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*A nested case-control study using the DANBIO Register*

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*Published in:*  
Rheumatology

*DOI (link to publication from Publisher):*  
[10.1093/rheumatology/keab192](https://doi.org/10.1093/rheumatology/keab192)

*Publication date:*  
2021

*Document Version*  
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

### *Citation for published version (APA):*

Vela, J., Cordtz, R. L., Kristensen, S., Torp-Pedersen, C., Petersen, K. K., Nielsen, L. A., & Dreyer, L. (2021). Is pain associated with premature mortality in patients with psoriatic arthritis? A nested case-control study using the DANBIO Register. *Rheumatology*, 60(11), 5216-5223. <https://doi.org/10.1093/rheumatology/keab192>

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# Is pain associated with premature mortality in patients with psoriatic arthritis? A nested case-control study using the DANBIO Register

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## Abstract

**Background:** It has been hypothesized that the presence of chronic pain causes excess mortality. Since chronic pain is prevalent among patients with psoriatic arthritis this potential association should be explored.

**Objectives:** To investigate whether higher cumulative pain intensity is associated with an excess mortality risk in patients with psoriatic arthritis.

**Methods:** A nested case-control study using data from the nationwide DANBIO register and Danish healthcare registers. Cases were patients who died and corresponding to the date of death, matched on sex, year of birth and calendar period at the time of death with up to five controls. Exposure of interest was mean pain intensity reported during the time followed in routine rheumatology practice. Pain intensity was measured using a visual analogue scale from 0 to 100 and conditional logistic regression was used to calculate odds of mortality per 5 unit increase in pain while adjusting for confounders.

**Results:** The cohort consisted of 8019 patients. 276 cases were identified and matched with 1187 controls. Higher mean pain intensity was associated with increased odds of mortality (OR 1.06, 95%CI 1.02 to 1.10) in the crude model, but there was no association (OR 0.99, 95%CI 0.95 to 1.03) when adjusting for additional confounders. Factors shown to increase the odds of mortality were recent glucocorticoid use, concomitant chronic obstructive pulmonary disease, diabetes mellitus, cancer and cardiovascular disease.

**Conclusion:** These results indicate that experienced pain in itself is not associated with premature mortality in patients with psoriatic arthritis. However, recent glucocorticoid use and concurrent comorbidities were.

## Keywords

Spondylarthropathies, Epidemiology, Chronic pain syndromes, DMARDs, Biological therapies

## Key messages

- Self-reported pain intensity was not associated with mortality when controlling for confounders related to mortality.
- Recent glucocorticoid use and comorbidities were associated with among psoriatic arthritis patients.
- Health Assessment Questionnaire Disability Index score was not associated with mortality when controlling for confounders.

## Background

Psoriatic arthritis (PsA) is a systemic inflammatory disease, characterized by psoriasis and arthritis of the axial or peripheral joints<sup>1</sup>. Pain is a common symptom in patients with PsA<sup>2,3</sup> and persistent pain is frequent despite anti-inflammatory treatment options<sup>4-6</sup>.

Furthermore, patients with PsA have an increased risk of developing a number of comorbid conditions such as obesity, type 2 diabetes mellitus, hypertension and cardiovascular disease, which in and off themselves are associated with increased mortality<sup>7</sup>. Currently, the evidence is inconclusive as to whether patients with PsA are at an actual increased risk of excess mortality<sup>8-17</sup> compared with people without PsA. This could be due to the heterogenous nature of the disease, thus examining potential risk factors are warranted.

Only two studies have examined potential risk factors for excess mortality among patients with PsA. Gladman et al. found an association between high baseline erythrocyte sedimentation rate (ESR), absence of nail changes at first visit, radiographic damage and increased mortality<sup>18</sup>.

Juneblad et al. found that patients with PsA with a high disease activity index were 1.88 times more likely to die prematurely<sup>19</sup>.

A recent meta-analysis<sup>20</sup> demonstrated a modest though non-significant relationship between the presence of chronic pain and excess mortality in a heterogenous population of patients encompassing multiple painful conditions. However, none of the included studies measured the intensity of pain and it is therefore unclear if clinical pain intensity is a risk factor for excess mortality among patient with chronic pain, which should be studied. Thus, using data from the national Danish healthcare registers and the DANBIO register, we aimed to investigate the possible impact of cumulative pain experienced on mortality in patients with PsA.

## Patients and Methods

### Study design

A nested case-control study investigating the potential association between pain and all-cause mortality based on a nationwide cohort of patients with PsA registered in the DANBIO register between 2006 and 2018. A unique ten-digit Civil Personal Register (CPR) number assigned to all residents in Denmark and using the Danish Civil Registration System (CRS) allows for linkage of Danish registers<sup>21</sup>.

### Data Sources

The nationwide DANBIO rheumatology register, established in the year 2000, includes prospective data on more than 8000 patients with PsA treated in outpatient clinics<sup>22</sup>. Patient reported outcome measures are collected via digital questionnaires accessed through a touch screen. These include, the pain intensity, which is quantified using a 100mm visual analogue scale (VAS) where 0mm denotes no pain and 100mm the most intense pain imaginable. The text accompanying the pain VAS reads "How much arthritic pain do you have at present". Fatigue is recorded by the patient using a similar VAS scale graded from 0mm (no fatigue) to 100mm (maximal fatigue). Disability is quantified using the Stanford Health Assessment Questionnaire and Disability Index (HAQ-DI) ranging from 0-3 where higher score indicates worse functioning. C-reactive protein (CRP) is measured prior to each visit and recorded in DANBIO by the physician. Physician reported outcomes include the EULAR28 tender and swollen joint count score<sup>23</sup>; the physicians global assessment of the disease activity recorded using a VAS; and information regarding use of biological DMARDs (bDMARDs) and conventional synthetic DMARDs (csDMARDs). The disease activity score 28 (DAS28) composite outcome is also included. PsA specific disease activity indices were not included due to incomplete information on the EULAR 66/68 joint scores, presence of enthesitis and psoriasis severity in DANBIO.

The Danish National Patient Register (DNPR) was established in 1977 and includes information on somatic in- and outpatient contacts with Danish hospitals<sup>24</sup>. The DNPR registers administrative data including identification of the patient, identification of hospital ward, date and time of activity and primary diagnoses, surgical procedures and up to 19 secondary diagnosis all recorded

in accordance with the International Classification of Diseases 10<sup>th</sup> version (ICD-10) since 1994 and forward.

The Danish Register of Causes of Death (DRCD) is a Danish national register administered by the department of healthcare data<sup>25</sup>. It contains information on the time of death and cause of death as evaluated by the physician filling out the death certificate.

The CRS contains individual-level updated information on date of birth, sex, migration and vital status on all persons residing in Denmark since 1968.

The Danish Income Statistics Register covers more than 160 variables including socioeconomic status on taxpayers who reside in Denmark over the age of 14<sup>26</sup>.

The Danish National Database of Reimbursed Prescriptions started in 1994 and includes information on redeemed prescriptions<sup>28</sup>. In the present study it is used to gather data on systemic glucocorticoid use.

### Study population

Patients diagnosed with PsA and registered in DANBIO constituted the source population from which nested cases and matched controls were identified.

All patients who according to the DRCD had died were cases. Each case was matched with up to 5 controls from the PsA cohort using incidence density sampling<sup>29</sup>. Controls were matched by sex, birth-year (3-year intervals), and calendar year at date of death for cases (3-year intervals).

### Exposure

Our primary exposure of interest was mean pain intensity averaged during the entire observational period from registration in DANBIO to time of death or matching using a 100 mm visual analogue scale ranging from 0 (no pain) to 100 (maximal pain).

### Statistical analyses

Normally distributed data were presented as means and standard deviations (SD) and non-normally distributed with medians and interquartile ranges (IQR), for descriptive statistics. Odds ratios (OR) for mortality and 95% confidence intervals (CIs) were calculated in conditional logistic regressions with a crude analysis and two multivariable models.

Model 1 was adjusted for age in addition to the matching on birth year and calendar period, sex, calendar period of first DANBIO registration, average CRP during the entire observation period in DANBIO, average swollen joint count during the observational period, average HAQ-DI during the observational period and disease duration. An initial analysis also included age as both linear and quadratic terms to ensure that the age adjustment was sufficient as a continuous variable. The quadratic term was then left out as it had no effect on the primary outcome.

Model 2 was adjusted for the before mentioned covariates and additionally for tender joint count, socioeconomic status defined by quintiles of the age-standardised average income in the 5 years leading up to the date of matching, and the following comorbidities: cardiovascular disease (ICD-10 I20-I25, I50, I60-I64 and ICD-8 41.x), chronic obstructive pulmonary disease (ICD-10 J41-J44), diabetes mellitus (ICD-10 E10—E14) and cancer (ICD-10 C01-C99 except C44, non-melanoma skin cancer).

All data management and analyses were carried out using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

### Multiple Imputation

To account for missing data of VAS pain, VAS fatigue, VAS physician global, VAS patient global disease activity, CRP levels, tender and swollen joint counts and HAQ-DI, multiple imputation (MI) was carried out. The MI approximate method has previously been shown to perform well in nested case-control studies<sup>30</sup>. We imputed 100 datasets, and all of the above variables were imputed using the predictive mean matching with distance aided donor selection approach with the MICE package for R<sup>31</sup>.

### Secondary analysis

In a secondary analysis, we investigated the potential impact of pain intensity limited to the last year and the final 5 years, leading up to the case-control matching date.

### Sensitivity analyses

In our primary analysis, HAQ-DI was considered a confounder and thus included in the model, but in a sensitivity analysis, it was left out of the model as it could also be argued that it is an

intermediary variable due to the relationship between pain and HAQ-DI<sup>32</sup> and HAQ-DI and mortality seen in RA<sup>33</sup>.

Furthermore, we applied the average pain level as a categorical variable with VAS Pain groups of non-to-mild (VAS: 0-33), moderate (VAS: 34-66), and severe (VAS: 67-100) pain. These cut-offs were decided upon after having carried out and assessed a restricted cubic spline model with death as outcome and pain as a time-dependent covariate on the entire DANBIO PsA cohort. Finally, the conditional logistic regression analysis on the complete case dataset was assessed and patients with missing data on one or more of the covariates included in the respective models, were excluded from analysis in question.

## Results

### Baseline characteristics

We identified 8019 patients with PsA in the DANBIO source cohort. Among them, 276 cases were identified and matched with 1187 controls corresponding to 4.3 controls per case. Demographic characteristics, DMARD use and comorbidities of the cases and controls are presented in Table 1. Cases had more average visits 7 vs 3, a greater pain average 46 vs 37 respectively and were more likely to use bDMARDs and glucocorticoids compared with matched controls. Furthermore, cases had lower recorded income, lower education level and were more likely to suffer from diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease and cancer. Missing values were 2.9%, 3.7%, 2.3% and 1.6% for pain VAS, HAQ-DI, CRP and swollen joint count respectively. There were no other missing values for the variables included in the models (see supplementary table 1).



Table 1. Summary of demography and characteristics for patients with PsA who died and their matched imputed controls.

	Cases	Controls
N	276	1187
Age, median [IQR]	72.2 [62.5, 80.9]	70.7 [62.2, 78.6]
Women, n (%)	152 (55.1)	640 (53.9)
Year of registration in DANBIO, n (%)		
2006 to 2010	17 (6 %)	72 (6 %)
2011 to 2012	22 (8 %)	106 (9 %)
2013 to 2014	42 (15 %)	200 (17 %)
2015 to 2016	132 (48 %)	524 (44 %)
2017 to 2018	63 (23 %)	285 (24 %)
Income quintile, n (%)		
Lowest	81 (29)	230 (19)
Below median	73 (26)	267 (22)
Median	61 (22)	226 (19)
Above median	39 (14)	234 (20)
Highest	22 (8)	230 (19)
Education level, n (%)		
Low	113 (41)	401 (34)
Medium	148 (54)	729 (61)
High	9 (3)	39 (3)
Unknown	6 (2)	18 (2)
Pain VAS* mm, median [IQR]	46 [27, 60]	37 [22, 55]
HAQ-DI*, median [IQR]	1 [0.4, 1.6]	0.7 [0.3, 1.2]
DAS28*, median [IQR]	3.1 [2.4, 4.0]	2.8 [2.3, 3.4]
CRP* mg/L, median [IQR]	6 [3, 11]	4 [2, 8]
Fatigue VAS* mm, median [IQR]	54.7 [26.7, 70.1]	43.7 [22.3, 62]
Physician global VAS* mm, median [IQR]	13 [7, 22]	11 [6, 17]
Swollen joint count, median [IQR]	0.6 [0.0, 1.7]	0.5 [0.1, 1.4]

Tender joint count, median [IQR]	2[0.4, 5.6]	1.6 [0.5, 3.7]
bDMARD use, n (%)	54 (19.6)	180 (15.2)
csDMARD use, n (%)	166 (60.1)	862 (72.6)
Prescribed glucocorticoids in past year, n (%)	137 (49.6)	157 (13.2)
Diabetes mellitus (%)	71 (25.7)	126 (10.6)
Chronic obstructive pulmonary disease (%)	67 (24.3)	107 (9.0)
Cardiovascular disease (%)	143 (51.8)	300 (25.3)
Cancer (%)	126 (45.7)	117 (9.9)

\* Measure represents the mean value during the observational period

Abbreviations: bDMARD, biological disease modifying antirheumatic drug; csDMARD conventional synthetic disease modifying antirheumatic drug; CRP, C-reactive protein; DAS28, disease activity score 28; HAQ-DI, Health assessment questionnaire disability index; IQR, Interquartile Range; VAS Visual analogue scale

### Association between pain and mortality

The crude conditional logistic regression analysis showed a statistically significant association between average VAS pain intensity and mortality: OR 1.06 (95%CI 1.02 to 1.10) per 5 VAS unit increase. However, this association was attenuated when adjusting for additional confounders in Models 1 and 2 (Table 2). Odds per 1 VAS unit increase can be found in supplementary table 3.

Table 2. Odds ratios (OR) for mortality per 5 unit increase in average VAS pain using a 0-100 scale.

Analysis	Odds Ratio (95%CI)
Crude	1.06 (1.02 to 1.10)
Model 1*	0.99 (0.94 to 1.03)
Model 2**	0.99 (0.95 to 1.04)

\* Adjusted for age, average CRP, average HAQ, average swollen joint count, bDMARD use, csDMARD use and being prescribed glucocorticoids during the last year.

\*\* Same as Model 1 with the addition of income level, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus and cancer.

## Secondary analysis

Similar results were demonstrated in the secondary analysis where only the average pain in the most recent year OR 1.06 (95%CI 1.02 to 1.09) and average pain in the recent 5 years were investigated OR 1.06 (95%CI 1.02 to 1.09). These associations were also attenuated when adjusting for additional confounders (Table 3).

Table 3. Odds ratios per 5 unit increase in pain during the recent year and 5 years before death.

Analysis	Recent year	Recent 5 years
	OR (95%CI)	OR (95%CI)
Crude	1.06 (1.02 to 1.09)	1.06 (1.02 to 1.09)
Model 1*	0.99 (0.95 to 1.04)	0.99 (0.94 to 1.03)
Model 2**	0.98 (0.94 to 1.04)	0.99 (0.93 to 1.04)

\* Adjusted for age, average CRP, average HAQ, average swollen joint count, bDMARD use, csDMARD use and being prescribed glucocorticoids during the last year.

\*\* Same as Model 1 with the addition of income level, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus and cancer.

## Sensitivity analysis

Finally, the complete case analysis found an association between pain intensity and mortality in the crude analysis, OR 1.07 (95%CI 1.03 to 1.11), but with no associations in neither model 1, OR 0.97 (95%CI 0.92 to 1.02) nor model 2, OR 0.96 (95%CI 0.91 to 1.02).

Omitting HAQ-DI from model 1 and 2 did not alter the findings: ORs for VAS pain 1.03 (95%CI 0.99 to 1.07) and OR 1.00 (95%CI 0.96 to 1.05), respectively.

Using the average pain intensity as a categorical variable resulted in increased likelihoods of mortality for patients with averaged pain intensities ranging from 34 to 66 on a VAS scale compared to those with pain intensities ranging from 0 to 33 in the crude model: pain levels from 34 to 66 resulted in an OR of 1.13 (95%CI 0.90 to 1.42) and from 67 to 100, in an OR of 1.84 (95%CI 1.36 to 2.47). As with the primary analyses, these associations for the higher pain levels

attenuated when adjusting for additional confounders: in model 1 the OR was 1.15 (95%CI 0.89 to 1.49) and in model 2 the OR was 1.10 (95%CI 0.74 to 1.65) for those with pain levels from 67 to 100 compared with 0 to 33.

#### Associations between other variables and mortality

Table 4 shows the ORs for all covariates included in Model 2 in the primary analysis. Recently prescribed oral glucocorticoids was associated with increased mortality OR of 5.60 (95%CI 3.71 to 8.45) , while csDMARD use was associated with decreased mortality OR 0.56 (95%CI 0.39 to 0.82). Diabetes mellitus OR of 1.86 (95%CI 1.19 to 2.90), Cardiovascular disease OR 3.04 (95%CI 2.06 to 4.49) and Cancer OR 7.17 (95%CI 4.70 to 10.94) were all associated with increased mortality. Complete case analysis showed similar results with no difference in significant findings (See Supplementary Table 2).

Table 4. Odds ratios for all variables included in model 2

Variable	OR (95% CI)
Pain VAS (per 5 unit increase)	0.99 (0.94 to 1.05)
Age (per 1-year increase)	1.06 (0.97 to 1.17)
CRP (per 5 unit increase)	1.21 (0.99 to 1.48)
Average HAQ-DI	1.16 (0.81 to 1.65)
Average swollen joint count	0.99 (0.90 to 1.11)
bDMARD use	1.18 (0.82 to 1.65)
csDMARD use	0.56 (0.39 to 0.82)
Prescribed oral glucocorticoids during past year	5.60 (3.71 to 8.45)
Diabetes Mellitus	1.86 (1.19 to 2.90)
Cardiovascular disease	3.04 (2.06 to 4.49)
Chronic obstructive pulmonary disease	1.72 (1.06 to 2.80)
Cancer	7.17 (4.70 to 10.93)
Age-adjusted income quintile	
Lowest	2.90 (1.61 to 5.22)

Lower	2.90 (1.62 to 5.19)
Median	2.73 (1.51 to 4.93)
Above median	1 (Ref.)
Highest	0.58 (0.28 to 1.19)

Abbreviations: bDMARD, biological disease modifying antirheumatic drug; csDMARD conventional synthetic disease modifying antirheumatic drug; CRP, C-reactive protein; HAQ-DI Health assessment questionnaire; VAS, Visual analogue scale

## Discussion

This nationwide Danish study is the first to examine the impact of chronic pain intensity on mortality in patients with PsA. Although a statistically significant positive association was observed in the crude analysis of the accumulated average chronic pain intensity and the likelihood of all-cause mortality, the association attenuated when adjusting for age, sex, calendar time, average CRP, swollen joint count, HAQ-DI, bDMARD use, csDMARD use and being prescribed glucocorticoids during the last year. The results were robust in line of sensitivity analyses.

To our knowledge, this study is the first of its kind to examine the impact of prospectively collected pain intensity scores in PsA and risk of mortality.

### Impact of pain on mortality

The results of the current study are in agreement with previous findings in the general population. Smith et al. performed a meta-analysis of seven studies examining the association between the presence of chronic pain, including widespread pain, and excess mortality in community-dwelling adults<sup>20</sup>. Overall they found a small but non-statistical significant increase in mortality rate ratio with an effect size of 1.14 and the results were similar when only including studies that examined widespread chronic pain (effect size 1.22)<sup>20</sup>. A more recent meta-analysis, examining participants who reported widespread pain, showed an increased risk of mortality (mortality rate ratio 1.57) when compared with patients without widespread pain; however in contrast to Smith et al., the authors of this study only extracted data from crude analyses and residual confounding is likely.<sup>34</sup>

Previous studies have examined predictors of mortality in rheumatoid arthritis (RA) and pain intensity as a single baseline measurement was not associated with excess mortality<sup>35,36</sup> and neither was multiple pain intensity measurements<sup>33,37–39</sup> over time. Conclusively, this could indicate that pain intensity alone does not contribute significantly to excess mortality in arthritis.

### Risk factors of mortality in PsA

In the present study prescribed glucocorticoids during the last year, concurrent chronic obstructive pulmonary disease, diabetes mellitus, cancer and cardiovascular disease were all associated with early mortality.

Two previous studies have explored factors associated with excess mortality in patients with PsA. In a single-centre based study, Gladman et al<sup>18</sup> examined a range of predictors at a single point in time for 428 patients with PsA, and found an increased risk of excess mortality among patients with ESR (relative risk 3.77, 95%CI 3.77 to 10.83) and severe radiological damage at baseline (relative risk 3.88, 95%CI 1.32 to 11.35). However, their model did not include comorbidities, lifestyle factors or glucocorticoid use. Similarly, Juneblad et al<sup>19</sup> examined the risk of mortality from cardiovascular disease among 463 patients with PsA. They found increased risk of mortality for use of glucocorticoid ever, disease activity index and duration of psoriasis in a univariable single factor model; however, when applying a multivariable model, only disease activity index was a significant predictor (OR 1.88, 95% CI 1.30 to 2.72).

### Use of glucocorticoids

Systemic glucocorticoids use is generally not recommended in patients with PsA<sup>41</sup> but is prescribed for different comorbidities including chronic pulmonary disease (COPD) and some forms of cancer. In the present cohort, 49% of cases and 13% controls had been prescribed glucocorticoids during the last year.

Gladman et al<sup>18</sup> found increased risk of death among patients with prior use of oral glucocorticoids (RR 4.12, 95%CI 1.16-14.65) when compared to non-users, but no increased risk with current use (RR 1.08 95%CI 0.48-2.44) . Juneblad et al<sup>19</sup> found an association between ever having had

glucocorticoid treatment and mortality risk (OR 2.00, 95%CI 1.07-3.76). However, there were no associations when a multivariable model was applied. We found a 3-fold increased likelihood of mortality for those that had redeemed a prescription for glucocorticoids in the year leading up to matching, even when accounting for markers of inflammation like CRP and swollen joint count, and comorbidities like COPD and cancer. This finding is mirrored in RA where glucocorticoid use has been associated with an increased risk of death (Hazard ratio 1.97 95%CI 1.81-2.15)<sup>42</sup>.

### Strengths and limitations

Our study has a number of limitations that needs mentioning. We focused on the association between pain intensity and excess mortality and even though widespread pain and fibromyalgia are common among patients with PsA, with prevalence estimates ranging from 15% to 33%<sup>43-46</sup>, the DANBIO register does not include data which makes a diagnosis of fibromyalgia or widespread pain possible. Widespread pain in itself has been associated with increased risk of excess mortality even in patients with inflammatory arthritis<sup>47</sup> and these patients represent a subpopulation which could be examined further with relation to pain intensity and mortality.

Due to a large proportion of missing data, neither smoking status nor body mass index could be included in the analysis. We did, however include the presence of cardiovascular disease, chronic pulmonary disease, diabetes mellitus and cancer, all of which are associated with smoking and some with body mass index.

The present study does have several strengths. It is based on a nationwide cohort of patients with PsA and the Danish Health registers which, among other advantages, has complete registration of death in the DRCD. Several different models of pain intensity quantification were applied to ensure that the results were robust. Furthermore, we adjusted for several strong confounders of pain and mortality.

### Conclusion

The current study is the first large-scale national cohort study to examine pain intensity and early mortality in patients with PsA. The study demonstrated that, pain intensity was associated with

excess mortality in patients with PsA in a crude analysis, but this association was attenuated once several confounders were adjusted for.

These results indicate that, pain intensity has limited predictive value for preterm or excess mortality whereas recent glucocorticoid use, chronic pulmonary disease, diabetes, cancer and cardiovascular disease were all associated with an increased risk of early death.

## Acknowledgements

### Contributors

JV and RLC are the primary contributors to the conception and design of the protocol and JV is responsible for drafting of the manuscript. LD has contributed to the conception and both LD and CTP has contributed to the design.

SK, KKP, LD, LAN and CTP have all contributed substantially during manuscript revision and approved of the final draft.

### Funding

This work was supported by the Danish Psoriasis Foundation Grant number 210417, the Danish Rheumatism Foundation Grant number R179-A6299, from Aalborg University and Aalborg University hospital (2016-017615). Centre for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121).

### Competing interests

All authors report nothing to declare

### Ethical approval

The study was approved by the Danish Data Protection agency (ID number 2018-54). No requirement for ethical approval is needed for register-based studies in Denmark.



## Data availability statement

Data is available upon reasonable request by contacting the corresponding author.

Accepted author manuscript

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*Semin Arthritis Rheum.* 2020;000:1-8. doi:10.1016/j.semarthrit.2020.02.005

Accepted author manuscript