The burden of psoriatic arthritis in the biological era: data from the Belgian Epidemiological Psoriatic Arthritis Study (BEPAS)

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Short title :

Epidemiology of PsA in Belgium: burden of the disease

Abstract

Objectives: To characterize the frequency of PsA subtypes, as well as to estimate the severity based on damage and inflammation, and to estimate the impact of PsA on patients' health-related quality of life.

Methods: Longitudinal observational study in 17 academic and non-academic centres in Belgium. Patients with PsA fulfilling CASPAR criteria were recruited. Three visits were scheduled: at baseline (T0), at one year (± one month) (T1) and at two years (± one month) (T2) of follow-up. Demographics, clinical data and patient reported outcome measures were collected at T0, T1 and T2. X-rays of hand and feet were collected yearly (T0, T1 and T2). X-rays of the spine were collected at T0 and T2. Here we report on the burden of disease based on the clinical data and patient reported outcomes**.**

Results: 461 patients were recruited. 73.5% have combined peripheral and axial involvement. 13.7% had hip involvement. Plaque psoriasis was predominant (83.9%). At inclusion respectively 42.7% and 58.8% had no tender or swollen joints. Dactylitis and enthesitis were still present in 13.7% and 24.1% of the patients respectively. 68% and 44,2% of patients was treated with DMARD's and/or anti TNF, respectively. Forty-three percent of the patients had a state of minimal disease activity and 62% considered the actual state as satisfactory (PASS). The mean HAQ score was 0.7% with 32.5% of patients who had score normal score (<0.3).

Conclusion: Despite the availability of different treatment options, including biologicals (anti-TNF), still a substantial number of patients have active disease and have a high disease burden.

Key words (max 10)

Epidemiology, psoriatic arthritis, Belgium, subtypes, severity, quality of life, natural history, burden.

Key messages

1. In the era of biologicals psoriatic arthritis is still associated with high burden of disease.
2. Minimal disease activity is an achievable target in real life and daily practice
3. The role of comorbidities on the disease activity and outcome is still unclear

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease associated with the chronic skin disorder psoriasis. PsA is characterized by its heterogeneous presentation: peripheral arthritis, dactylitis, enthesitis, axial inflammation and any combination. Skin and nail disease, inflammatory bowel disease and uveitis, as well as metabolic, cardio-vascular and psychiatric co-morbidities further contribute to the disease burden. Recent epidemiological data have clearly demonstrated that PsA is not a benign form of arthritis, as disease progression leads to joint deformity, joint destruction, disability and social exclusion in a substantial number of patients. The impact of PsA is similar to this of rheumatoid arthritis (RA) [1-3].

Careful clinical observations lead to the description of five different subtypes of PsA [4]. Recently a simple breakdown of clinical phenotypes was proposed with PsA presentations classified as peripheral, axial or both [5]. Recognizing the presenting subtype of disease is important as treatment options may be different among these groups. Nevertheless, the clinical presentation of PsA may also vary over time, even beyond the definition of PsA itself towards other presentations of the spondyloarthritis concept, in which PsA is traditionally included (ref).

For a long period, therapeutic options for patients with PsA have been limited and remained unsatisfactory. Underestimation of the disease severity and an approach that copied strategies, trial design and outcome assessments from RA consequently lead to a paucity of controlled therapeutic studies in PsA, with target populations frequently only representative of those with polyarticular disease. Despite these limitations, the recent advent of new therapies including biologicals targeting tumour necrosis factor alpha (TNF-α) and the interleukin (IL)-23 - IL-17 axis, have an unprecedented effect on patient management and dramatically improve outcome and prospects for PsA patients [6,7]. Simultaneous presence of extra-articular manifestations and comorbidities may influence the choice of therapy [8].

Further efforts towards personalized medicine approaches for PsA patients require better characterisation of the patients at the group and individual level. However, epidemiological data for PsA, including surveys of disease severity and disability, remain scarce [9]. In particular, epidemiological data on disease impact, severity and management need to be updated after nearly two decades of biological therapies. Here, we present the Belgian Epidemiological Psoriatic Arthritis Study (BEPAS), a prospective population study set up (1) to generate a comprehensive database that characterizes the clinical presentation and the frequency of the distinct PsA subtypes; (2) to estimate the prevalent severity of disease based on disease activity scores, active inflammation and structural damage; (3) to estimate the impact of PsA in Belgium in terms of health-related quality of life and (4) to evaluate progression of structural damage and loss of function in patients with PsA over time. In this initial BEPAS report, we focus on the baseline characteristics of the patient population and the burden of the disease.

Methods

BEPAS is a national, epidemiological, multicentre, non-interventional trial. The main objectives of the study were to characterize the frequency of PsA subtypes, to estimate the severity based on damage and inflammation, and to estimate the impact of PsA on patients' health-related quality of life.

Adult subjects with a diagnosis of PsA and fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR) [10] were selected to participate in the trial. Every week, the first, third and fifth eligible PsA patient presenting at the different sites was asked to participate in the study. Using this method, an unbiased systematic selection of patients was obtained. All patients gave their written informed consent and the study was conducted in agreement GCP/ICH guidelines and the Declaration of Helsinki. The protocol was approved by the central Ethics Committee (University Hospitals Leuven) on 27 July 2012 (B322201215141).

Three visits were scheduled: baseline (T0), at one year (T1) and at two years (T2) of follow-up. The trial activities and study procedures, specific to each visit, are described in Supplementary Table 1.

Rheumatologists in 17 centres across the whole territory of Belgium were asked to participate in the study. Both academic, city hospital and private practice centres were involved. All centres were allowed to include up to 60 eligible patients. The inclusion had to be terminated when 600 patients had been enrolled or when the enrolment period had exceeded 18 months.

Patient reported outcome for measuring burden of disease:

Healthy Assessment Questionnaire (HAQ-DI) is a questionnaire for the of physical disability, with a score ranging from 0 to 3 with 3 as the maximum score of difficulty.

Short Form-36 consists of eight scaled scores, which are the weighted sums of the questions in their section and are directly transformed into a 0-100 scale. The lower the score the more disability. In general population the score for the different eight items are higher than 60 varying according each item. Population scores for the Belgium population are not available.

The Dermatology Life Quality Index (DLQI) is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA) are calculated in those patients who have respectively at least 5 and all 7 domains available.

SAS (Version 9.2) for Windows was used for all the statistical analyses. They were conducted in the eligible population, i.e. all subjects enrolled in the study, having given their informed consent and who were not enrolled after the maximum number of patients that could be enrolled in a centre was reached, broken down by time since diagnosis (disease duration inferior to two

years, or superior or equal to two years). For this study, statistics were descriptive: number of patients, mean, standard deviation, median, interquartile intervals, minimum and maximum for continuous variables; and total number of patients, number of patients in each category and percentage of patients in each category for discrete variables.

For differentiation between academic and non-academic centres of demographics, quality of life and clinical symptoms ANOVA for repeated measures was used.

Results

A total of 461 patients (57.0% males; 93.3% white Caucasians) were enrolled by 17 centres between November 2012 and July 2014.

Demographics

The demographics, medical history, clinical patterns and family history of patients are summarized in Table 1. Patients were 52.8 ± 12.3 years-old (mean ± standard deviation) with a minimum of 21 years and a maximum of 85 years. The duration of PsA at inclusion was 8.5 ± 9.3 years. 27.5% of the patients had a disease duration of less than 2 years. The delay between first symptoms and diagnosis was 0.7 years (IQR: 0.55 -2.55 yrs). At least 25% of the patients was obese (BMI $\geq$30).

Classification of PsA and clinical pattern of psoriatic disease

The axial and peripheral involvement patterns are summarized in Table 1 . The large majority of patients reported both axial and peripheral symptoms (73.5%). Peripheral involvement includes arthritis as well as enthesitis and dactylitis. Axial symptoms were considered positive if patients mentioned at least one of following symptoms: axial pain, pain at night, axial morning stiffness lasting for at least 30', buttock pain and anterior chest wall pain. Hip involvement was reported by 63 patients (13.7%) but only one patient had mono-articular hip

involvement. Enthesitis or dactylitis as unique presentations were recorded in 4 patients; 2 patients had enthesitis and dactylitis without synovitis.

The duration of psoriasis symptoms at inclusion was 11.9 ± 10.8 years. Type 1 psoriasis (onset < 40 years) was present in 61.8% of patients and type 2 psoriasis (onset ≥ 40 years) in 34.5% of patients. Plaque psoriasis was the predominant type of psoriasis (83.9%). Nail involvement ever was reported in 39.9 % of the patients. A family history of psoriasis and PsA was present for 42.5% and 10.2% of patients, respectively (table 1). Other extra-articular manifestations reported were uveitis in 5.2% of patients, Crohn's disease in 0.9% of patients and ulcerative colitis in 0.9% of patients.

Articular and skin characteristics at inclusion

Data on articular, enthesitis, dactylitis and skin involvement were captured by the physician, and included the number of tender and swollen joints (78/76), the number of digits affected by dactylitis, the number of enthesitis locations, nail involvement, and the percentage of patients with a body surface area (BSA) over 3% (Figure 1). The mean 78-tender and 76-swollen joint count was 4.1 ± 7.3 and 2.1 ± 4.5, respectively. At inclusion a total of 42.7 % of patients had no tender joint and 58.8% had no swollen joints. Oligoarticular involvement (< 4 joints) and including monoarticular involvement for tender and swollen joints was found respectively in 25.6% and 22.1% of the patients. A substantial number of patients had polyarticular involvement (≥: 4 joints) at the time of inclusion (tender joints: 31.7%, swollen joints: 19.1%). Dactylitis in at least one digit was present in 13.7% of the patients and was independent of the disease duration. The majority of patients (79.4%) had 1 or 2 digits involved. Enthesitis was detected in 24.1% of the patients and at least 50% had more than 2 entheseal localisations involved. Enthesitis was observed more frequently in female patients. (females vs males: 30.3 vs 19.4%). Patients with a recent onset of disease (<2 years) had more swollen and tender joints, more dactylitis and enthesitis reflecting more active articular disease (Figure 1).

Psoriasis was present at inclusion in 66.8% of patients. The mean BSA was 5.25% (SD +/- 10.5%). Twenty percent had an affected BSA of at least 3%. The mean Psoriasis Area and Severity Index (PASI) was 2.4 ± 4.3. Nail involvement was found in 26% of the patients.

Minimal disease activity state (MDA) is present in 43% (146/346 pts) of the patients at inclusion but more frequent in those patients with a longer disease duration (≥ 2 years). 12.8% (31/243 pts) are in a state of very low disease activity at baseline. Some patients have very high values both in terms of tender/swollen joints, number of digits with dactylitis and enthesitis, as well as in terms of BSA and PASI (Figure 2).**Medication at inclusion**

The prior and concomitant medications are summarized in Table 2. DMARDs and anti-TNF-α drugs are currently used respectively by 69.4% and 45.02% of patients. Analgesics and NSAIDs are concomitantly used by 44.4% and 47.2% of patients, respectively. Corticosteroids are still taken by 28.4% of the patients. The majority of patients never had physiotherapy (70.4%).

Burden of disease

Burden of disease is evaluated based on the health-related quality of life and the degree of clinical activity.

In terms of physical health, the mean Health Assessment Questionnaire (HAQ) total score was 0.7 ± 0.6 (32.5% of patients having a score ≤0.3). Patients in the 4th quartile had very high HAQ scores, representing a higher degree of disability (Figure 3). 32% of the patients have a normal HAQ (< 0.3).

Patient global health is captured by the SF-36. All mean values of the SF-36 domains and components were in a range between 39 and 47 with standard deviations ranging between 10 and 15, are systematically reduced compared to the values in the healthy population and was unrelated to disease duration (Figure 4). The health-related quality of life in patients with psoriasis of adult patients suffering from a skin disease was assessed to measure impact of skin

disease on articular involvement. The mean DLQI was 3.45 ± 5.13 , with a very large effect (≥10) in about 10% of the patients (possible maximum score is 30) (Figure3).

The patient acceptable symptom state (PASS) or the Minimal clinically important state (MCIS) are comprehensive measures of satisfaction of the treatment and impact of the disease. On the Minimal Clinically Important State (MCIS) scale, a total of 62% of patients would consider their present state satisfactory if it would continue during the next months.

Comorbidities and disease related surgery are also considered as a part of the biomedical burden of disease (supplementary Table 2). The most frequent comorbidities are hypercholesterolemia, arterial hypertension and hyperuricemia, affecting 31.0%, 26.5% and 13.5% of patients, respectively.Joint replacement surgery prior to baseline is performed in 35 patients (7.6%). Osteoporosis is only documented in 3.5% of the patients.

Academic versus non-academic patients

At inclusion patients in non-academic centres had significantly more swollen and tender joints but these differences disappeared at visit 2 and 3 (p: 0.023).Plaque psoriasis and nail psoriasis were more prevalent in academic centres compared to non-academic centres (respectively Fisher Exact :0.045 and 0.001). Disease duration (11.9 ± 10.8 years)was comparable (p: 0.171) but the frequency of patients with a disease duration < 2 years was more frequent in non-academic centres.

Discussion

The lack of appropriate epidemiological studies, the late recognition of PsA as a separate disease entity and the underestimation of its severity has led to an incomplete appraisal of the disease spectrum of PsA and its impact on the patients and society, including comorbidities, quality of life, disability, social exclusion and even mortality. [10,11,12]

Clinical features of PsA, including comorbid conditions and disease activity, contribute to reduced physical and psychosocial health-related quality of life. The clinical burden of PsA contributes to direct medical costs attributable to the utilization of health care. As a result of the physical functioning limitations imposed by PsA, indirect costs such as disability and lost productivity are substantial drivers of the total costs of care [13]. More recently, the psychological and social burden of PsA, including sleep disorders, fatigue, low-level stress, depression and mood/behavioural changes, poor body image, and reduced work productivity on patient's quality of life has been assessed [14].

The Belgian Epidemiological Psoriatic Arthritis Study (BEPAS) is a national, epidemiological, multicentre, non-interventional trial. This large cohort paints a real-life heterogeneous presentation of PsA in academic and non-academic centres in Belgium. It corroborates the two above-mentioned reviews, by confirming the huge burden the disease for patients in terms of deterioration of quality of life. The gender distribution as well as the age of onset is as expected but the cohort illustrates the large spectrum of disease duration, age of onset, clinical articular and extraarticular involvement and impact on quality of life in patients with psoriatic arthritis. This partly in contrast with the PsA populations participating in clinical trials.

Although PsA has been included in the spondyloarthritis concept, it is often considered to be predominantly peripheral. In the BEPAS cohort the large majority of the patients are classified as having a polyarticular pattern (74.7%) at some time point during the disease course confirming previous reports [15,16]. At inclusion still about 40% of the patients had active

peripheral joint involvement (painful and/or swollen joints) despite active treatment.22.1% of the patients have ongoing oligarticular involvement and 19.1% polyarticular involvement at inclusion.

13.6% of the patients also reported hip involvement, more prevalent in those with longer disease duration (>2 years) (data not shown), comparable to what is cited in the literature [16]. Early recognition of hip involvement is important since it contributes substantially to physical impairment and may lead to early joint replacement. In our cohort 2% of the patients underwent a hip replacement (suppl table 2)

Axial involvement in PsA is poorly defined and remains an important point of discussion. Earlier studies focussed on radiographic changes on x-rays in comparison to ankylosing spondylitis [19,20]. We looked for the different components of inflammatory low back pain anchored onto axial pain such as pain at night, axial morning stiffness lasting for at least 30 minutes, buttock pain and anterior chest wall pain. This study reports a higher frequency of spinal complaints, with 74.2% of patients (0.7% with a pure axial disease and 73.5% with combined peripheral and axial involvement) reporting at least one axial symptom. It is unlikely that all these patients have inflammatory axial involvement as a manifestation of psoriatic arthritis. Further analysis, including imaging, is needed to evaluate how many of the patients fulfil the criteria of inflammatory back anchored on the presence of axial pain.

The skin involvement is in line with what we could expect for a cohort of PsA patients. In our cohort, nail involvement at inclusion is reported in 25.8% of patients, far less than what is usually reported (41–93%) [21]. Most of these reports date from before the biological era. The lower than expected frequency could be explained by the frequent use of biological DMARD's in this cohort.BDMARDS were used in 44% of the patients. In contrast to cDMARD's bDMARDS are much more effective on skin and nail involvement.

In this real-life cohort DMARD's were ever initiated in 90,1% of the patients and at inclusion the large majority is on cDMARD's (69,4%). 8,7% of the patient were ever treated with anti TNF while the large majority of these patients (45%) is still on biological treatment at inclusion. This reflects the establised use of bDMARD's in the psoriatic arthritis population. The high use of cDMARD's and bDMARDs reflects partially the severity of the disease.

Despite the long disease duration and ongoing active treatment and follow-up , almost half of the patients have signs of ongoing active peripheral disease reflected by the presence of painful and or swollen joints, dactylitis or enthesitis at inclusion

Surprisingly 28.4% of the patients are taking steroids, reflecting insufficient symptomatic disease control by DMARDs and/or anti-TNF.

The frequent use of concomitant medications such as corticosteroids, NSAID's and analgesics aiming mostly for symptom control rather than disease control may explain the discrepant high percentage of patients (62%) with a satisfactory PASS compared to low number of patients in VLDA.

43% of the patients have a state of minimal disease activity and 12,8 % of the patients are in VLDA. Although there was no clear predefined strategy as in the TICOPA trial these percentage are in a comparable range of what is observed in this trial. [22,23] The low frequency of MDA and VLDA as well the high frequency of disability (HAQ >0.3) may partially be explained by the delay between symptoms and diagnosis. The median lag time between first symptoms and final diagnosis is 7 months. It is demonstrated that a 6-month delay from symptom onset to the first visit with a rheumatologist contributes to the development of peripheral joint erosions and worse long-term physical function [24]

PsA is now considered a disease with a high burden. In BEPAS we focussed on the biomedical burden of the disease and health related quality of life aspects. Recent studies showed that

compared with RA and SPA, patients with PsA had greater odds of depression, hypertension, hyperlipidaemia, diabetes and a history of ischaemic heart disease [25,26]. Our study confirms the high prevalence of hypercholesterolemia (31.0%), hypertension (26.5%), hyperuricemia (13,5% and diabetes mellitus type II (7,6%)of PsA patients. With a mean BMI of 27.5 kg/m² and maximum values reaching 50 kg/m² the patient population of the current study is clearly overweighted to obese. Obesity seems to be a risk factor for incident psoriasis and aggravates existing psoriasis. Weight reduction may improve the severity of psoriasis in overweight individuals. Overweight may interfere with the medical treatment and adds to the cardiovascular risk profile in these patients. [27]. Disease related surgery might be a measure for the impact of damage. There was a relative low use of joint replacing surgery.

PsA and by extension psoriatic disease have an overall impact on quality of life, disability and overall health, including physical, social and mental health. Overall the physical health was good to acceptable (HAQ mean score 0.7) with 32% of patients having a normal HAQ (< 0.3) (28). But at least 25% of the patients had a high score on the disability index (HAQ) reflecting a major impact on their physical function. PsA affects also quality of life reported here by the SF-36. All domains of the SF-36 are affected by the disease and show lower scores than the global population. The physical component seems somehow to be more affected than the mental component, irrespective of disease duration.

In general minor differences in the patient characteristics are observed between the academic and non-academic centres. This might be partly a national health system specific finding since the access to second line (non-academic) and third line (academic) specialist care is unrestricted for the patient.

In conclusion despite the availability of many therapeutic options including conventional DMARDs and anti TNF at the time of recruitment, still many patients experience much burden of the disease, including active articular involvement, biomedical burden such as comorbidities

but also a reduced quality of life and substantial disability. Furthermore, the implementation of treatment targets incorporated in a personalised treatment strategy could improve the outcome and the quality of life and reduce or prevent disability. The BEPAS cohort is a unique opportunity to study interfering factors with the natural history and outcome of the disease.

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Table 1. Baseline characteristics of the Belgian Epidemiological Psoriatic Arthritis Study (BEPAS) patient population

Parameter	N	Mean	SD	IQ25	Median	IQ75	Min	Max
Age (year)	461	52.8	12.3	44.0	53.0	61.0	21.0	85.0
Body Mass Index (kg/m²)	431	27.5	4.9	24.0	27.0	30.3	16.8	50.8
Psoriatic arthritis duration at inclusion (year)	459	8.5	9.3	1.6	5.7	11.9	0.0	50.2
Psoriasis symptoms duration at inclusion (year)	450	11.9	10.8	4.0	9.1	16.1	0.1	59.8

Parameter	Category (N=461)	n	%
Gender	Male	263	57.0
	Female	198	43.0
Working status	Unemployed	233	50.5
	Working part-time	52	11.3
	Working full-time	164	35.6
	Working without other precisions	9	2.0
	Student	1	0.2
Family disease history	Psoriasis	196	42.5
	Psoriatic arthritis	47	10.2
Description of psoriasis	Plaque psoriasis	387	83.9
	Pustular psoriasis	18	3.9
	Palmoplantar pustulosis	34	7.3
	Psoriasis guttata	49	10.6
	Psoriasis inversa	27	5.9
	Erythrodermia	20	4.3
	Other	1	0.2
Clinical involvement evaluated by treating physician		**n**	**%**
	Axial clinical involvement only	3	0.7
	Peripheral clinical involvement only	117	25.4
	Axial and peripheral clinical involvement	339	73.5
	No axial or peripheral clinical involvement	1	0.2
Specific Locomotor manifestations (present at least one timepoint during disease evolution)			
	Hip arthritis	63	13.7
	Dactylitis (finger/toe)	213	46.2
	Enthesitis	184	39.9
Extra-articular manifestations			
	Uveitis	24	5.2
	Crohn's disease	4	0.9
	Ulcerative colitis	4	0.9

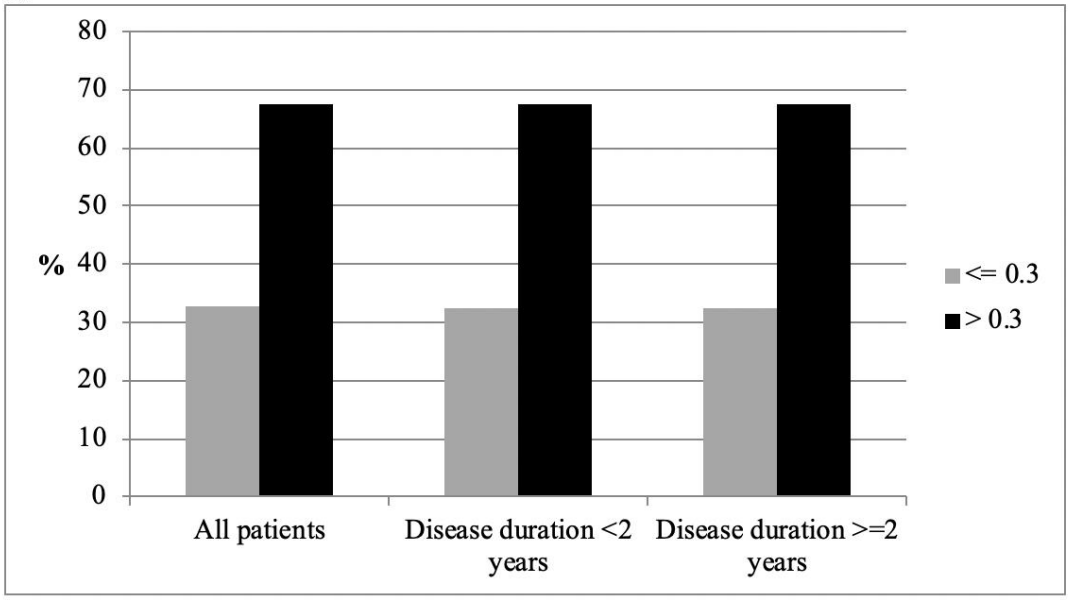
Table 2. Belgian Epidemiological Psoriatic Arthritis Study (BEPAS): Prior and concomitant medications

Type of treatment	Never used		Only previously used		Previously and currently used		Total	
	n	%	n	%	n	%	n	%
DMARDs	41	9,1	97	21.5	313	69,4	451	100.0
Anti-TNF	233	51,3	17	3.7	204	45,0	454	100.0
Physiotherapy	319	70,4	80	17.7	54	11.9	453	100.0

Other currently used concomitant medications	N	n	%
Concomitant use of analgesics	448	199	44.4
Concomitant use of NSAIDs	453	214	47.2
Concomitant use of corticosteroids	461	131	28.4

DMARDs = Disease-Modifying Antirheumatic Drugs; TNF = Tumour Necrosis Factor; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

A:



B:

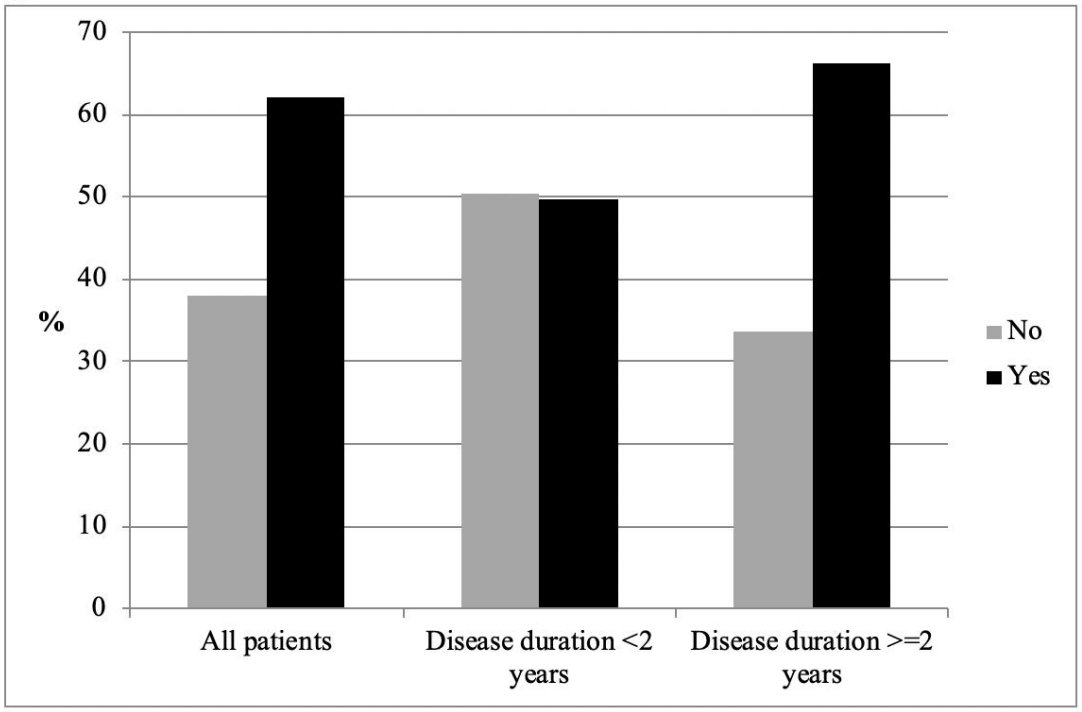


Figure 1. Baseline characteristics of the BEPAS patient population:
A: Patient-reported burden in terms of HAQ (% of patients ≤0.3 and >0.3) and
B: MCIS (% of patients answering 'no' or 'yes')

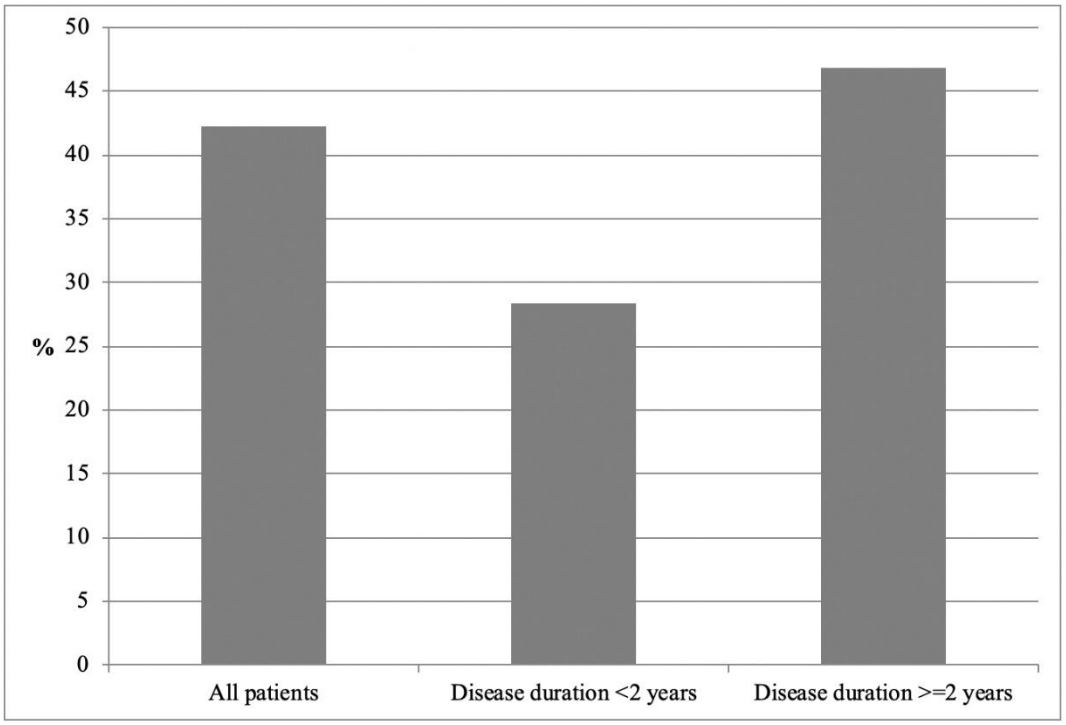


Figure 2. Baseline characteristics of the Belgian Epidemiological Psoriatic Arthritis Study (BEPAS) patient population: Global reported burden in terms of % of patients with minimal disease activity (MDA)

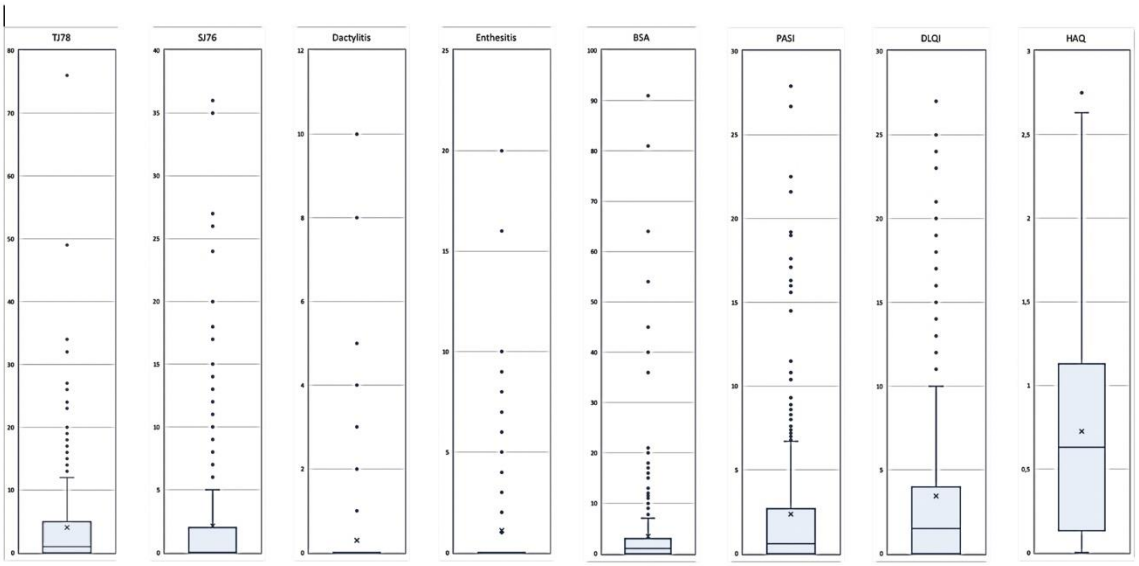


Figure 3: Baseline characteristics of the Belgian Epidemiological Psoriatic Arthritis Study (BEPAS): joint count 78/76 (tender and swollen joint count), dactylitis (number of digits), enthesitis (number of sites), psoriasis (BSA and PASI), DLQI and HAQ. Results are given as boxplots.
The horizontal line indicates the median, the cross indicates the mean. The lower and upper hinges correspond to the first and third quartiles.
Data beyond the end of the whiskers are outliers and are plotted individually.

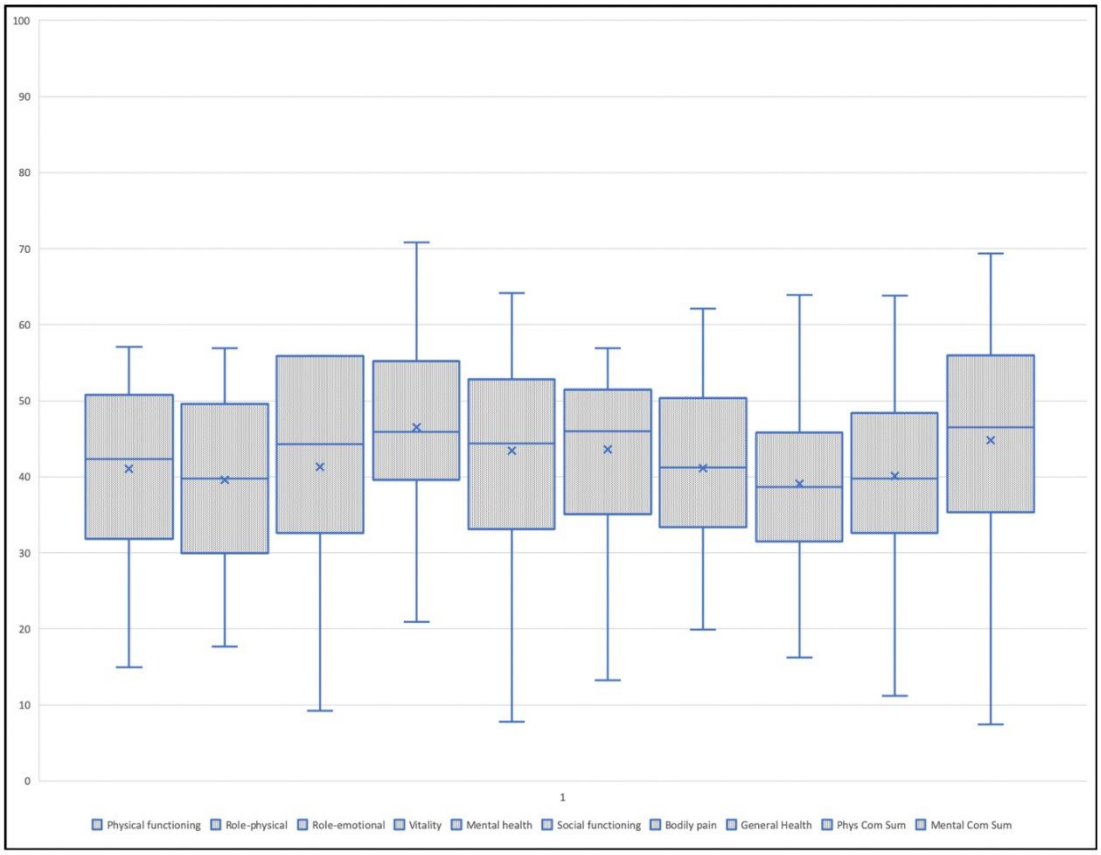


Figure 4: Baseline characteristics of the Belgian Epidemiological Psoriatic Arthritis Study (BEPAS): SF-36. Results are given as boxplots. The horizontal line indicates the median, the cross indicates the mean. The lower and upper hinges correspond to the first and third quartiles