In Psoriatic Arthritis fatigue is driven by inflammation, disease duration, and chronic pain: An observational DANBIO registry study

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KEY INDEXING TERMS: Psoriatic Arthritis / Fatigue / Principal Component Analysis

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RUNNING HEAD: Fatigue in Psoriatic Arthritis

ABSTRACT

Objective: Fatigue is one of the most significant symptoms, and an outcome of great importance, in patients with psoriatic arthritis (PsA), but associations between underlying components of fatigue experienced by patients in relation to the disease have been sparsely investigated. The objectives were to describe the degree of fatigue in PsA patients, and secondly to explore important components associated with fatigue.

Methods: We performed a cross-sectional survey including patients registered in the Danish nationwide registry DANBIO from December 2013 to June 2014. Principal component analysis was used to identify factors associated with fatigue.

Results: A total of 1,062 PsA patients were included in the study. A principal component analysis reduced co-variables into three components explaining 63% of fatigue in patients. The first component, contributing to 31% of fatigue, was composed of inflammatory factors including swollen and tender joints, doctors' global assessment, elevated CRP, and high Pain Detect Questionnaire (PDQ) score; the second component, contributing to 17%, consisted of increasing age and long disease duration. The third component, contributing to 15%, consisted of high PDQ score, tender joint count, increasing age, and concomitant low CRP, suggestive of a chronic pain component consisting of central pain sensitization or structural joint damage.

Conclusion: Fatigue in PsA patients may be driven by clinical inflammatory factors, disease duration, and chronic pain in the absence of inflammation.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease with a prevalence of 0.2% in Denmark (1). The disease confers a considerable socioeconomic disease burden with decreased work productivity and increased healthcare utilization (2, 3). Moreover, patients with PsA are characterised by having a decreased quality of life compared to other patient groups and often fatigue is reported to be the limiting factor in terms of participation in daily activities (4, 5).

Fatigue defined as sustained physical tiredness, mental exhaustion, and a lack of energy, is a well-known symptom of many chronic diseases (6, 7) and often a crucial aspect in the management of chronic diseases (8). It is a common symptom in PsA that is by patients deemed to be one of the most significant symptoms (9, 10) and furthermore rated by patients as the worst symptom after pain and skin problems (7, 9, 11).

Though fatigue is considered an important outcome measure for patients with PsA this outcome is not yet fully embedded in clinical practice or in the scientific thinking within this disease-area where reporting of fatigue as patient-reported outcome is rare and studies on fatigue are limited (7, 12).

However, the focus on fatigue is increasing and fatigue is now considered a core outcome according to the updated PsA core domain set from 2016 (13). Recent studies have described the association between fatigue in patients with PsA and pain, female gender, physical disability, medication status, psychological distress, longstanding sick leave, and loss of ability to work (8, 11). Furthermore, biological agents have been shown to improve fatigue, which suggests a link between fatigue and inflammatory signalling (14-19). And so the inflammatory pathway is believed to be associated with several clinical manifestations of PsA.. As for pain in PsA, it is traditionally considered to be of

inflammatory origin, but despite better control of inflammation, some patients still report pain as a significant concern. This suggests that PsA may prompt central sensitisation and thus being linked to other central mechanisms such as fatigue why it is relevant to study the quality of pain, i.e. by using Pain Detect Questionnaire (PDQ) rather than just measuring quantity in terms of visual analogue scale (VAS) pain.

The objective of this study was to describe the degree of fatigue in patients with PsA in a nationwide study, and secondly to explore important components associated with fatigue.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

The study was designed as a cross-sectional survey including patients registered in the Danish nationwide registry, DANBIO (20). Recording of data in DANBIO was mandatory for patients in treatment with biological disease-modifying antirheumatic drugs (bDMARDs), but DANBIO also contain treatment information on patients treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). PDQ was implemented on the DANBIO touch screens in Danish outpatient clinics at 22 of 24 Departments of Rheumatology for a period of six months (1st of December 2013 to 1st of June 2014). The study was conducted in accordance with the STROBE-statement (suppl. file S1) and according to a pre-specified protocol available and published as open-access at the official website of the Parker Institute (www.parkerinst.dk). All patients registered as having PsA were invited to participate in the survey. Patients with a complete response to PDQ and a PDQ score above 0 were included in the analyses. Patient consent was obtained on the touch screen prior to the redirection to the PDQ. In accordance with Danish legislation surveys do not require approval by Ethics Committees. Registrations and publications of data from clinical registries that do

not pertain to human biological samples do not require patient consent or approval by Ethics Committees.

VARIABLES AND OUTCOME MEASURES

The VAS is a single-item measure (0-100 mm) composed to measure patient-reported pain, fatigue and global health (VAS pain, VAS fatigue, VAS global health). The VAS scale has shown good reliability and performs as well as other questionnaires when assessing fatigue (21). In this study the VAS was used to measure patient-reported fatigue during the last week, with '0' representing "no fatigue" and '100' representing "worst imaginable fatigue" (22). We defined moderate-to-severe fatigue as fatigue scores ≥57 (chosen as 57 was the median VAS fatigue score for the population). PDQ is a mechanism-based pain classification instrument based on patient self-reported somatosensory signs and symptoms, assigning patients to one of three categories depending on the quality of the experienced pain; neuropathic (PDQ score >18), unclear (PDQ score 13-18) or nociceptive (PDQ score <13) pain. PDQ was originally developed to screen for a neuropathic pain component (23) and based on pain phenotypic similarities to assess neuropathic pain features as a proxy of central sensitization (23-25).

STATISTICAL ANALYSIS

Patient characteristics were given with median and interquartile ranges (IQRs) for continuous variables. Spearman's Rho Correlation coefficients were calculated to assess any potential association between fatigue scores and clinical indices. Two-sided P-values < 0.05 were regarded as statistically significant.

To explore components explaining fatigue a principal component analysis (PCA) was conducted. Variables were a priori selected based on clinical relevance with a pre-defined maximum allowed

collinearity of 0.4. Variables included for further analysis consisted of age, disease duration, swollen/tender joint count (28 joints), pain detect score, CRP level, patient and doctors VAS global health score (0-100mm). Health assessment questionnaire (HAQ) score were excluded from the PCA due to collinearity. To assess the variability and association of components to fatigue in the entire population multiple linear regression was conducted for VAS fatigue with the three primary components identified in the PCA. A sensitivity analysis based on the principal component analysis was constructed on VAS pain and gender stratification, respectively, to explore any possible similarities or differences explaining fatigue when including PDQ score versus VAS pain and male versus female. IBM SPSS version 20 was used carrying out the analyses.

RESULTS

A total of 2,388 patients were diagnosed with PsA in DANBIO of which 2,114 had a VAS fatigue score. Of these 1,062 chose to participate in the study and were included for analysis as they had a recorded PDQ score above 0. The median VAS fatigue score was 57 mm for the population, and scores of 57 mm or more were considered moderate-to-severe fatigue. Patients with moderate-to-severe fatigue were predominantly female, and with higher DAS28CRP as well as higher VAS pain, VAS global health, PDQ score, and higher Health Assessment Questionnaire (HAQ) scores, respectively, compared with subjects with none-to-mild fatigue scores. Moreover, these patients had higher scores in doctors' global assessment, more tender and swollen joints, increased use of corticosteroids, and more often switching bDMARDs (table 1).

In the principal component analysis (suppl. file S2; PCA biplot) the clinical co-variables were reduced to three components explaining 63% of fatigue (figure 1). The first component, contributing to 31%, was mainly constituted by inflammatory factors such as more swollen and tender joints, higher doctors' global assessment, higher DAS28CRP, and higher PDQ scores, whereas the second

component mainly consisted of contributions from higher age and longer disease duration, explaining 17% of fatigue. The third component, contributing to 15%, consisted of higher PDQ scores, more tender joint counts, increasing age, and by concomitant low CRP.

The multiple linear regression analysis on the overall population with VAS fatigue as the dependent variable and the three identified components as independent variables showed an overall significant association of increasing fatigue with a correlation coefficient of 0.39 (p-value < 0.001). For the first and third component the correlation coefficients were 0.73 and 0.35 respectively with statistical significant p-value below 0.001. For the second component the regression coefficient was 0.06 with p-value 0.45. In the sensitivity analysis, the principal component analysis reduced the clinical co-variables to three major components explaining 64% of experienced fatigue (suppl. file S3). The components identified including VAS pain in the analysis were almost identical to the components identified including PDQ score. Comparing PCA performed on male versus female also resulted in similar components explaining 68% and 61% of experienced fatigue, respectively, though with a difference from the primary PCA in the inflammatory component; 36% in males and 29% in females (suppl. file S4).

DICUSSION

The median fatigue score in this population-based PsA cohort including patients treated with csDMARDs and bDMARDs was ≥ 57 mm VAS, underscoring the great importance of fatigue as patient-reported disease manifestation. Our findings from the principal component analysis in the population with fatigue above the median suggested that fatigue was constituted by an inflammatory component, disease duration, and chronic pain in the absence of inflammation. Moreover, the multiple

linear regression analysis showed that there was a significant and clinical relevant association with the three components and increasing fatigue in the entire population.

Conducting the principal component analysis lead to three components that impacted and explained 63% of experienced moderate-to-severe fatigue in patients with PsA. The first component was driven by clinical inflammatory factors such as DAS28CRP, doctors' global assessment, and swollen and tender joints revealing one of the underlying explanations of fatigue to be actual inflammatory disease activity - highlighting the importance of targeted treatment of PsA. The second component consisted of disease duration and age leading our attention to the important aspect of a link between fatigue and disease chronicity. The third component was defined by an inverse relationship between low CRP and high pain indicators. High PDQ scores in the moderate-to-severe fatigue group suggested central pain sensitisation, though the contribution from tender joints to the third component might be explained to a degree of structural damage as well (26). When substituting PDQ scores with VAS pain, the same components were identified underscoring the experienced pain as an important driver of fatigue independent of cause or origin for the pain. PDQ scores were in general higher in patients with moderate-to-severe fatigue implying a higher degree central derived pain in this group. Chronic pain conditions are common within rheumatic diseases and this further indicate the importance of differentiating patients in order to provide patients best possible care.

Previous studies showed that bDMARD and targeted treatments improved symptoms of fatigue in patients with psoriasis arthritis compared to placebo-controlled groups (14, 17-19)) indicating an inflammatory component in the nature of fatigue also found in the present study. From the percentages experiencing no change in fatigue (18,19) one could consider whether this to a degree is treatment-refractory due to other components influencing experienced fatigue.

In line with previous research (11), the present study found that the moderate-to-severe fatigue group consisted of statistical significant more females, had higher pain scores and higher HAQ scores. Additionally, the present study also found that concomitant use of corticosteroids and patients more often switching bDMARDs were associated with having moderate-to-severe fatigue.

Limitations of this current study were; 1) the incompleteness of baseline data, however, the proportion of missing data did not exceed 25% for any variable, and 2) the risk for selection bias of the patients as recording of data in DANBIO was only mandatory for patients treated with bDMARDs, which may lead to overrepresentation of patients with more severe disease on highly effective therapies. Nonetheless, pain and fatigue remain of outmost importance to patients, and the current study offers new insights into the mechanisms leading to fatigue.

CONCLUSION

In conclusion this study showed a strong association between fatigue and clinical important features including inflammation, disease duration, and chronic pain which are relevant to take into account when treating PsA. The three components explained in total 63% of the experienced fatigue in the moderate-to-severe fatigue population of patients with PsA.

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LEGENDS

FIGURE 1: PRINCIPAL COMPONENT ANALYSIS INDICATING 3 COMPONENTS EXPLAINING FATIGUE

*The three components explaining fatigue included 1) Clinical inflammatory manifestations, 2) Chronicity and 3) Chronic pain. *High impact variables contributing to the component. Each variable is presented with the correpsonding loading factor. PCA; principal component analysis, VAS; visual analogue scale, CRP; C-reactive protein.*

SUPPLEMENTARY FILE S1: STROBE CHECKLIST

Study title: In Psoriatic Arthritis fatigue is driven by inflammation, disease duration, and chronic pain: An observational DANBIO registry study

SUPPLEMENTARY FILE S2: ASSESSING ASSOCIATIONS BETWEEN VARIABLES INCLUDED IN THE PRINCIPAL COMPONENT ANALYSIS

CRP; C-reactive protein, VAS; visual analogue scale

SUPPLEMENTARY FILE S3: PRINCIPAL COMPONENT ANALYSIS INCLUDING VAS PAIN AS THE VARIABLE

*Including VAS pain in the analysis were almost identical to the components identified including Pain Detect Questionnaire (PDQ) score. *High impact variables contributing to the component. Each variable is presented with the correpsonding loading factor PCA; principal component analysis, VAS; visual analogue scale, CRP; C-reactive protein.*

SUPPLEMENTARY FILE S4: COMPARING COMPONENTS OF FATIGUE BETWEEN MALE AND FEMALE

Principal component analysis was conducted for male and female, respectively, after grouping by gender. Similar components were identified, though with CRP showing lower influence on components, whereas PDQ score showed higher influence on components. PCA; principal component analysis, VAS; visual analogue scale, CRP; C-reactive protein.

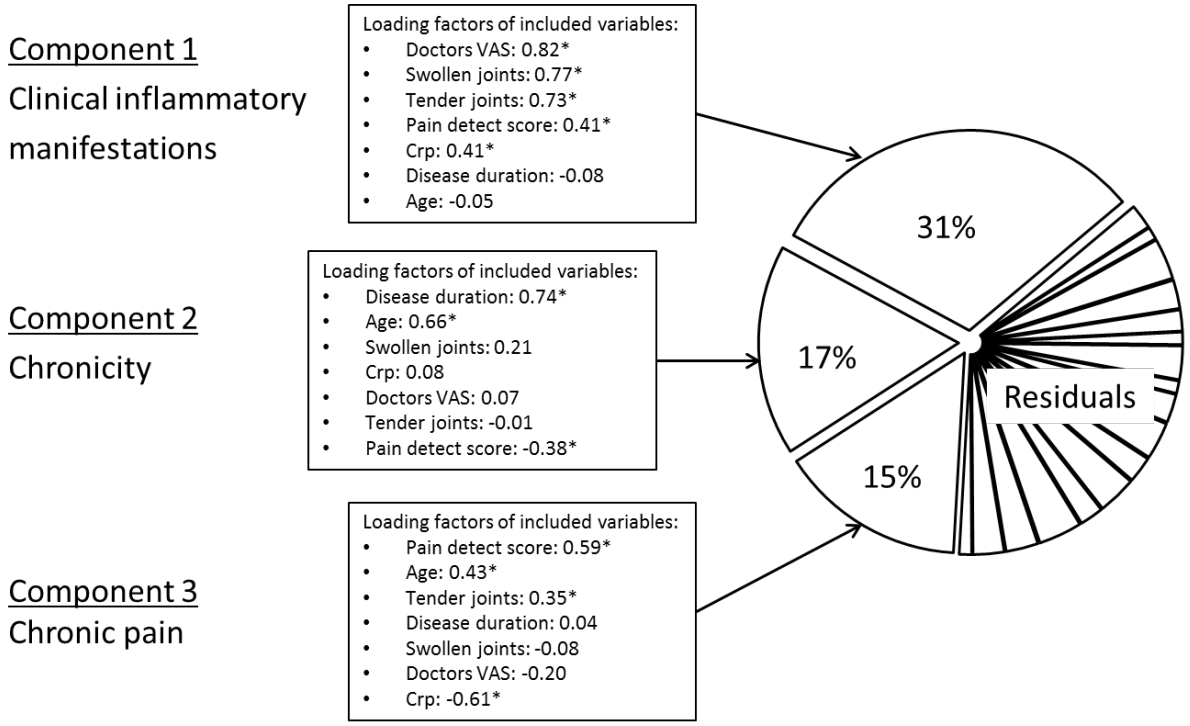
TABLE 1: PATIENT CHARACTERISTICS

Characteristics	**Fatigue; Non to mild VAS score <57 (n=520)**		**Fatigue; Moderate to severe VAS score ≥57 (n=542)**		
		n		n	p-value
Female, n (%)	253 (48.7%)	520	358 (66.1%)	542	<0.001
Age, years	53.0 (44.0-62.0)	520	52.0 (42.8-60.0)	542	0.070
Disease duration, years	6.0 (3.0-11.5)	449	5.0 (2.0-10.0)	456	0.022
Previous use of DMARDs, n (%):		520		542	0.046
None	449 (86.3%)		443 (81.7%)		
1	44 (8.5%)		50 (9.2%)		
2	26 (5.0%)		49 (9.0%)		
3+	1 (0.1%)		0 (0.0%)		
Use of MTX, n (%)	316 (60.8%)	520	313 (57.7%)	542	0.319
Concomitant corticosteroid, n (%)	6 (1.2%)	520	29 (5.4%)	542	<0.001
Biological treatment, status, n (%)		520		542	<0.001
Never treated with bio	272 (52.3%)		279 (51.5%)		
In current treatment	224 (43.1%)		195 (36.0%)		
Previous use	24 (4.6%)		68 (12.5%)		
Swollen joint count (SJC): 0-28 *	0.47 ±1.3	455	0.94 ±2.2	459	<0.001
Tender joint count (TJC): 0-28 *	1.73 ±3.6	456	5.0 ±6.4	469	<0.001
C-reactive protein, mg/L	3.0 (1.0-6.0)	421	4.0 (2.0-7.0)	464	0.008
Patient pain assessment, 0-100 mm VAS	25.0 (15.0-38.0)	520	66.0 (49.0-78.0)	542	<0.001

Patient global assessment, 0-100 mm VAS	27.0 (15.0-43.0)	520	75.5 (61.0-86.0)	542	<0.001
Doctors global assessment 0-100 mm VAS	7.0 (3.0-15.0)	432	14.0 (7.0-14.0)	438	<0.001
Pain detect score (PDQ score)	9.0 (6.0-14.0)	520	17.0 (13.0-23.0)	542	<0.001
DAS28-CRP	2.3 (1.8-2.9)	400	3.5 (2.6-4.4)	418	<0.001
HAQ score, 0-3	0.4 (0.1-0.8)	507	1.1 (0.8-1.6)	530	<0.001

*Unless otherwise stated data was given as median with interquartile ranges (IQR). * swollen and tender joints; mean ±SD. VAS; visual analogue scale, DMARD; disease-modifying antirheumatic drugs, MTX; methotrexate, PDQ; pain detect questionnaire, DAS28-CRP; disease activity score, HAQ; health assessment questionnaire*

FIGURE 1: PRINCIPAL COMPONENT ANALYSIS INDICATING 3 COMPONENTS EXPLAINING FATIGUE



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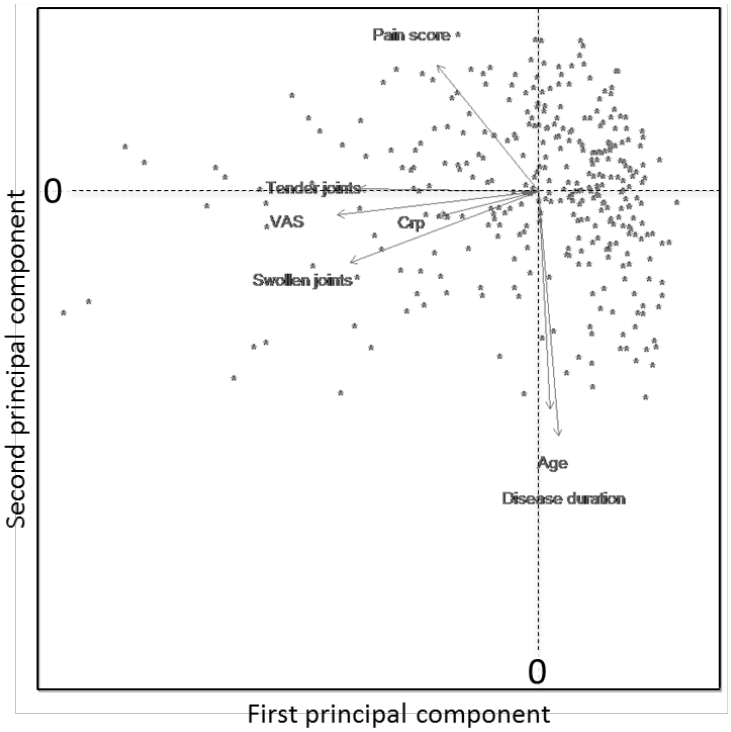
2 **SUPPLEMENTARY FILE S1: STROBE STATEMENT – CHECKLIST OF ITEMS INCLUDED IN**
3 **REPORTS OF CROSS-SECTIONAL STUDIES**

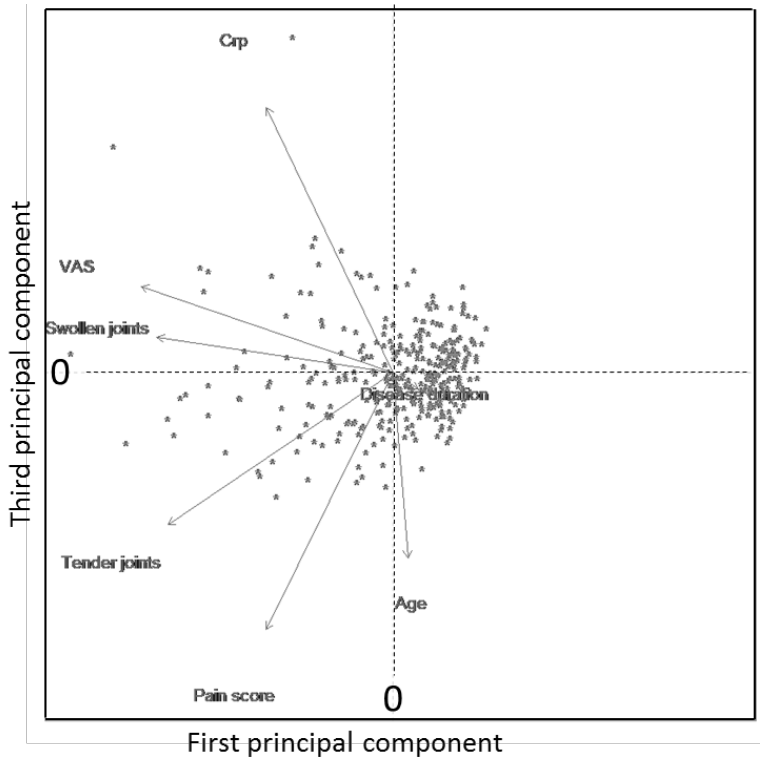
4

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15	Report numbers of outcome events or summary measures	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10

Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

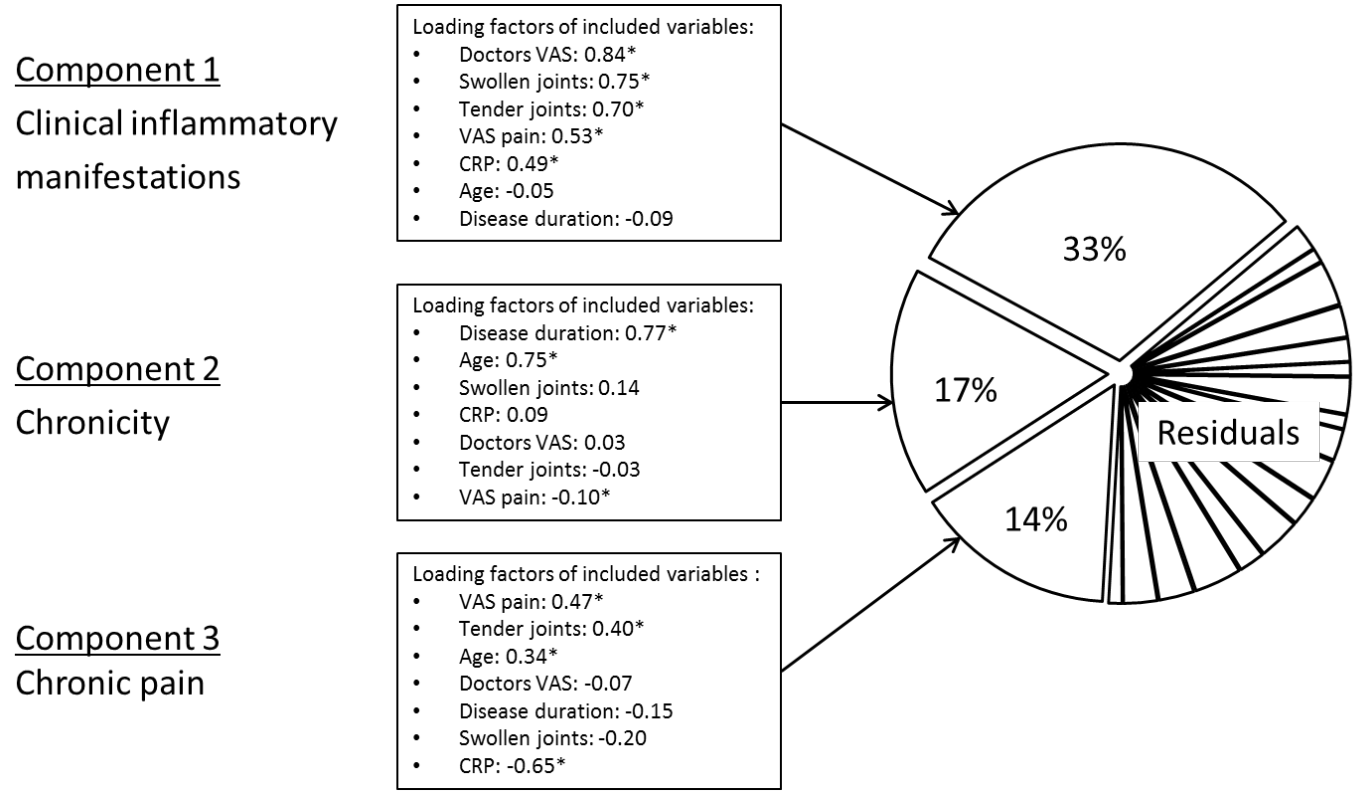
SUPPLEMENTARY FILE S2: ASSESSING ASSOCIATIONS BETWEEN VARIABLES INCLUDED IN THE PRINCIPAL COMPONENT ANALYSIS





CRP; C-reactive protein, VAS; visual analogue scale

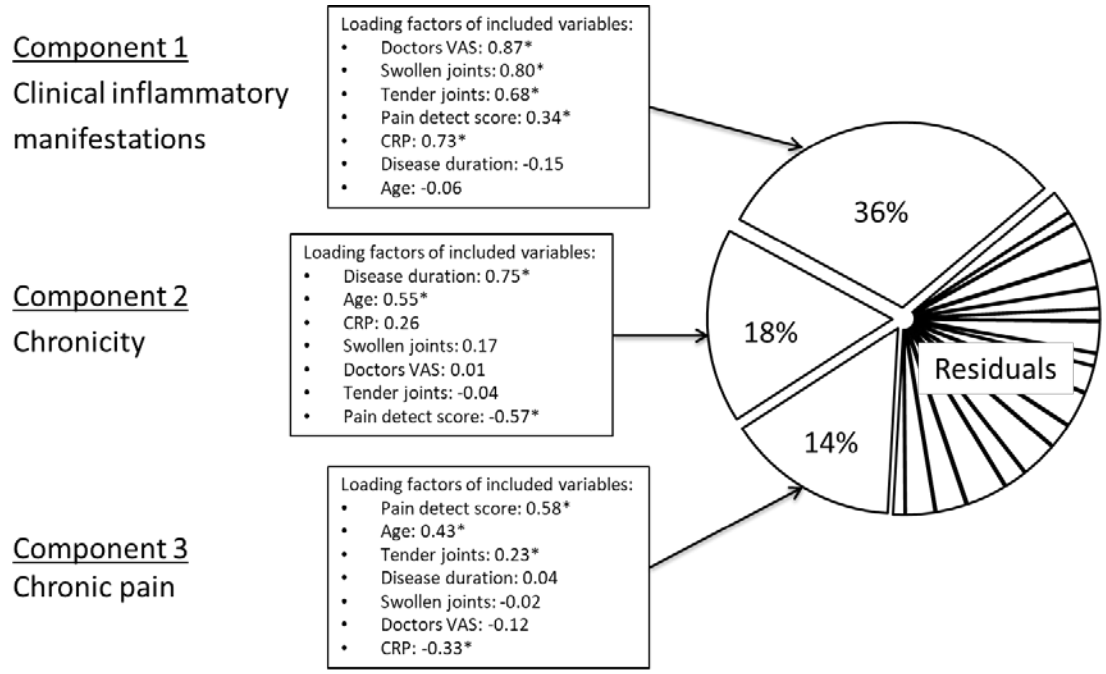
SUPPLEMENTARY FILE S3: PRINCIPAL COMPONENT ANALYSIS INCLUDING VAS PAIN AS THE VARIABLE



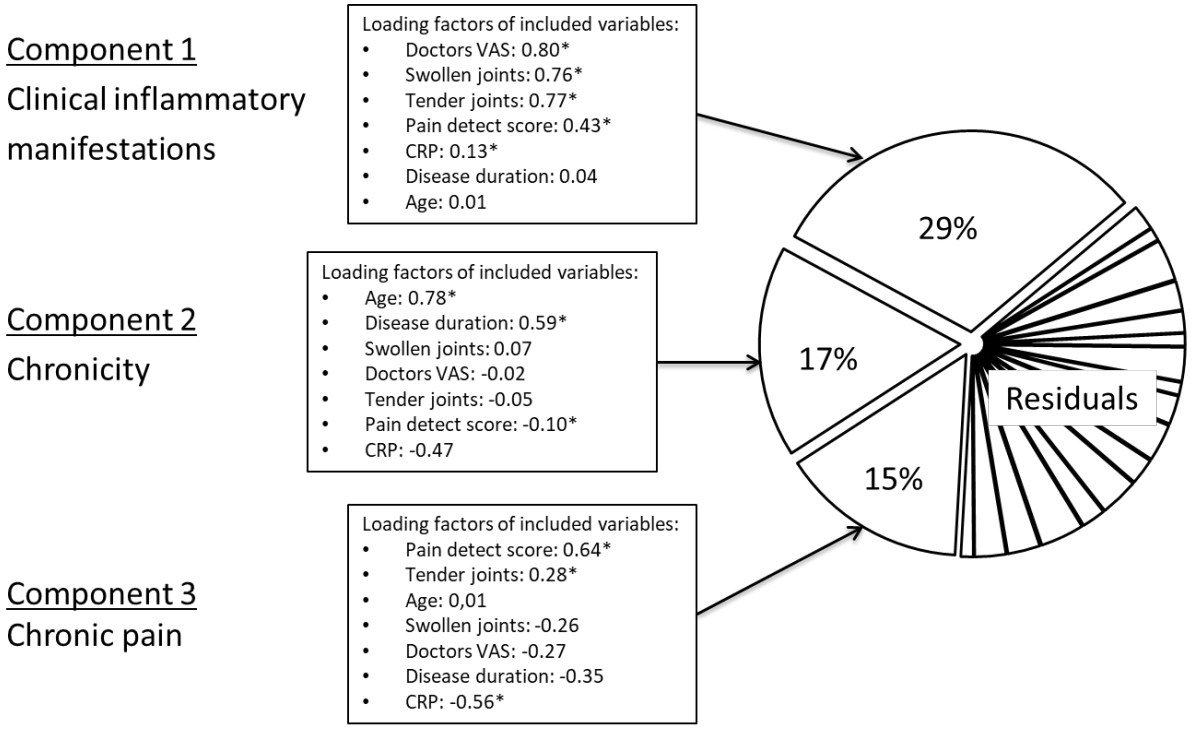
*Including VAS pain in the analysis were almost identical to the components identified including Pain Detect Questionnaire (PDQ) score. *High impact variables contributing to the component. Each variable is presented with the correpsonding loading factor PCA; principal component analysis, VAS; visual analogue scale, CRP; C-reactive protein.*

SUPPLEMENTARY FILE S4: COMPARING COMPONENTS OF FATIGUE BETWEEN MALE AND FEMALE

Male:



Female:



A principal component analysis was conducted for male and female, respectively, after grouping by gender. Similar components were identified, though with CRP showing lower influence on the components in women, whereas PDQ score showed higher influence on the components. PCA; principal component analysis, VAS; visual analogue scale, CRP; C-reactive protein.