Severity of fatigue in people with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis – Results of a cross-sectional study

Trine Pilgaard[1], Lise Hagelund[1], Sandra Elkjær Stallknecht[2]*, Henrik Holm Jensen[2], Bente Appel Esbensen[3,4]

1 Pfizer Denmark A/S, Ballerup, Denmark, **2** Incentive, Holte, Denmark, **3** Copenhagen Center for Arthritis Research, Centre for Rheumatology and Spine Diseases, Centre for Head and Orthopaedics, Rigshospitalet, Glostrup, Denmark, **4** Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

* ses@incentive.dk

Abstract

Background

Despite improvements in treatment for rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (axSpA), several key unmet needs remain, such as fatigue. The objective of this study was to describe the severity of fatigue, disease characteristics and socio-economic factors in people with RA, PsA and axSpA.

Methods

The study was designed as a cross-sectional survey collecting patient characteristics such as disease characteristics, socioeconomic factors and fatigue in people with RA, PsA and axSpA in Denmark. Respondents were consecutively recruited for the study over a six-month period in 2018 via routine visits to outpatient rheumatology clinics. Study nurses collected information on diagnosis, current disease-related treatment and disease activity from medical journals. People were invited to complete a questionnaire related to socioeconomic factors and containing the FACIT-Fatigue subscale. Descriptive statistics were analyzed using SAS.

Results

We invited 633 people to participate, and 488 (77%) completed the questionnaire. Women constituted 62% of respondents, and the mean age was 53.5 years. Respondents had on average been diagnosed between 11 and 15 years ago. Overall, 79% had no changes to their disease-related treatment during the past year, and the average disease activity as indicated by DAS28 for RA and PsA was 2.48 and 2.36, respectively, and BASDAI for axSpA was 28.40. Fatigue was present in all three diagnoses (mean: 34.31). The mean fatigue score varied from respondents answering that they suffered from no or little fatigue

(mean: 45.48) to extreme fatigue (mean: 10.11). Analyses demonstrated that the respondents were not considerably different from nonrespondents, and the study population is considered representative compared with Danish RA and axSpA patients in the Danish National Rheumatology Registry, the DANBIO database.

Conclusion

We found that the majority of the study population were fatigued (61%). They had low disease activity and few disease-related treatment changes.

Introduction

Fatigue is described as extreme tiredness, typically resulting from mental or physical exertion or illness [1]. However, an internationally accepted definition of fatigue does not exist [2]. One of the most commonly known illnesses to cause fatigue is inflammatory arthritis, and several studies have demonstrated that fatigue is a prevalent symptom in people with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (axSpA) [3–12]. Clinically important levels of fatigue are reported in 42% of the patients [13], while prevalence rates of 80% or more have also been reported in adults with RA [14–17], and it is perceived as a dominating problem with a greater impact on everyday life than pain [18].

In recent years, there has been an increased focus on fatigue and how fatigue correlates with other symptoms or conditions. According to a recent review of fatigue and RA, severe fatigue is common among individuals with RA and has a significant impact on quality of life [3]. In addition, RA-related factors (e.g., inflammation, pain) are associated with greater fatigue, but other factors, such as physical inactivity, sleep disturbance and depression, explain the major differences in fatigue [3]. Despite this recent increased focus on fatigue in arthritis, there is still a lack of research analyzing the severity of fatigue across diagnoses in inflammatory arthritis such as PsA and axSpA. Further, there is a lack of studies analyzing a potential correlation between fatigue and disease-specific characteristics and socioeconomic factors [3–12].

The prevalence of RA, PsA and axSpA varies globally. In Europe, the estimated prevalence is between 0.3% and 1% for RA [19], 0.001% and 0.42% for PsA [20], and 0.2% and 1.61% for axSpA [21]. Still, RA, PsA and axSpA are the most common types of inflammatory arthritis in the outpatient rheumatology clinics in Denmark. The estimated prevalence in the Danish population is 0.7% for RA [22], 0.1%-0.2% for PsA [23] and 0.3% for axSpA [24].

The objective of this study was to describe the severity of fatigue, disease characteristics and socioeconomic factors in people with RA, PsA and axSpA.

Materials and methods

Study population

This study was designed as a cross-sectional study of people with RA, PsA and axSpA currently enrolled at one of Rigshospitalet's two outpatient clinics in Glostrup and Frederiksberg, Denmark. We aimed to recruit a representative sample of people with RA, PsA and axSpA, amounting to 527 (11% of patients with RA, PsA and axSpA enrolled in one of the two outpatient clinics). Inclusion criteria were people 18 and older with a confirmed diagnosis of RA, PsA or axSpA; who had been enrolled at one of the two clinics for more than four weeks; who

were able to read, understand and write Danish; and who signed an informed consent to participate in the study. People were consecutively recruited between January and June 2018.

Characteristics of respondents from medical journals

We developed a questionnaire, which was used by the study nurse to collect informed consent and characteristics from each respondent's medical journal (S1 and S2 Files). Characteristics such as type of arthritis, age, gender, treatment (disease-modifying antirheumatic drug (DMARD) or biologic), treatment changes and disease activity score (Disease Activity Score-28 (DAS28), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and/or Bath Ankylosing Spondylitis Functional Index (BASFI)) were obtained. For respondents eligible to participate, but not wishing to do so, information on diagnosis (RA, PsA, axSpA), gender, year of birth and reason for not wanting to participate in the study was collected if the respondent gave permission. This information was used for the dropout analysis.

Patient-reported outcomes

We developed a patient questionnaire, which was used to collect patient demographics (S3 and S4 Files). It included outcomes such as years since diagnosis, marital status, education, employment status and household income. The questionnaire also included several other patient-reported outcomes (PROs), of which only the results of fatigue are reported in this study. The other results will be reported elsewhere. We used two scales to measure fatigue: the single visual analog scale (VAS) item from the Health Assessment Questionnaire (HAQ) [25] and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale [26], both validated to measure fatigue in patients with chronic illnesses, among others, in RA and PsA populations [10,27]. In the HAQ, people were asked: "How tired are you?" The scale ranges from 0 to 100, where 0 represents no fatigue and 100 represents severe fatigue. The FACIT-Fatigue scale is a 13-item questionnaire assessing self-reported fatigue. Originally developed as an addition to the Functional Assessment of Cancer Therapy measurement system, the FACIT-Fatigue scale developers have demonstrated that the fatigue subscale can stand alone as a brief, reliable and valid measuring tool. Items in the FACIT-Fatigue scale are scored 0–4 (five answer categories), and the total FACIT-Fatigue score ranges from 0 to 52 [28]. Based on this and to enable an analysis of severity of fatigue, we divided the responses into four grades of severity: respondents with no or little fatigue (composite score between 40 and 52), some fatigue (composite score between 27 and 39), quite a lot of fatigue (composite score between 14 and 26) and extreme fatigue (composite score between 0 and 13). If respondents scored 39 or lower on the FACIT-Fatigue scale, we categorized the respondents as suffering from fatigue. Thus, higher scores on the FACIT-Fatigue scale indicate less fatigue, while the opposite is true for the VAS where lower scores indicate less fatigue.

Other measurements

This study is a part of a larger study "The impact of fatigue in patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis in Denmark". Besides the abovementioned, data on work productivity, health related quality of life, sleep and depression were collected, and will be reported elsewhere (in preparation).

Data collection

The questionnaires were pilot-tested among five people with RA (not included in the analysis). The pilot was conducted in the same setting as the study cohort on a random day with people

with RA, PsA and axSpA visiting the clinics for routine visits. The questionnaire was tested for comprehensibility, user friendliness and time consumption. As the primary part of the questionnaire was made up of validated scales, we did not test the comprehensibility of the specific scales but of the entire questionnaire, as well as the flow in the questionnaire. In general, the pilots answered within an expected time frame and found the questionnaire acceptable and understandable.

People with RA, PsA or axSpA were approached by a study nurse in each clinic and enrolled in the study based on informed consent. The study nurse collected characteristics via a medical journal while the person completed a self-reported questionnaire on an iPad. If the respondent preferred to complete the questionnaire at home, the respondent was either given a link to the online questionnaire or a paper version of the questionnaire and a stamped, addressed envelope and was asked to return the questionnaire by ordinary mail. Study participation was encouraged by the study nurse for those people who agreed to participate in the survey but for some reason did not answer the questionnaire. The study was conducted with approval from the Danish Data Protection Agency (j.nr. 2012-41-1199) and approval from the Ethics Committee of the Capital Region of Denmark (Protocol 17021125). The Danish Medicines Agency was informed about the execution of the study, as per current Danish guidelines (case no. 2017071026).

Database and statistical analysis

The questionnaires were both set up in SurveyXact, an online questionnaire collection program developed by Rambøll. The answers of those respondents choosing to complete the questionnaire on paper were entered manually into SurveyXact. Statistical analyses were conducted in SAS and Microsoft Excel. Where applicable, we applied analysis of variance and Pearson's chi-square test to test for significant differences between groups.

Results

We invited 633 people to complete the questionnaire, and of those, 488 completed it (77% response rate). Of the 145 (23%) who did not complete the questionnaire, 18 (3%) refused to participate, 117 (18%) agreed but never started the questionnaire, and 10 (2%) partly completed the questionnaire (Fig 1).

Study population

In total, 488 respondents completed the questionnaire (450 electronically and 38 on paper). Of the 488, 60% had a diagnosis of RA, 17% a diagnosis of PsA and 23% a diagnosis of axSpA
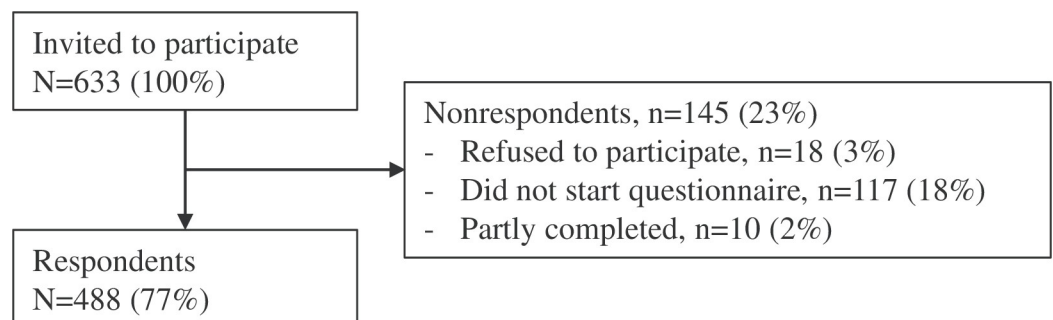

Fig 1. Flow chart.

(Table 1). Of all respondents, 62% were women; however, the distribution across the three diagnoses was uneven, with 79% of the RA respondents being women while 46% and 30% of the PsA and axSpA respondents were women, respectively. The youngest population was found among the axSpA respondents (mean age: 43.6), with 35% of the axSpA respondents being between 18 and 39 years of age, compared with 13% and 16% for RA and PsA, respectively. The oldest population was found among the RA respondents (mean age: 57.4), with 49% of RA respondents being above 60 years of age. The majority of the respondents did not change treatment within the past 12 months (79%), a number that is very consistent across the three diagnoses (RA: 81%; PsA: 79%; axSpA: 73%). The current treatment varied across diagnoses, but on average, 39% were receiving biosimilar DMARD (bsDMARD), 18% conventional synthetic DMARD (csDMARD) and 42% both (1% no current treatment). The average disease activity as indicated by DAS28 for RA and PsA was 2.48 (standard deviation (SD): 1.11) and 2.36 (SD: 0.99), respectively, and BASDAI for axSpA was 28.40 (SD: 23.78). BASFI was 30.93 (SD: 22.93) for PsA and 27.65 (SD: 23.93) for axSpA.

Patient-reported socioeconomic characteristics

Among the newly diagnosed (0–5 years), the highest share of respondents was among those with axSpA (30%) (Table 2). More than half of the respondents (64%) were married/living together with a partner (with or without children) and there was little variation between the diagnoses. Almost half of the respondents (46%) had a bachelor's degree or higher, and the majority of the population belonged to the active workforce (58%). Finally, more than half had a household income above 400,000 DKK.

Table 1. Characteristics from medical journals.

	All	RA	PsA	axSpA
	N (%)	n (%)	n (%)	n (%)
All	488 (100%)	293 (60%)	85 (17%)	110 (23%)
Sex				
Male	185 (38%)	62 (21%)	46 (54%)	77 (70%)
Female	303 (62%)	231 (79%)	39 (46%)	33 (30%)
Age				
18–39 years	91 (19%)	38 (13%)	14 (16%)	39 (35%)
40–59 years	221 (45%)	111 (38%)	46 (54%)	64 (58%)
60+ years	176 (36%)	144 (49%)	25 (29%)	7 (6%)
Age in years, mean (SD)	53.5 (14.5)	57.4 (14)	52.6 (13.2)	43.6 (11.9)
Treatment change in the past 12 months				
0	385 (79%)	238 (81%)	67 (79%)	80 (73%)
1	92 (19%)	46 (16%)	17 (20%)	29 (26%)
2 or more	11 (2%)	9 (3%)	1 (1%)	1 (1%)
Current treatment				
bsDMARD	191 (39%)	69 (24%)	33 (39%)	89 (81%)
csDMARD	90 (18%)	68 (23%)	22 (26%)	0 (0%)
bsDMARD and csDMARD	204 (42%)	155 (53%)	29 (34%)	20 (18%)
No current treatment	3 (1%)	1 (0%)	1 (1%)	1 (1%)
Disease activity status				
DAS28, mean (SD)	2.45 (1.08)	2.48 (1.11)	2.36 (0.99)	2.35 (0.9)
BASDAI, mean (SD)	30.59 (23.56)	NA	33.54 (23.07)	28.40 (23.78)
BASFI, mean (SD)	29.05 (23.51)	NA	30.93 (22.93)	27.65 (23.93)

The sum of percentages does not reach 100% due to rounding errors.

Table 2. Socioeconomic characteristics (patient-reported).

	All	RA	PsA	axSpA
	N (%)	n (%)	n (%)	n (%)
All	488 (100%)	293 (60%)	85 (17%)	110 (23%)
Years since diagnosis				
0–5 years	105 (22%)	57 (19%)	15 (18%)	33 (30%)
6–10 years	105 (22%)	62 (21%)	24 (28%)	19 (17%)
11–15 years	110 (23%)	71 (24%)	17 (20%)	22 (20%)
16–20 years	70 (14%)	39 (13%)	14 (16%)	17 (15%)
More than 20 years	98 (20%)	64 (22%)	15 (18%)	19 (17%)
Type of household				
Married/living together[a]	312 (64%)	185 (63%)	56 (66%)	71 (65%)
Single[b]	162 (33%)	103 (35%)	25 (29%)	34 (31%)
Living at home with parents or house sharing with other adults	13 (3%)	4 (1%)	4 (5%)	5 (5%)
Highest obtained education				
Elementary school or high school	99 (20%)	58 (20%)	20 (24%)	22 (20%)
Secondary or short-cycle tertiary	166 (34%)	94 (32%)	33 (39%)	39 (35%)
Bachelor's or higher	222 (46%)	141 (48%)	32 (38%)	49 (45%)
Employment status				
Employed[c]	281 (58%)	148 (51%)	48 (57%)	85 (77%)
Unemployed	19 (4%)	8 (3%)	7 (8%)	4 (4%)
Retired[d]	123 (25%)	100 (34%)	17 (20%)	6 (5%)
Homemaker, student or other	62 (13%)	35 (12%)	12 (14%)	15 (14%)
Total household income				
Below 400,000 DKK	183 (38%)	112 (39%)	28 (33%)	43 (39%)
400,000 DKK or more	250 (52%)	140 (48%)	48 (56%)	62 (56%)
Refused to answer	51 (11%)	37 (13%)	9 (11%)	5 (5%)

The sum of percentages does not reach 100% due to rounding errors. Some socioeconomic information was not available for all respondents.

[a]Married/living together with or without children.

[b]Single with or without children.

[c]Employed full time, part time or flexible hours.

[d]Age-related retirement or health-related early retirement because of arthritis or other reason.

Nonrespondents

When analyzing the nonrespondents according to characteristics, it became evident that non-respondents were distributed evenly across the diagnoses compared with respondents (Table 3). However, there were significantly more men in the nonrespondent group (50%) than the respondent group (38%) (p = 0.0075). The average age of the nonrespondents was 50 years vs. 53 in the respondent group (p = 0.0489). The percentage of nonrespondents was higher in the youngest age group (18–39) than in the respondent group (28% vs. 19%), and, finally, there was no difference with regard to treatment changes.

Representativity

In Denmark, data on people with RA and axSpA currently receiving DMARDs is routinely collected at scheduled visits to rheumatology centers in the Danish National Rheumatology Registry, the DANBIO database. However, the DANBIO database do not include information on people with PsA. The data collected includes age and gender, type of treatment, and treatment

Table 3. Analysis of nonrespondents.

	Nonrespondents	Study population	P-value chi-square test
	n (%)	n (%)	
All	145 (100%)	488 (100%)	
Diagnosis			0.3446
RA	79 (54%)	293 (60%)	
PsA	25 (17%)	85 (17%)	
axSpA	41 (28%)	110 (23%)	
Sex			0.0075
Male	73 (50%)	185 (38%)	
Female	72 (50%)	303 (62%)	
Age			0.0489
18–39 years	40 (28%)	91 (19%)	
40–59 years	63 (43%)	221 (45%)	
60+ years	42 (29%)	176 (36%)	
Mean age	50	53	
Treatment change in the past 12 months[a]			0.3861
0	93 (73%)	385 (79%)	
1	30 (24%)	92 (19%)	
2 or more	4 (3%)	11 (2%)	

[a]Out of 145 nonrespondents, 18 did not register a treatment change within the past 12 months (n = 127).

changes registered by the nurse or physician as well as patient-reported data (HAQ scale) [25,29]. This data allows us to analyze whether the study cohort is representative of both the Glostrup/Frederiksberg cohort and the full Danish RA and axSpA population.

In 2017, there were 4,788 people with RA, PsA and axSpA enrolled at the Glostrup and Frederiksberg outpatient rheumatology clinics [30]. We targeted 527 people with RA, PsA and axSpA, and of those, 488 (93% of target) completed the questionnaire, with 96% of RA, 83% of PsA and 91% of axSpA participating in the study (Table 4).

When comparing the study cohort with the Glostrup and Frederiksberg cohort from DAN-BIO 2017, the RA respondents are slightly younger than the average Glostrup and Frederiksberg cohort from 2017 (56/60 vs. 61/60 for RA and 45/42 vs. 45/41 for axSpA, respectively) (Table 5). Further, there are slightly more RA women in the study cohort than in the cohort from Glostrup and Frederiksberg (78%/80% vs. 77%/76%) and slightly fewer axSpA women in the study cohort than in the cohort from Glostrup and Frederiksberg (29%/31% vs. 35%/34%) [31]. When comparing the study cohort with the full Danish RA and axSpA population from DANBIO 2017, the RA and axSpA respondents are slightly younger than the DANBIO cohort

Table 4. Respondents.

	RA	PsA	axSpA	Total
Number of people enrolled, in total	2,764	924	1,100	4,788
Glostrup	1,600	557	656	2,813
Frederiksberg	1,164	367	444	1,975
Target	304	102	121	527
Invited/eligible people	NA	NA	NA	633
Respondents	293	85	110	488
Percentage of target	96%	83%	91%	93%

Table 5. Representability compared with DANBIO data.

	Study population (Glostrup)		Study population (Frederiksberg)		Study population (all)		DANBIO (Glostrup)		DANBIO (Frederiksberg)		DANBIO (all Denmark)	
	RA	axSpA	RA	axSpA	RA	axSpA	RA	axSpA	RA	axSpA	RA	axSpA
Women (%)	78%	29%	80%	31%	79%	30%	77%	35%	76%	34%	71%	40%
Mean age	56	45	60	42	57	44	61	45	60	41	63	45

https://doi.org/10.1371/journal.pone.0218831.t005

average (57 vs. 63 for RA and 44 vs. 45 for axSpA, respectively). Further, there are more RA women and fewer axSpA women in the study cohort than in the DANBIO cohort (79% vs. 71% for RA and 30% vs. 40% for axSpA, respectively) [31].

Fatigue

The mean fatigue scores on the VAS were 42.16 (SD: 29.95), 49.69 (SD: 29.18) and 45.01 (SD: 29.57) for RA, PsA and axSpA, respectively. The mean VAS fatigue scores did not vary statistically significantly among the three diagnoses (p = 0.11). On the FACIT-Fatigue scale, the mean fatigue score was 34.31 (SD: 6.08), and fatigue was present in all three diagnoses (Table 6). The mean fatigue scores across diagnoses was not significant (p = 0.078). The mean fatigue score was 34.86 (SD: 11.04) among RA respondents, 31.83 (SD: 10.89) among PsA respondents and 34.77 (SD: 11.44) among axSpA respondents. The mean fatigue score varied among respondents, indicating that they suffered from no or a little fatigue (mean: 45.48; SD: 3.62) to extreme fatigue (mean: 10.11; SD: 3.61). In total, 61% of the respondents expressed fatigue (some, quite a lot or extreme).

Discussion

In this study, 488 respondents (77% response rate) completed the questionnaire, and fatigue was frequent in all three diagnoses (RA, PsA and axSpA). Women constituted 62% of respondents, and the mean age was 53.5 years, which is in accordance with other studies that have found that more fatigue has been reported in association with advancing age [32,33] and female sex [32–35]. We also found that the study population had low disease activity and was

Table 6. Fatigue measured by FACIT-Fatigue score.

	Mean (SD)	All	RA	PsA	axSpA
		N (%)	n (%)	n (%)	n (%)
Number		487 (100%)	292 (100%)	85 (100%)	110 (100%)
Mean fatigue (SD)		34.31 (6.08)	34.86 (11.04)	31.83 (10.89)	34.77 (11.44)
Severity of fatigue					
No or little fatigue[a]	45.48 (3.62)	189 (39%)	120 (41%)	23 (27%)	46 (42%)
Some fatigue[b]	33.05 (3.69)	171 (35%)	99 (34%)	39 (46%)	33 (30%)
Quite a lot of fatigue[c]	20.91 (3.57)	109 (22%)	62 (21%)	19 (22%)	28 (25%)
Extreme fatigue[d]	10.11 (3.61)	18 (4%)	11 (4%)	4 (5%)	3 (3%)

Higher fatigue scores indicate less fatigue.

[a]FACIT-Fatigue score: 40–52.

[b]FACIT-Fatigue score: 27–39.

[c]FACIT-Fatigue score: 14–26.

[d]FACIT-Fatigue score: 0–13.

https://doi.org/10.1371/journal.pone.0218831.t006

relatively stable, with 79% reporting no changes to their disease-related treatment during the past year.

Despite this, the study population suffered from fatigue. We measured fatigue in two ways. On the VAS, we found a mean fatigue score of 42.16 (SD: 29.95), 49.69 (SD: 29.18) and 45.01 (SD: 29.57) for RA, PsA and axSpA, respectively. Our findings are consistent with mean fatigue scores previously documented in a cross-sectional Norwegian study (mean fatigue score on the VAS: 39.9, 43.6 and 43.6 for RA, PsA and axSpA, respectively) [36]. We also used the FACIT-Fatigue instrument to evaluate fatigue. Fatigue was present in all three diagnoses, with a mean FACIT-Fatigue score of 34.31 (SD: 6.08) across diagnoses, which was lower than previously reported among a large representative sample (N = 2,426) of the average German population (mean: 43.5; SD: 8.3) [37] and a large sample (N = 1,010) of the general U.S. population (mean: 43.6; SD: 9.4) [38]. Among the studies we identified measuring fatigue by the FACIT-Fatigue score in people with RA, the score ranged from 34.6 to 42 [39–41] (the fatigue score of 42 was found among RA patients with low disease activity), which is somewhat higher than the mean fatigue score identified in the current study (mean: 34.86; SD 11.04). The mean FACIT-Fatigue score among PsA patients was slightly lower (mean: 31.83; SD: 10.89) than previously reported in a study of Canadian people with PsA (mean: 35.8) [10]. To date, no studies have, to our knowledge, measured fatigue by the FACIT-Fatigue score among axSpA patients. In total, 61% (RA: 59%; PsA: 73; axSpA: 58%) of the respondents expressed that fatigue was a symptom they were affected by to some extent. This is in line with the prevalence of fatigue previously reported among patients with RA, found to vary from 40% to 80% [3,42,43], and the prevalence among PsA patients, found to vary from 44.7% to 78.2% [11,12]. The prevalence of fatigue by FACIT-Fatigue score among axSpA patients has not been estimated in any previous research.

The study population from both disease-specific and socioeconomic perspectives was a well-functioning group of people. Also, overall, the population belonged to the active work-force (58%). This is noteworthy because a recently published study that aimed to determine factors associated with work productivity found a strong association of fatigue with all work measures as well as with daily activity impairment [44]. This emphasizes the need for focusing on increased knowledge about and focus on how to reduce fatigue, which may help optimize work status in people with inflammatory arthritis.

To date, the FACIT-Fatigue scale has been used to measure progress in fatigue in both cross-sectional and longitudinal studies. These studies have reported a minimal important difference of 3–8.3 on the FACIT-Fatigue scale from 0 to 52 [45].

Strengths and limitations

Our study has several strengths. One of the main strengths of the study is the data source for the patient characteristics, which were recorded by trained study nurses from the respondents' medical journals. This method excludes potential recall biases seen in surveys exclusively based on patient-reported data. Another strength of the study is the recruitment method, which has ensured a high response rate. Similarly, the dropout analysis showed that the respondents were not considerably different from the nonrespondents. Finally, our study is considered representative of the Danish RA, PsA and axSpA populations.

We acknowledge, however, that the study has some limitations. The study is cross-sectional and can therefore not provide any conclusions concerning causality. It can generate only hypotheses, which can be further analyzed in future prospectively conducted studies. Despite a good representation in the study cohort of both genders and age groups, the study cohort is slightly older and consists of more women than the group of nonrespondents. The same

tendency is seen in other surveys [46]. The study is further limited by its geographical scope, which is limited to two clinics in the Capital Region of Denmark. The study cohort is slightly younger than the average Danish DANBIO population, and there were slightly more RA women and fewer axSpA respondents in the study cohort. But as the data collection method did not differ from that of DANBIO, we assume that the explanation is due to chance, as the data collection period did not last a full year but covered only six months.

Scales differ in their focus, some measuring severity only and others duration and impact on a range of functions as well as different aspects of fatigue. In this study, we focused on measuring the severity of fatigue using both VAS and FACIT-Fatigue scores, which measured one aspect of fatigue (unidimensional) and not the multidimensional aspects of fatigue, which can be viewed as a limitation.

Conclusion

We found that the majority of the study population was fatigued. The study cohort represents a stable group with low disease activity, few disease-related treatment changes and strong attachment to the labor market. The study cohort is considered representative, and the results warrant further analyses of how fatigue correlates with other PROs and how it differs across the diagnoses.

Supporting information

S1 File. Nurse questionnaire in Danish (original language).
(DOCX)

S2 File. Nurse questionnaire in English.
(DOCX)

S3 File. Patient questionnaire in Danish (original language).
(DOCX)

S4 File. Patient questionnaire in English.
(DOCX)

Acknowledgments

Author Contributions

Conceptualization: Trine Pilgaard, Lise Hagelund, Sandra Elkjær Stallknecht, Henrik Holm Jensen, Bente Appel Esbensen.

Data curation: Sandra Elkjær Stallknecht, Henrik Holm Jensen.

Formal analysis: Sandra Elkjær Stallknecht, Henrik Holm Jensen.

Funding acquisition: Trine Pilgaard, Lise Hagelund.

Investigation: Trine Pilgaard, Lise Hagelund, Sandra Elkjær Stallknecht, Henrik Holm Jensen, Bente Appel Esbensen.

Methodology: Trine Pilgaard, Lise Hagelund, Sandra Elkjær Stallknecht, Henrik Holm Jensen, Bente Appel Esbensen.

Project administration: Trine Pilgaard, Lise Hagelund.

Resources: Trine Pilgaard, Lise Hagelund.

Validation: Trine Pilgaard, Lise Hagelund, Bente Appel Esbensen.

Writing – original draft: Trine Pilgaard, Lise Hagelund, Sandra Elkjær Stallknecht, Bente Appel Esbensen.

Writing – review & editing: Trine Pilgaard, Lise Hagelund, Sandra Elkjær Stallknecht, Henrik Holm Jensen, Bente Appel Esbensen.

References

1. O'Connell K. What causes fatigue? [Internet]. 2016 [cited 2018 Dec 5]. Available from: https://www.healthline.com/symptom/fatigue

2. Hewlett S, Hehir M, Kirwan JR. Measuring fatigue in rheumatoid arthritis: a systematic review of scales in use. Arthritis Rheum. 2007 Apr 15; 57(3):429–39. https://doi.org/10.1002/art.22611 PMID: 17394228

3. Katz P. Fatigue in Rheumatoid Arthritis. Curr Rheumatol Rep [Internet]. 2017 May [cited 2018 Nov 2]; 19(5). Available from: http://link.springer.com/10.1007/s11926-017-0649-5

4. Madsen SG, Danneskiold-Samsøe B, Stockmarr A, Bartels E. Correlations between fatigue and disease duration, disease activity, and pain in patients with rheumatoid arthritis: a systematic review. Scand J Rheumatol. 2016 Jul 3; 45(4):255–61. https://doi.org/10.3109/03009742.2015.1095943 PMID: 26690505

5. Nikolaus S, Bode C, Taal E, van de Laar MAFJ. Fatigue and Factors Related to Fatigue in Rheumatoid Arthritis: A Systematic Review: Studies in RA That Examined Factors Related to Fatigue. Arthritis Care Res. 2013 Jul; 65(7):1128–46.

6. Lopez-Medina C, Schiotis RE, Font-Ugalde P, Castro-Villegas MC, Calvo-Gutierrez J, Ortega-Castro R, et al. Assessment of Fatigue in Spondyloarthritis and Its Association with Disease Activity. J Rheumatol. 2016 Apr 1; 43(4):751–7. https://doi.org/10.3899/jrheum.150832 PMID: 26879350

7. Gossec L, Dougados M, D'Agostino M-A, Fautrel B. Fatigue in early axial spondyloarthritis. Results from the French DESIR cohort. Jt Bone Spine Rev Rhum. 2016 Jul; 83(4):427–31.

8. Bianchi WA, Elias FR, Carneiro S, Bortoluzzo AB, Gonçalves CR, da Silva JAB, et al. Assessment of fatigue in a large series of 1,492 Brazilian patients with Spondyloarthritis. Mod Rheumatol. 2014 Nov; 24(6):980–4. https://doi.org/10.3109/14397595.2014.906049 PMID: 24884480

9. Stebbings SM, Treharne GJ, Jenks K, Highton J. Fatigue in patients with spondyloarthritis associates with disease activity, quality of life and inflammatory bowel symptoms. Clin Rheumatol. 2014; 33 (10):1467–74. https://doi.org/10.1007/s10067-013-2445-6 PMID: 24322832

10. Chandran V, Bhella S, Schentag C, Gladman DD. Functional Assessment of Chronic Illness Therapy-Fatigue Scale is valid in patients with psoriatic arthritis. Ann Rheum Dis. 2007 Jul 1; 66(7):936. https://doi.org/10.1136/ard.2006.065763 PMID: 17324972

11. Husted JA, Tom BD, Schentag CT, Farewell VT, Gladman DD. Occurrence and correlates of fatigue in psoriatic arthritis. Ann Rheum Dis. 2009 Oct; 68(10):1553–8. https://doi.org/10.1136/ard.2008.098202 PMID: 18930991

12. Gudu T, Etcheto A, de Wit M, Heiberg T, Maccarone M, Balanescu A, et al. Fatigue in psoriatic arthritis - a cross-sectional study of 246 patients from 13 countries. Jt Bone Spine Rev Rhum. 2016 Jul; 83 (4):439–43.

13. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol. 1996 Aug; 23(8):1407–17. PMID: 8856621

14. Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol. 1995 Apr; 22(4):639–43. PMID: 7791155

15. Pinals R, Masi A, Larsen R. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum. 1981; 24(10):1308–15. PMID: 7306232

16. Repping-Wuts H, van Riel P, van Achterberg T. Fatigue in patients with rheumatoid arthritis: what is known and what is needed. Rheumatol Oxf Engl. 2009 Mar; 48(3):207–9.

17. Hewlett S, Chalder T, Choy E, Cramp F, Davis B, Dures E, et al. Fatigue in rheumatoid arthritis: time for a conceptual model. Rheumatol Oxf Engl. 2011 Jun; 50(6):1004–6.

18. Feldthusen C, Björk M, Forsblad-d'Elia H, Mannerkorpi K, University of Gothenburg Centre for Person-Centered Care (GPCC). Perception, consequences, communication, and strategies for handling fatigue in persons with rheumatoid arthritis of working age–a focus group study. Clin Rheumatol. 2013 May; 32 (5):557–66. https://doi.org/10.1007/s10067-012-2133-y PMID: 23292480

19. World Health Organization. Chronic rheumatic conditions [Internet]. 2018 [cited 2018 Dec 5]. Available from: https://www.who.int/chp/topics/rheumatic/en/

20. Liu J-T, Yeh H-M, Liu S-Y, Chen K-T. Psoriatic arthritis: Epidemiology, diagnosis, and treatment. World J Orthop. 2014 Sep 18; 5(4):537–43. https://doi.org/10.5312/wjo.v5.i4.537 PMID: 25232529

21. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global prevalence of spondyloarthritis: A systematic review and meta-regression analysis. Arthritis Care and Research. 2015; 68(9).

22. Sorensen K. Rheumatoid Arthritis in Denmark. Two population studies. Dan Med Bull. 1973; 20(3):86–93. PMID: 4766155

23. Pedersen OBV, Svendsen AJ, Ejstrup L, Skytthe A, Junker P. The occurrence of psoriatic arthritis in Denmark. Ann Rheum Dis. 2008 Oct; 67(10):1422. https://doi.org/10.1136/ard.2007.082172 PMID: 18208866

24. The Danish Council for the Use of Expensive Hospital Medicines (RADS). Baggrundsnotat for biologiske og syntetiske targeterede lægemidler til behandlinger af aksiale spondylatropatier (aSPA) [in English: Background memo for biological and synthetic targeted drugs for the treatment of axial spondyloarthritis] [Internet]. 2016 [cited 2018 Dec 5]. Available from: https://rads.dk/media/4362/bgn-aspa-31-237690.pdf

25. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol. 2003 Jan; 30(1):167–78. PMID: 12508408

26. FACIT. Questionnaires [Internet]. 2018 [cited 2018 Dec 5]. Available from: http://www.facit.org/facitorg/questionnaires

27. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005 May; 32(5):811–9. PMID: 15868614

28. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16; 1:79. https://doi.org/10.1186/1477-7525-1-79 PMID: 14678568

29. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Feb; 23(2):137–45. PMID: 7362664

30. Meincke R. Patients' numbers from DANBIO. 2017.

31. DANBIO. National årsrapport [in English: National annual report]. 2017.

32. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. Onkologie. 2003 Apr; 26(2):140–4. https://doi.org/10.1159/000069834 PMID: 12771522

33. Watt T, Groenvold M, Bjorner JB, Noerholm V, Rasmussen NA, Bech P. Fatigue in the Danish general population. Influence of sociodemographic factors and disease. J Epidemiol Community Health. 2000 Nov; 54(11):827–33. https://doi.org/10.1136/jech.54.11.827 PMID: 11027196

34. Basu N, Yang X, Luben RN, Whibley D, Macfarlane GJ, Wareham NJ, et al. Fatigue is associated with excess mortality in the general population: results from the EPIC-Norfolk study. BMC Med. 2016 20; 14 (1):122. https://doi.org/10.1186/s12916-016-0662-y PMID: 27543008

35. Fieo RA, Mortensen EL, Lund R, Avlund K. Assessing fatigue in late-midlife: increased scrutiny of the Multiple Fatigue Inventory-20 for community-dwelling subjects. Assessment. 2014 Dec; 21(6):706–12. https://doi.org/10.1177/1073191114541143 PMID: 24986784

36. Michelsen B, Fiane R, Diamantopoulos AP, Soldal DM, Hansen IJW, Sokka T, et al. A Comparison of Disease Burden in Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis. Zhang C, editor. PLOS ONE. 2015 Apr 8; 10(4):e0123582. https://doi.org/10.1371/journal.pone.0123582 PMID: 25853482

37. Montan I, Löwe B, Cella D, Mehnert A, Hinz A. General Population Norms for the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. Value Health [Internet]. 2018 [cited 2018 Sep 18]; Available from: https://doi.org/10.1016/j.jval.2018.03.013

38. Cella D, Lai J-S, Chang C-H, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002 Jan 15; 94(2):528–38. https://doi.org/10.1002/cncr.10245 PMID: 11900238

39. Diniz LR, Balsamo S, Souza TY de, Muniz LF, Martins WR, Mota LMH da. Measuring fatigue with multiple instruments in a Brazilian cohort of early rheumatoid arthritis patients. Rev Bras Reumatol Engl Ed. 2017 Sep; 57(5):431–7. https://doi.org/10.1016/j.rbre.2017.05.004 PMID: 28663038

40. Bechman K, Tweehuysen L, Garrood T, Scott DL, Cope AP, Galloway JB, et al. Flares in Rheumatoid Arthritis Patients with Low Disease Activity: Predictability and Association with Worse Clinical Outcomes. J Rheumatol. 2018 Nov; 45(11):1515–21. https://doi.org/10.3899/jrheum.171375 PMID: 30173149

41. Singh H, Arya S, Talapatra P, Lather K, Mathur R, Singhania A, et al. Assessment of Fatigue in Rheumatoid Arthritis (by Functional Assessment of Chronic Illness Therapy–Fatigue Score) and Its Relation to Disease Activity and Anemia: JCR J Clin Rheumatol. 2014 Mar; 20(2):87–90. https://doi.org/10.1097/RHU.0000000000000073 PMID: 24561411

42. Repping-Wuts H, Fransen J, van Achterberg T, Bleijenberg G, van Riel P. Persistent severe fatigue in patients with rheumatoid arthritis. J Clin Nurs. 2007 Nov; 16(11c):377–83. https://doi.org/10.1111/j.1365-2702.2007.02082.x PMID: 17931330

43. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology. 2006 Jul 1; 45(7):885–9. https://doi.org/10.1093/rheumatology/kel021 PMID: 16449363

44. Espahbodi S, Bassett P, Cavill C, Freeth M, Hole J, Sengupta R. Fatigue contributes to work productivity impairment in patients with axial spondyloarthritis: a cross-sectional UK study. Clin Exp Rheumatol. 2017 Aug; 35(4):571–8. PMID: 28240589

45. Nordin Å, Taft C, Lundgren-Nilsson Å, Dencker A. Minimal important differences for fatigue patient reported outcome measures–a systematic review. BMC Med Res Methodol. 2016 May; 16:62–62. https://doi.org/10.1186/s12874-016-0167-6 PMID: 27387456

46. Løppenthin K, Esbensen BA, Østergaard M, Jennum P, Tolver A, Aadahl M, et al. Physical activity and the association with fatigue and sleep in Danish patients with rheumatoid arthritis. Rheumatol Int. 2015 Oct; 35(10):1655–64. https://doi.org/10.1007/s00296-015-3274-5 PMID: 25947325