidemiology Statement.<sup>39–41</sup> Crude and adjusted estimates will be reported. All analyses will be carried out using R software V.3.6.2 (2019-12-12). Baseline variables will be described for all participants. Continuous data and ordinal scales will be reported descriptively using Means and SDs or medians and IQRs depending on data distribution. Dichotomous data will be reported as an absolute number as well as the relative number (%).

**Analysis population:** The primary analyses will be based on the Intention to Survey (ITS) population, that is, based on the first 1000 patients enrolled in the cohort study. The ITS principle asserts the effect of being enrolled in the DANFIB cohort study (that is, the planned survey regimen), rather than the actual survey given (ie, it is independent of survey adherence), irrespective of their adherence to the planned course of survey (ie, independent of drop-outs).

All 95% CIs and p values will be two sided. Explicit adjustments for multiplicity will not be applied, instead the Statistical Analysis Plan will prespecify how the secondary and tertiary objectives will be analysed in a prioritised order (eg, 'gatekeeping procedure').<sup>42</sup>

**Analysis model:** The prognostic value will be studied through a (multivariable) logistic regression model also calculating the OR. The primary outcome will be the dichotomous work status ('employed and working' *vs* 'not working' according to box 1) in participants with CWP at baseline and 3 years from baseline. The coefficients associated with each potential prognostic factor will be estimated.

**Missing data:** Every effort will be made to minimise missing outcome data. Multiple imputation will be used to account for participants who have the measurement at baseline but are missing the outcome at follow-up, for example, due to maternity leave, emigration or death. No adjustment is expected in the analysis regarding missing data for any of the 14 covariates (age, sex, level of education, etc).

**Sensitivity analyses:** Four explicit sensitivity analyses for the primary aim will be performed to assess the strength

of the results and to account for missing data. The first sensitivity analysis involves specifying a pessimistic imputation model (all participants are not working), the second sensitivity analysis involves specifying an optimistic imputation model (all participants are working), the third sensitivity analysis involve reanalysis of the primary aim using data from the 'per-protocol' population, and finally the fourth analysis set will be based on the 'Data As Observed' population.

## DISCUSSION

Work disability is a serious concern in patients with CWP at both the individual and societal level. It is reported that among FM patients encountered in tertiary care settings, only about one third are part of the work force at the time of referral.<sup>21</sup> Early intervention and individual adjustments in the work situation matching the level of ability may improve retention in employment.<sup>43</sup> Acknowledging the substantial negative impact of CWP on the individual's capacity for normal employment, the proposed cohort study aims to identify prognostic factors for the development of work disability and unemployment in this patient population. The results from this cohort study are anticipated to contribute with relevant knowledge that may be used to guide future intervention matching and delivery of stratified interventions based on prognostic classification.

### Ethics and dissemination

The DANFIB registry has been approved by the Danish Data Protection Agency and granted authorisation for the period January 2018 to January 2033 (j.nr.: 2012-58-0004). The cohort study is approved by the regional scientific ethical committee (j.nr.: P-2020-967). Sensitive personal data will be anonymised according to regulations stipulated by the Danish Data Protection Agency, and informed consent are obtained from all patients before enrolment in the DANFIB registry. The registry data analysed at Statistics Denmark will replace the original CPR numbers with other personal identification numbers in order to make the people in the dataset anonymous to the researchers. Consequently, the project does not require approval from the Danish Data Protection Agency. Papers will be submitted for publication in international peer-reviewed journals. Results will also be presented orally and as posters at international conferences and at the Danish Society of Rheumatology's annual meetings.

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**Contributors** KA is research coordinator and daily manager of the DANFIB registry. PHD is the principal investigator for this clinical cohort study. KA, PHD, RC, MH and KT will be responsible for data extraction and data analysis. PHD, HL, EEW, RC, LEK, HB, MH, KT and KA participated in the design of the cohort study and drafting of the protocol. All authors have given final approval for the protocol to be published.

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**Competing interests** MH: Advisory Board member at the Thuasne Group. LEK: received fees for speaking and/or consultancy from Pfizer, AbbVie, Amgen, UCB, Celgene, BMS, Biogen, Sanofi, MSD, Novartis, Eli Lilly, Janssen Pharmaceuticals. PHD, HL, EEW, RC, KT, HB and KA: none.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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