# Original article

# Change in psoriatic arthritis outcome measures impacts SF-36 physical and mental component scores differently: an observational cohort study

Marie Skougaard <sup>(b)</sup> <sup>1</sup>, Tanja S. Jørgensen<sup>1</sup>, Mia J. Jensen<sup>1</sup>, Christine Ballegaard<sup>1</sup>, Jørgen Guldberg-Møller<sup>1</sup>, Alexander Egeberg <sup>(b)</sup> <sup>2</sup>, Robin Christensen<sup>1,3</sup>, Peter Benzin<sup>1</sup>, Zara R. Stisen<sup>1</sup>, Joseph F. Merola<sup>4</sup>, Laura C. Coates <sup>(b)</sup> <sup>5</sup>, Vibeke Strand <sup>(b)</sup> <sup>6</sup>, Phillip Mease <sup>(b)</sup> <sup>7</sup> and Lars Erik Kristensen<sup>1</sup>

## Abstract

**Objective.** The objective was to investigate interplay and physical and mental component scores between change ( $\Delta$ ) in health-related quality of life (HRQoL) quantified by the physical component score (PCS) and mental component score (MCS) retrieved from short-form health survey (SF-36), change in disease activity ( $\Delta$ DAS28CRP) and manifestations of PsA.

**Methods.** PsA patients initiating new medical therapy were enrolled. Independent disease measures evaluating disease activity, enthesitis, psoriasis, pain and fatigue were collected at treatment initiation and after 4 months. Interplay between independent disease measures and dependent outcome measures,  $\Delta$ PCS and  $\Delta$ MCS, was described with univariate regression analyses. Multivariate regression analyses were applied to assess the impact of independent variables, such as individual disease outcome measures vs  $\Delta$ DAS28CRP on  $\Delta$ PCS and  $\Delta$ MCS.

**Results.** One hundred and eight PsA patients were included. In the univariate regression analyses, improvement in fatigue, pain and disability were associated with improvement in  $\Delta$ PCS ( $\beta$ ; -2.08, -0.18 and -13.00, respectively; all *P* < 0.001) and  $\Delta$ MCS ( $\beta$ ; -1.59, -0.12 and -6.07, respectively; *P* < 0.001, *P* < 0.001 and *P* = 0.003, respectively). When patient-reported outcomes were included in the final multivariate models, improvements in  $\Delta$ PCS and  $\Delta$ MCS were associated with improvements in pain, fatigue and disability (*P* < 0.001). Improvement in enthesitis impacted  $\Delta$ PCS positively ( $\beta$  -0.31, *P* < 0.001). No association was found between change in skin psoriasis,  $\Delta$ PCS and  $\Delta$ MCS ( $\beta$  0.15, *P* = 0.056 and  $\beta$  0.05, *P* = 0.561, respectively).

**Conclusion.** In this PsA patient cohort, diminishing pain, disability and fatigue improved PCS and MCS significantly. Changes in enthesitis and psoriasis did not grossly impact HRQoL compared with DAS28CRP. Individual PsA manifestations influence HRQoL differently, which is important clinically when targeting treatment.

Trial registration. ClinicalTrials.gov, http://clinicaltrials.gov, NCT02572700.

Key words: PsA, health-related quality of life, DAS28CRP, fatigue, pain, psoriasis, enthesitis

<sup>6</sup>Division of Immunology/Rheumatology, Stanford University, Palo Alto, CA, USA and <sup>7</sup>Swedish Medical Centre/Providence St. Joseph Health and the University of Washington, Seattle, WA, USA Submitted 1 June 2021; Accepted: 28 September 2021

Correspondence to: Marie Skougaard, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Nordre Fasanvej 57, Road 8, Entrance 19, 2000 Frederiksberg, Denmark. E-mail: marie.skougaard@regionh.dk

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

<sup>&</sup>lt;sup>1</sup>The Parker Institute, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark, <sup>2</sup>Department of Dermatology, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark, <sup>3</sup>Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Odense, Denmark, <sup>4</sup>Department of Dermatology and Department of Medicine, Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, <sup>5</sup>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK,

#### Key messages

- Clinical manifestations and patient-reported outcomes are factors well known to impair quality of life in patients with PsA.
- Diminishing factors such as pain, fatigue and physical disability improve both physical and mental component scores independent of change in DAS28CRP.
- Increasing health-related quality of life for PsA patients necessitates treatment targeting both inflammatory arthritis and patient-reported outcomes.

#### Introduction

PsA is a chronic immune-mediated inflammatory disease with increasing prevalence and negative societal impact [1–3] affecting up to one in four patients with psoriasis [4]. The diverse clinical manifestations of PsA, including joint swelling and tenderness, skin psoriasis, enthesitis, dactylitis and nail psoriasis, together with patient-reported outcomes including fatigue, pain and physical impairment, are well-known causes of decreased health-related quality of life (HRQoL) [5].

The heterogeneous manifestations of PsA often complicate treatment aiming to improve HRQoL and are often combined with a discrepancy in perception of disease activity between patients and physicians [6] indicating that features such as fatigue, pain, disability, tender and swollen joint counts are of most importance in contributing to this discrepancy [7]. Treating physicians prioritize reduction in joint pain, swelling and stiffness [8], whereas patients often rank pain, cutaneous manifestations and fatigue as their priority symptoms of focus [9, 10]. Several studies investigating decreased HRQoL in PsA patients have been conducted in crosssectional settings to assess associations with individual clinical manifestations [11-14], whereas studies that included follow-up examining the relationship between changes in individual PsA manifestations and change in quality of life (QoL) have been sparse [15, 16].

Treatment of PsA aims to decrease disease activity, often by using medical therapies such as conventional synthetic DMARDs (csDMARDs) and/or biological DMARDs (bDMARDs). Available medical therapies are well known to reduce inflammation of joints and skin effectively [17], albeit with minor effect on patient-reported fatigue [18]. This demonstrates the relevance of investigating the impact of different PsA disease outcomes on patient-reported HRQoL and whether changes in clinical manifestations and patient-reported outcomes will contribute to change in HRQoL in patients with PsA.

The objective of this study was to investigate the interplay between changes in composite joint disease outcome (DAS28RP) and individual clinical PsA manifestation, including skin psoriasis and enthesitis, in addition to patientreported pain, physical disability, and fatigue as predictors of change in patient-reported HRQoL assessed by the physical component score (PCS) and mental component score (MCS), respectively, retrieved from the Short Form 36 (SF-36) questionnaire. In this set-up, PCS and MCS are considered dependent factors.

## **Methods**

#### Study design

The study was designed as an observational cohort study including patients from the Parker Institute's consecutive PsA patient cohort (the PIPA cohort) [19] registered at ClinicalTrials.gov (NCT02572700). The study was conducted in compliance with national legislation approved by the Danish Ethics Committee (H-15009080) and in accordance with the General Data Protection Regulation (BFH-2015-043) approved by the Capital Region of Denmark. The pre-specified protocol was made available from the Parker Institute's website (www.parkerinst.dk).

#### Participants

Patients diagnosed with PsA were recruited from departments of rheumatology in Region Zealand and the Capital Region of Denmark. Patients were included if they fulfilled the Classification Criteria for PsA (CASPAR) [20], were  $\geq$ 18 years of age and were scheduled to initiate a new course of treatment. Before inclusion, patients provided written informed consent. Patients attended a baseline visit at treatment initiation and at follow up after 4 months.

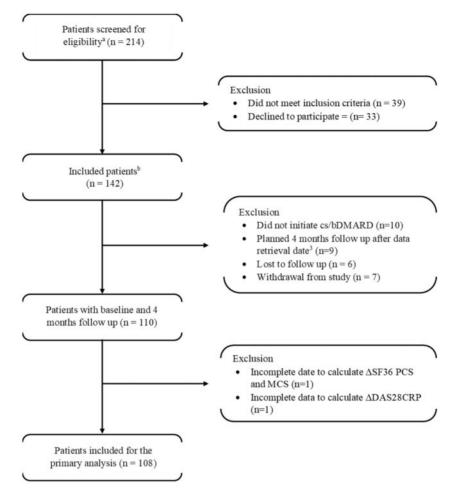
#### Sampling and sample size

Data were retrieved from the on-going consecutive PIPA cohort, and sample size was based on the cut-off date of 12 November 2020, when data on all included PIPA patients were obtained from the PIPA database. For the present study, additional inclusion criteria were deemed relevant, and only data on patients with a complete response to SF-36 and complete data to calculate disease activity (DAS28CRP) were included for analysis.

#### Variables and outcome measures

The primary outcome analysed included change in ( $\Delta$ ) PCS and MCS as a function of independent variables  $\Delta$ DAS28CRP,  $\Delta$ pain,  $\Delta$ fatigue, change in Spondyloarthritis Research Consortium of Canada enthesitis index (SPARCC) ( $\Delta$ SPARCC) and  $\Delta$ HAQ. The Danish version of SF-36 was included for the investigation of HRQoL [21]. SF-36 assesses eight health domains, namely physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH), on scales from 0 to 100, with 0 representing maximum health impairment

#### Fig. 1 Patient inclusion flow chart



Data were included from the PIPA cohort study [19]. <sup>a</sup>Patients were screened for eligibility by initial interviews at departments of rheumatology or by telephone and later clinical assessment. <sup>b</sup>Inclusion criteria included age  $\geq$ 18 years, diagnosed with PsA fulfilling the CASPAR criteria, presenting with peripheral joint involvement and about to initiate a new conventional synthetic DMARD or biological DMARD treatment course. Data were retrieved on 18 November 2020 from the consecutive cohort.

and 100 no health impairment [22]. From eight general domains, two domains have been identified, the PCS and the MCS by component analyses [23]. During the present study, PCS and MCS were used as a proxy for physical HRQoL and mental HRQoL, respectively.

Independent explanatory variables included clinical measures evaluated by a physician. Assessments were performed of swollen and tender joints (66/68 joint count), skin psoriasis quantified by the Psoriasis Area Severity Index (PASI) and enthesitis evaluated with the SPARCC. Blood biochemistry was conducted to measure blood CRP for the calculation of DAS28CRP. Additionally, patient-reported outcomes were obtained from questionnaires implemented on touch screens at the outpatient clinic of the Parker Institute and filled in by patients on the same day as the clinical examination. The HAQ was included for the assessment of physical function during activities of daily living. The HAQ

consisted of 20 questions yielding a total score from 0 to 3, with higher numbers indicating increasing disability [24]. A visual analog scale (VAS) was developed to measure patient-reported pain, fatigue and global health on a 0–100 mm scale [25]. VAS pain was used in the present study, with 0 representing no pain and 100 the worst imaginable pain [26]. Fatigue measures were retrieved from the PsA Impact of Disease (PsAID) questionnaire, which requires patients to rate their fatigue on a scale from 0indicating no fatigue to 10 indicating total exhaustion [26].

#### Statistical analysis

Patient characteristics are presented as medians with the corresponding interquartile range (IQR) for continuous variables and number with the corresponding percentage for categorical variables. Changes in ( $\Delta$ ) clinical

#### TABLE 1 Patient characteristics

Characteristic	n	Baseline	Follow-up	Mean change	P-value
				[95% CI]	
Female, n (%)	108	61 (56.48)	-	-	-
Age, years	108	52.70 (42.95–61.30)	-	-	-
Disease duration, years Treatment characteristics	108	2.88 (0.50–10.00)	-	-	-
csDMARD monotherapy, n (%)	108	41 (37.96)	_	_	_
bDMARD all, <i>n</i> (%)	108	67 (62.04)	_	_	_
bDMARD monotherapy, n (%)	108	36 (33.33)	_	_	_
Clinical outcome		()			
DAS28CRP	108	4.27 (3.57-4.28)	3.09 (2.50-4.24)	-0.97 [-4.25, 2.31]	<0.001
SPARCC enthesitis (0–16)	108	4.50 (2.00–7.00)	3.00 (0.50–6.00)	-4.10 [-28.08, 19.88]	0.031
PASI (0–72)	103 <sup>a</sup>	4.00 (0.00–10.45)	0.50 (0.00–3.93)	-4.49 [-32.07, 23.09]	< 0.001
Patient-reported outcome		, , , , , , , , , , , , , , , , , , ,			
HAQ (0–3)	108	0.88 (0.50-1.25)	0.63 (0.22-1.00)	-0.25 [-2.01, 1.50]	<0.001
PsAID Fatigue (0-10)	108	7.00 (3.00-8.00)	4.50 (2.00-7.25)	-1.14 [-9.36, 7.08]	<0.001
VAS Pain (0–100)	108	57.00 (28.00-74.00)	25.00 (10.00-63.25)	-15.73 [-94.86, 63.40]	<0.001
SF-36 data					
SF-36 PCS (0–100)	108	32.26 (27.10–38.87)	37.69 (31.99–47.72)	5.00 [-24.42, 34.41]	< 0.001
SF-36 MCS (0–100)	108	48.35 (37.88–57.18)	53.12 (40.53–59.03)	2.76 [-31.59, 37.11]	0.012
SF-36 PF (0–100)	108	55.00 (45.00–75.00)	70.00 (53.75–85.00)	9.58 [-56.71, 75.88]	<0.001
SF-36 RP (0–100)	108	0.00 (0.00–50.00)	25.00 (0.00–100.00)	17.82 [–94.53, 130.18]	<0.001
SF-36 BP (0–100)	108	41.00 (22.00–52.00)	52.00 (38.75-82.00)	15.08 [-54.88, 85.05]	<0.001
SF-36 GH (0–100)	108	45.00 (26.50–62.00)	50.00 (35.00–73.25)	5.64 [-59.02, 70.30]	0,002
SF-36 VT (0–100)	108	35.00 (20.00–56.25)	50.00 (30.00–75.00)	10.23 [-61.48, 81.94]	<0.001
SF-36 SF (0–100)	108	75.00 (50.00–100.00)	87.50 (62.50–100.00)	4.63 [-76.19, 85.45]	0.005
SF-36 RE (0–100)	108	50.00 (0.00–100.00)	100.00 (33.33–100.00)	15.43 [–98.71, 129.57]	0.001
SF-36 MH (0–100)	108	74.00 (55.00–84.00)	84.00 (60.00–92.00)	4.81 [-56.47, 66.10]	0.004

Data are presented as the median with interquartile range or number with percentage. <sup>a</sup>PASI was not calculated for pustulosis palmoplantaris. bDMARD; biological DMARD; BP: bodily pain; csDMARD: conventional synthetic DMARD; GH: general health; MCS: mental component score; MH: mental health; PASI: Psoriatic Area Severity Index; PCS: physical component score; PF: physical functioning; PsAID: PsA Impact of Disease; RE: role emotional; RP: role physical; SF: social functioning; SF-36: Short Form Questionnaire; SPARCC: Spondyloarthritis Research Consortium of Canada enthesitis index; VAS: visual analog scale; VT: vitality.

and patient-reported outcome measures from baseline (treatment initiation) to 4 months follow-up were described as the mean change with 95% Cls. Wilcoxon signed-rank test was applied to evaluate statistically significant changes. Two-sided P-values < 0.05 were considered statistically significant. SF-36 domain scores were normalized and z-transformed, and a spydergram was configured to evaluate the contribution of each SF-36 domain score over time in comparison to Danish normative SF-36 data [27]. Before the complete case analysis, the Pearson correlation coefficient comparing  $\Delta PCS$  and  $\Delta MCS$  was evaluated. Univariate regression analysis was applied to assess the association between individual clinical and patient-reported outcome measures, such as DAS28CRP/  $\Delta$ SPARCC/ $\Delta$ PASI/ $\Delta$ VAS pain/ $\Delta$ HAQ/ $\Delta$ PsAID fatigue with  $\Delta$ PCS and  $\Delta$ MCS, respectively. To address the study objectives, multivariate regression analysis was performed, including  $\Delta DAS28CRP$ ,  $\Delta PCS/\Delta MCS$  and individual disease outcome measures (i.e. ΔSPARCC/ΔPASI/ ΔVAS pain/ΔHAQ/ΔPsAID fatigue, respectively), respectively. Only clinical and patient-reported measures considered predictors of change in PCS and MCS were

included in a multivariate analysis (e.g. univariate regression analysis with *P*-value <0.05). Results from regression analyses were presented as beta coefficients ( $\beta$ ) with 95% CI, s.e. and  $R^2$ . Additionally,  $R^2$ -change was included to evaluate the contribution of  $\Delta$ SPARCC/ $\Delta$ PASI/ $\Delta$ VAS pain/ $\Delta$ HAQ/ $\Delta$ PSAID fatigue, respectively, when included in the multivariate regression analyses with  $\Delta$ DAS28CRP and  $\Delta$ PCS/ $\Delta$ MCS. Results of the multivariate regression analyses with blue arrows indicating positive change and red arrows negative change in the relevant outcome measure. The PCS and MCS were calculated in accordance with the Danish SF-36 guide [27]. Statistical analysis was carried out using R Statistics software with the additional packages MASS, plyr and plot3D.

## Results

#### Patient characteristics and outcome measures

A total of 108 PsA patients were included in the complete case analysis (Fig. 1). Included patients were defined by

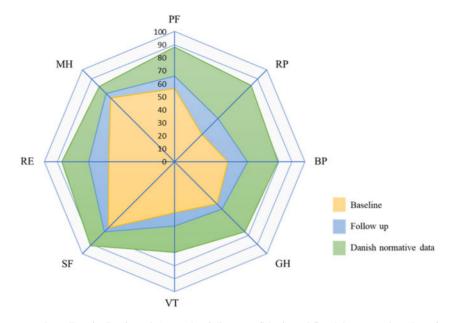


Fig. 2 SF-36 spydergram for PsA patients before and 4 months after treatment compared with Danish SF-36 normative data

Mean SF-36 scores at baseline (yellow) and 4 months follow-up (blue) and Danish normative data (green). BP: bodily pain; GH: general health; MH: mental health; PF: physical functioning; RE: role emotional; RP: role physical; SF: social functioning; VT: vitality.

56.48% being female, a median age of 52.70 years (IQR 42.95–61.3 years), and with median disease duration of 2.88 years (IQR 0.50–10.00 years) (Table 1). Treatment characteristics showed that 37.96% of included PsA patients initiated treatment with csDMARDs as monotherapy, whereas 62.04% were initiating bDMARD treatment, with 33.33% being bDMARD monotherapy. The majority of patients in bDMARD monotherapy had a history of previous csDMARD use.

Statistically significant changes were seen between baseline and 4 months follow-up for all clinical and patient-reported outcome measures evaluated (Table 1). Mean changes in clinical and patient-reported outcomes from baseline to follow-up,  $\Delta DAS28CRP$ ,  $\Delta PASI$ ,  $\Delta$ SPARCC,  $\Delta$ HAQ,  $\Delta$ PsAID fatigue and  $\Delta$ VAS pain, were all statistically significant (Table 1), representing a decrease in disease activity measures, whereas the statistically significant increases for  $\Delta PCS$  and  $\Delta MCS$ , indicate an improvement in HRQoL over time. After 4 months of treatment, an increase, indicating improvement, in all SF-36 domain scores was seen, with statistically significant mean changes in seven of eight domains. Only SF was not statistically significant (P = 0.005) (Table 1). Lowest scores at baseline were seen in RP and VT (median score of 0.00 and 35.00, respectively). Greatest improvements over time were reported in RP and RE (mean change of 17.82 and 15.43, respectively), whereas only minor improvements were seen in GH, SF and MH (mean change of 5.64, 4.63 and 4.81, respectively) (Table 1; Fig. 2). PsA patient domain scores at both baseline and follow-up were low compared with Danish normative data, demonstrating decreased scores in all domains of PsA patients compared with Danish norms (Fig. 2). The Pearson correlation coefficient for  $\Delta$ PCS and  $\Delta$ MCS was 0.11, indicating no association between  $\Delta$ PCS and  $\Delta$ MCS (Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online).

## Patient-reported outcomes as predictors of change in PCS and MCS

Results from the univariate regression analyses including patient-reported outcomes,  $\Delta PsAID$  fatigue,  $\Delta VAS$ pain and  $\Delta$ HAQ, vs  $\Delta$ PCS and  $\Delta$ MCS, respectively, were all statistically significant (P < 0.001) and considered possible predictors of change in both PCS and MCS (Table 2). Inclusion in the multivariate regression analyses with DAS28CRP was deemed relevant. Multivariate analyses suggest changes in DAS28CRP and HAQ/PsAID fatigue/VAS pain, respectively, to be associated with changes in PCS and MCS (Table 3), with statistically significant P-values (P < 0.001). The multivariate regression analysis demonstrating the interplay between (1)  $\Delta$ PCS and  $\Delta$ MCS, (2)  $\Delta$ DAS28CRP and (3) patient-reported outcome,  $\Delta PsAID$  fatigue, and  $\Delta VAS$  pain are illustrated in Fig. 3A and B, with a statistically significant contribution (all P < 0.001) from  $\Delta$ HAQ to the  $\Delta$ PCS model with  $\beta = -11.75$ , s.e. = 1.65,  $\Delta$ PsAID with  $\beta = -1.79$ , s.e. = 0.29, and  $\Delta VAS$  pain with  $\beta\!=\!-0.16\!=\!s.\text{E}.$  0.03, and to the  $\Delta MCS$  model with

#### TABLE 2 Univariate regression analyses with change in physical and mental component scores

Variable	ΔPCS					ΔMCS					
	β	95% CI	S.E.	<b>R</b> <sup>2</sup>	<i>P</i> -value	β	95% CI	S.E.	R <sup>2</sup>	P-value	
ΔDAS28CRP ΔPASI ΔSPARCC ΔHAQ ΔPSAID fatigue ΔVAS pain	-3.19 0.15 -0.56 -13.00 -2.08 -0.18	-4.56, -1.82 0.00, 0.31 -1.11, -0.02 -15.92, -10.08 -2.62, -1.53 -0.24, -0.13	0.69 0.08 0.27 1.47 0.28 0.03	0.159 0.027 0.029 0.418 0.343 0.315	<0.001 0.056 0.043 <0.001 <0.001 <0.001	-2.71 0.05 -0.25 -6.07 -1.59 -0.12	-4.21, -1.20 -0.11, 0.21 -0.84, 0.33 -9.97, -2.16 -2.24, -0.95 -0.18, -0.06	0.76 0.08 0.30 1.97 0.33 0.03	0.098 -0.007 -0.002 0.073 0.176 0.109	<0.001 0.561 0.382 0.003 <0.001 <0.001	

Univariate regression analysis used  $\Delta$ PCS/ $\Delta$ MCS as dependent variables and displayed associations between individual outcome measures. Outcome measures considered predictors of change in PCS/MCS with statistically significant *P*-values (*P* < 0.05) were also included in a multivariate regression analysis with DAS28CRP and  $\Delta$ PCS/ $\Delta$ MCS. Results are presented with beta coefficients ( $\beta$ ) and corresponding s.e. DAS28CRP: DAS for 28 joints and CRP;  $\Delta$ : change in; MCS: mental component score; PASI: Psoriasis Area Severity Index; PCS: physical component score; PsAID; PsA impact of disease; SPARCC: Spondyloarthritis Research Consortium of Canada enthesitis index; VAS; visual analog scale.

#### TABLE 3 Multivariate regression analyses

Variable	ΔΡCS						AMCS					
	β	95% CI	S.E.	R <sup>2</sup>	R <sup>2</sup> change	<i>P</i> -value	β	95% CI	S.E.	R <sup>2</sup>	<i>R</i> ² change	P-value
∆SPARCC		-0.83, 0.21		0.162		< 0.001	-	_	-	-	_	-
ΔHAQ	-11.75	, -		0.427	0.268			-7.95, 0.69				<0.001
∆PsAID fatigue	-1.79	-2.37, -1.21	0.29	0.373	0.214	<0.001	-1.32	-2.02, -0.62	0.35	0.197	0.099	<0.001
$\Delta VAS$ pain	-0.16	-0.23, -0.10	0.03	0.316	0.157	<0.001	-0.08	-0.16, 0.00	0.04	0.124	0.026	<0.001

Explanatory outcome measures considered predictors of change in PCS/MCS with statistically significant *P*-values (P < 0.05) were added to a multivariate regression analysis with DAS28CRP and  $\Delta$ PCS/ $\Delta$ MCS. Results are presented with beta coefficients ( $\beta$ ) and corresponding s.E.,  $R^2$  and  $R^2$  change. The  $R^2$  change was calculated based on  $R^2$  of the univariate model with  $\Delta$ DAS28CRP and the  $R^2$  of the multivariate model after addition of  $\Delta$ SPARCC/ $\Delta$ HAQ/ $\Delta$ PsAID fatigue/ $\Delta$ VAS pain, respectively. DAS28CRP: DAS for 28 joints and CRP;  $\Delta$ : change in; MCS: mental component score; PCS: physical component score; PsAID: PsA impact of disease; SPARCC: Spondyloarthritis Research Consortium of Canada enthesitis index; VAS: visual analog scale.

 $\Delta$ HAQ with  $\beta = -3.63$ , s.e. = 2.18,  $\Delta$ PsAID fatigue with  $\beta = -1.32$ , s.e. = 0.35, and  $\Delta$ VAS pain with  $\beta = -0.008$ , s.e. = 0.124. The orientation of the regression planes displays the associations between included variables, indicating that improvements in either pain or fatigue measures were associated with the improvement in PCS (green regression plane) and MCS (blue regression plane) and to a larger extent than the joint disease outcome, DAS28CRP. The same association was seen when including HAQ (plot not shown).

# Clinical outcomes as predictors of change in PCS and $\ensuremath{\mathsf{MCS}}$

Univariate regression analyses including clinical disease outcome,  $\Delta DAS28CRP$  and  $\Delta SPARCC$ , *vs*  $\Delta PCS$  displayed statistical significance (*P* < 0.001 and *P* = 0.043,

respectively). Only  $\Delta DAS28CRP$  showed a statistically significant association with  $\Delta$ MCS (P < 0.001) (Table 2).  $\Delta$ SPARCC was not included in the multivariate regression analysis with  $\Delta DAS28CRP$  and  $\Delta MCS$ .  $\Delta PASI$ showed no clear association with the  $\Delta PCS$  and  $\Delta MCS$ response over time (P = 0.056 and P = 0.561, respectively) (Table 2). Associations between (1)  $\Delta PCS$  and ΔMCS, (2) ΔDAS28CRP and (3) individual clinical inflammatory outcomes,  $\Delta$ SPARCC and  $\Delta$ PASI are illustrated in Fig. 3C and D. The unclear associations between  $\Delta PCS/\Delta MCS$  and several outcome measures (e.g.  $\Delta$ PASI and  $\Delta$ SPARCC) were also indicated by the orientations of the regression planes. Improvements in  $\Delta PCS$  and  $\Delta MCS$  were primarily associated with decrease in the joint-related disease activity outcome (DAS28CRP), however, not grossly dependent on

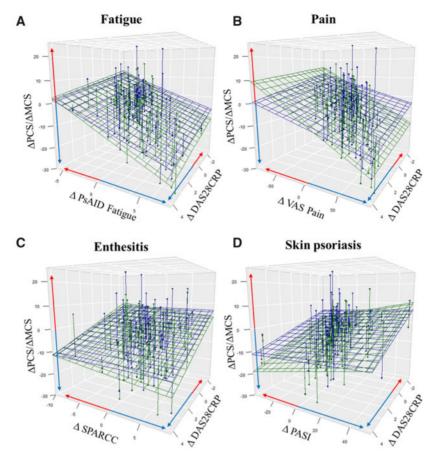


Fig. 3 3D associations between change in specific individual disease outcome measures,  $\Delta DAS28CRP$  and change in physical and mental component scores

Three-dimensional associations between outcome measures from baseline to follow-up ( $\Delta$ DAS28CRP and  $\Delta$ PCS/  $\Delta$ MCS) and  $\Delta$ PsAID fatigue (**A**),  $\Delta$ VAS pain (**B**),  $\Delta$ SPARCC (**C**) and  $\Delta$ PASI (**D**), respectively, presented in *xyz* plots, with blue arrows indicating positive change and red arrows negative change from baseline to follow-up. The green and blue regression planes represent  $\Delta$ PCS- and  $\Delta$ MCS-related data, respectively. DAS28CRP: DAS for 28 joints and CRP; MCS: mental component score; PASI: Psoriasis Area Severity Index; PCS: physical component score; PsAID: PsA impact of disease; SPARCC: Spondyloarthritis Research Consortium of Canada enthesitis index; VAS: visual analog scale.

concomitant improvement in SPARCC, which was also indicated in the regression analyses.

#### Discussion

In the present study, the influence and interplay of individual disease outcomes of PsA on HRQoL were investigated, and an assessment of the change in PCS and MCS as a proxy for physical and mental HRQoL was conducted. Although it is well known that PsA patients suffer from decreased HRQoL, the present study adds to existing knowledge that changes in individual manifestations of PsA affect changes in PCS and MCS differently. The evaluation of  $\Delta$ PCS and  $\Delta$ MCS in separate models was justified by the weak correlation, demonstrating no association between  $\Delta$ PCS and  $\Delta$ MCS (Pearson correlation coefficient = 0.11).

#### Patient-reported outcomes

Overall, results indicated that improvement in SF-36 component scores, PCS and MCS, were associated with improvement in the patient-reported measures of HAQ, PsAID fatigue and VAS pain. It became apparent that improvements in PCS and MCS were not necessarily dependent on improvements in PsA disease activity (DAS28CRP). In fact, changes in these patient-reported outcomes affected PCS and MCS to a larger extent than changes in DAS28CRP scores. Moreover, improvements in PCS and MCS were also seen in the combination of positive change in patient-reported outcome and negative change in DAS28CRP (Fig. 3). This is highly relevant to clinical practice and treatment of PsA, because it implies that improving disability, fatigue and pain measures can improve PCS and MCS scores and HRQoL independent of change in DAS28CRP. This

highlights the importance of including patient-reported outcome measures when monitoring treatment of PsA.

#### Clinical outcome

Assessing the impact of change in the clinical outcome measures, PASI and SPARCC, on change in SF-36 indicated that improvements in PCS and MCS were associated with decreasing joint-associated outcome, as measured by DAS28CRP, more than individual outcome measures from other domains of disease. This is in line with individual domain scores demonstrating a major impact on physical domains (PF, RP and BP), also reported in similar studies [28]. This does not exclude psoriasis and enthesitis as important factors in relationship to HRQoL but implies the close association between these clinical manifestations and DAS28CRP. The lack of association between PASI. PCS and MCS might also be explained by the relationship between positive and negative weights of domains in the calculation of PCS and MCS. Previous studies have shown that mental domains (VT, SF, RE and MH) are the main domains affected by psoriasis [28], of which SF and MH in this study scored 75.00 and 74.00, respectively, and presented as the domains less affected. Overall, the results indicate the joint disease outcomes, tender and swollen joints, are the most important clinical domain of disease in this patient cohort. Five PsA patients had no PASI scores registered because they were diagnosed with palmoplantar pustulosis; this was considered missing data and excluded from further analysis. The small amount of missing data was not considered to influence the results.

Interestingly, only minor improvements were reported in SF-36 domains, GH and MH, in response to medical treatment. These findings together with additional results are important to PsA patients and also important for physicians to consider in the case of treatment-resistant PsA, because it might be possible to change HRQoL for PsA patients independently of disease activity, demonstrating the relevance of integrating an interdisciplinary approach during treatment together with the shared decision-making including PsA patients themselves.

The sample size of 108 PsA patients was deemed sufficient for the evaluation of the study objective. However, it is believed that an increased number of participants might make associations stronger, increasing relevant statistically significant changes. Limitations might also include the results being largely dependent on the cohort examined, which might also explain the unclear association between  $\Delta PASI$ ,  $\Delta PCS$  and  $\Delta MCS$ , because the PsA patients included in the present study had relatively low PASI scores at baseline. In comparison, a similar study showed that diminishing skin psoriasis resulted in improved HRQoL [16]. A low PASI score might further reduce the importance of experienced pain associated with psoriatic skin and HRQoL [29]. The present study did not distinguish between skin-associated pain and joint-associated pain when using VAS pain.

Despite the limitations, this study provides important insight into the relationship between HRQoL and individual outcome measures in PsA patients.

Overall, it may be concluded that it is possible to improve HRQoL in PsA patients by improving individual manifestations of the disease. This study demonstrates that improving HRQoL for PsA patients necessitates the incorporation of both clinical measures from the various domains of arthritis (i.e. joints and entheses) and patient-reported outcome measures (i.e. disability, pain and fatigue) as a part of their individual treatment strategy. Thus, treating PsA patients to a single domain target, such as joint disease outcomes, will simply not fit all patients with heterogeneous manifestations.

## **Acknowledgements**

We wish to acknowledge all patients participating in this study and data manager Christian Cato Holm, the Parker Institute, for the assistance during collection and retrieval of data to conduct the study.

*Funding:* Funding has been received from the Danish Rheumatism Association, the Danish Psoriasis Association, Elisabeth and Karl Ejnar Nis-Hanssens Mindelegat, Minister Erna Hamiltons Legat for Videnskab og Kunst. The study is further supported by an unrestricted core grant to the Parker Institute from the Oak Foundation (OCAY-18-774-OFIL).

Disclosure statement: Marie Skougaard has received research funding from Overlæge Johan Boserup og Lise Boserups Legat, A. P. Møller Fonden, Fhv. Direktør Leo Nielsen og Hustru Karen Margrethe Nielsens Legat for Videnskabelig Grundforskning, Pfizer, Carl og Ellen Hertz's Legat til dansk læge- og naturvidenskab. Tanja S. Jørgensen has received fees for speaking and/or consultancy from Pfizer, AbbVie, Roche, UCB, Gilead, Biogen, Novartis and Eli Lilly. Jørgen Guldberg-Møller speaking fees from AbbVie. Novartis. Eli Lilly and BK Ultrasound outside the present work. Alexander Egeberg has received research funding from Pfizer, Eli Lilly, Novartis, Bristol-Myers Squibb, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from AbbVie, Almirall, Leo Pharma, Galápagos NV, Sun Pharmaceuticals, Samsung Bioepis Co., Ltd, Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, UCB, Mylan, Bristol-Myers Squibb and Janssen Pharmaceuticals. Joseph F. Merola is a consultant and/or investigator for Amgen, Bristol-Myers Squibb, Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Sun Pharma, Biogen, Pfizer and Leo Pharma. Laura C. Coates has received honoraria, grant/research support or consulting fees from AbbVie, Amgen, Boehringer-Ingelheim, BMS, Celgene, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Sun Pharma and UCB; and is a member of a speakers'

bureau for AbbVie, Amgen, Biogen, BMS, Celgene, Eli Lilly, Janssen, Medac, Novartis, Pfizer, Sun Pharma and UCB. Vibeke Strand is a consultant to Abbvie, Amgen Corporation, Arena, AstraZeneca, Bayer, BMS Boehringer Ingelheim, Celltrion, Galapagos, Genentech/ Roche, Gilead, GSK, Ichnos, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, R-Pharma, Samsung, Sandoz, Sanofi, Scipher, Sun Pharma and UCB. Phillip Mease has received honoraria, grant/research support or consulting fees from AbbVie, Amgen, Boehringer-Ingelheim, BMS, Celgene, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Novartis, Pfizer, Sun Pharma and UCB; and is a member of a speakers' bureau for AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer and UCB. Lars Erik Kristensen has received fees for speaking and consultancy from Pfizer, AbbVie, Amgen, UCB, Gilead, Biogen, BMS, MSD, Novartis, Eli Lilly and Janssen Pharmaceuticals. The remaining authors have declared no conflicts of interest.

## Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of the individuals who participated in the study. Data may be shared as part of research collaborations between participating institutions in line with GDPR and if approved by the Parker Institute and Danish authorities.

## Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

## References

- Egeberg A, Kristensen LE, Thyssen JP et al. Incidence and prevalence of psoriatic arthritis in Denmark: a nationwide register linkage study. Ann Rheum Dis 2017; 76:1591–7.
- 2 Kristensen LE, Englund M, Neovius M et al. Long-term work disability in patients with psoriatic arthritis treated with anti-tumour necrosis factor: a population-based regional Swedish cohort study. Ann Rheum Dis 2013;72: 1675–9.
- 3 Kristensen LE, Jørgensen TS, Christensen R et al. Societal costs and patients' experience of health inequities before and after diagnosis of psoriatic arthritis: a Danish cohort study. Ann Rheum Dis 2017;76:1495–501.
- 4 Alinaghi F, Calov M, Kristensen LE et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. J Am Acad Dermatol 2019;80:251–65.e19.
- 5 Gudu T, Gossec L. Quality of life in psoriatic arthritis. Expert Rev Clin Immunol 2018;14:405–17.

- 6 Furst DE, Tran M, Sullivan E *et al.* Misalignment between physicians and patient satisfaction with psoriatic arthritis disease control. Clin Rheumatol 2017;36:2045–54.
- 7 Eder L, Thavaneswaran A, Chandran V, Cook R, Gladman DD. Factors explaining the discrepancy between physician and patient global assessment of joint and skin disease activity in psoriatic arthritis patients. Arthritis Care Res 2015;67:264–72.
- 8 Van De Kerkhof PCM, Reich K, Kavanaugh A *et al.* Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. J Eur Acad Dermatology Venereol 2015; 29:2002–10.
- 9 Orbai A-M, Mease PJ, de Wit M *et al.* Report of the GRAPPA-OMERACT psoriatic arthritis working group from the GRAPPA 2015 annual meeting. J Rheumatol 2016;43:965–9.
- 10 Orbai AM, De Wit M, Mease PJ *et al.* Updating the psoriatic arthritis (PsA) core domain set: a report from the PsA workshop at OMERACT 2016. J Rheumatol 2017;44:1522–8.
- 11 Husted JA, Gladman DD, Farewell VT, Cook RJ. Healthrelated quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. Arthritis Care Res 2001;45:151–8.
- 12 Rosen CF, Mussani F, Chandran V et al. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. Rheumatology 2012;51:571–6.
- 13 Carneiro C, Chaves M, Verardino G et al. Evaluation of fatigue and its correlation with quality of life index, anxiety symptoms, depression and activity of disease in patients with psoriatic arthritis. Clin Cosmet Investig Dermatol 2017;10:155–63.
- 14 Skougaard M, Jørgensen TS, Rifbjerg-Madsen S *et al.* Relationship between fatigue and inflammation, disease duration, and chronic pain in psoriatic arthritis: an observational DANBIO registry study. J Rheumatol 2020; 47:548–52.
- 15 Owczarek K, Jaworski M. Quality of life and severity of skin changes in the dynamics of psoriasis. Adv Dermatology Allergol 2016;2:102–8.
- 16 Honma M, Cai Z, Burge R et al. Relationship between rapid skin clearance and quality of life benefit: post hoc analysis of Japanese patients with moderate-to-severe psoriasis treated with ixekizumab (UNCOVER-J). Dermatol Ther (Heidelb) 2020;10:1397–404.
- 17 Smolen JS, Schöls M, Braun J *et al.* Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018;77:3–17.
- 18 Reygaerts T, Mitrovic S, Fautrel B, Gossec L. Effect of biologics on fatigue in psoriatic arthritis: a systematic literature review with meta-analysis. Jt Bone Spine 2018; 85:405–10.
- 19 Højgaard P, Christensen R, Dreyer L *et al.* Pain mechanisms and ultrasonic inflammatory activity as

prognostic factors in patients with psoriatic arthritis: protocol for a prospective, exploratory cohort study. BMJ Open 2016;6:e010650.

- 20 Taylor W, Gladman D, Helliwell P *et al.*; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
- 21 Bjorner JB, Thunedborg K, Kristensen TS, Modvig J, Bech P. The Danish SF-36 health survey. J Clin Epidemiol 1998;51:991–9.
- 22 Ware JE. SF-36 Health Survey update. Spine (Phila Pa 1976) 2000;25:3130–9.
- 23 Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: scoping review. SAGE Open Med 2016;4:2050312116671725.
- 24 Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 23(5 Suppl 39):S14–8.
- 25 Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale

measures for chronic and experimental pain. Pain 1983; 17:45–56.

- 26 Gossec L, De Wit M, Kiltz U et al.; EULAR PsAID Taskforce. A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. Ann Rheum Dis 2014;73:1012–9.
- 27 Bjorner JB, Damsgaard MT Watt T, Beck P et al. Dansk manual til SF-36: et spørgeskema om helbredsstatus [Danish SF-36 manual: a questionnaire on health status]. Lægemiddelindustriforeningen 1997;1:70–140.
- 28 Strand V, Sharp V, Koenig AS et al. Comparison of health-related quality of life in rheumatoid arthritis, psoriatic arthritis and psoriasis and effects of etanercept treatment. Ann Rheum Dis 2012;71:1143–50.
- 29 Ljosaa TM, Mork C, Stubhaug A, Moum T, Wahl AK. Skin pain and skin discomfort is associated with quality of life in patients with psoriasis. J Eur Acad Dermatology Venereol 2012;26:29–35.