



## Determinants of health-related quality of life in spondyloarthritis and rheumatoid arthritis - data from the COMOSPA and COMORA studies

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### ABSTRACT

**Objectives:** To assess the hierarchy of outcomes contributing to health-related quality of life (HRQoL) in spondyloarthritis (SpA) and rheumatoid arthritis (RA).

**Methods:** Data from the international cross-sectional COMOSPA and COMORA studies were used. HRQoL was assessed using the EuroQOL 5-dimension 3-level (EQ-5D-3 L). First, multivariable linear regression models were used to identify associations between EQ-5D-3 L (dependent variable) and several demographic and clinical variables (independent variables). Second, a decision tree was built using Chi-square Automatic Interaction Detector, a method of unbiased hierarchical multivariable analysis (dependent variable: EQ-5D-3 L).

**Results:** In total, 3984 patients with SpA and 3920 patients with RA were included. In SpA, HRQoL was associated with BASFI (adjusted  $B = -0.006$ ; 95%CI =  $-0.007$  to  $-0.005$ ), ASDAS ( $-0.052$ ;  $-0.071$  to  $-0.033$ ), work productivity loss score ( $-0.002$ ;  $-0.003$  to  $-0.002$ ), NSAID treatment ( $-0.052$ ;  $-0.083$  to  $-0.020$ ), bDMARD treatment ( $-0.051$ ;  $-0.082$  to  $-0.021$ ), university education ( $-0.051$ ;  $-0.075$  to  $-0.027$ ) and radiographic sacroiliitis ( $0.035$ ;  $0.004$  to  $0.030$ ). In RA, HRQoL was associated with modified Health Assessment Questionnaire (MHAQ) ( $-0.220$ ,  $-0.253$  to  $-0.188$ ), DAS28-CRP-3v ( $-0.027$ ,  $-0.036$  to  $-0.018$ ), work productivity loss score ( $-0.003$ ,  $-0.003$  to  $-0.002$ ), presence of erosions ( $-0.042$ ,  $-0.065$  to  $-0.020$ ), alcohol consumption  $\geq 3$  units/day ( $0.012$ ,  $0.001$  to  $0.024$ ) and csDMARD treatment ( $0.034$ ,  $0.001$  to  $0.066$ ). The decision tree revealed BASFI and MHAQ as first variables with the most discriminative power on EQ-5D-3 L, followed by work productivity loss and disease activity, in both SpA and RA cohorts.

**Conclusion:** In SpA and RA, physical function is the main contributor to HRQoL measured by EQ-5D-3 L, followed by disease activity and work productivity loss.

### Introduction

The inflammatory state associated with spondyloarthritis (SpA) and rheumatoid arthritis (RA) may have significant consequences on several dimensions of patients' lives. The understanding of this impact on health-related quality of life (HRQoL), physical function and work

productivity, and their interplay, is of utmost importance for clinicians to conduct the most appropriate and valuable assessment of their patients in clinical practice, and to allow the governments and scientific societies to estimate the economic burden of such diseases.

Disability caused by radiographic axial SpA (axSpA), ie ankylosing spondylitis (AS), is well documented in the literature, and may be the

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most important predictor of direct and indirect health costs in this condition [1–3]. A study in 3 European countries found that each patient with radiographic axSpA had a mean annual societal direct cost of 2640€. In addition to disability, other predictors of higher costs were longer disease duration, lower education and disease activity [4].

The impact of SpA on HRQoL and work productivity is a matter of great concern to society, as these patients tend to be younger than those with RA, increasing its burden on the country's working capacity. The peak incidence for axial SpA is between 20 and 30 years-old [5–7] while for RA it is between 50 and 60 years-old (higher peak in men compared to women) [8]. In both RA and AS, the main factor associated with health costs seemed to be the level of disability [9].

RA patients are at higher risk of poor physical function, compared with the general population, and this effect is more prominent in younger patients [10]. The deleterious consequences of RA on work productivity and on the various dimensions of HRQoL are also well established [11]. Poor physical function has been described as one of the major risk factors for work disability in RA [12]. Direct and indirect costs of RA and their consequences have a major impact in the society. In 2005, in the US, those costs were estimated to be 19.3 billion dollars, an amount which could be doubled if intangible costs were taken in account [9].

Therefore, improvement of patients' HRQoL represents a beneficial outcome that political and health authorities are interested to invest in. Accurate identification of determinants of worse HRQoL may guide clinical practice and the understanding of the key drivers of SpA and RA disease burden. As some of those determinants are amenable to treatment, identification of these factors may further validate the use of directed therapeutic strategies in terms of their social and economic impact.

The objective of the present study was to assess the hierarchy of outcomes contributing to HRQoL in SpA and RA.

## Methods

### Study population

The COMOrbidities in SPondyloArthritis (COMOSPA) and COMOrbidities in Rheumatoid Arthritis (COMORA) initiatives are two multi-centre cross-sectional studies resulting from an international collaboration which enrolled 7904 consecutive patients with SpA and RA in 26 countries from five different continents. Details of these databases have been described elsewhere [13,14]. In short, patients at least 18 years old, who were able to understand and complete the questionnaires, fulfilling Assessment of SpondyloArthritis International Society (ASAS) criteria for axial or peripheral SpA or the 1987 American College of Rheumatology classification criteria for RA, were included in the COMOSPA and COMORA studies, respectively. These studies were conducted according to guidelines for good clinical practice in all countries and written informed consent was obtained.

### Outcome measures

HRQoL was assessed using the EuroQOL 5-dimension 3-level (EQ-5D-3 L). According to the National Institute for Health and Care Excellence (NICE), the EQ-5D-3 L is the preferred measure of HRQoL in adults. It is a standardised and validated instrument intended for use across a wide range of disease areas and comprising 5 dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression; each one of them evaluated in 3 levels of severity (no problems, some problems, or extreme problems). The 3 L system allows the classification of 243 (corresponding to 3<sup>5</sup>) health states. Additionally, a scoring set assigns a value to each of these states on the health utility scale, where 1 is considered equal to full health and 0 a state equivalent to being dead [15].

Physical function was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) for SpA patients (range 0 to 100) and the Modified Health Assessment Questionnaire (MHAQ) for RA patients (range 0 to 3). The MHAQ has a high correlation with the HAQ, the classical gold standard to assess physical function in RA [16]. For both BASFI and MHAQ, higher scores indicate worse physical function and greater disability.

In both SpA and RA, the overall work productivity loss score from the Work Productivity and Activity Impairment questionnaire (WPAI) was used to assess overall work impairment. The WPAI measures absenteeism (absence from paid work), presenteeism (at-work productivity loss), and overall work productivity loss (combination of absenteeism and presenteeism, i.e., reduced overall productivity). The work productivity loss score has been shown to be valid and reliable [17] and its use is currently supported by Outcome Measures in Rheumatology (OMERACT) [18]. Disease activity was assessed using the Ankylosing Spondylitis Disease Activity Score C-reactive protein (ASDAS-CRP) [19] and the Disease Activity Score 28-CRP-3 variables (DAS28-CRP-3v) [20] for SpA and RA patients, respectively.

Patient's treatment was also assessed in both cohorts, including the following dichotomic variables (yes/no): NSAID intake during the last 3 months, current conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) and current biological disease-modifying anti-rheumatic drugs (bDMARD) therapy.

### Statistical analysis

SpA and RA were analysed separately. As missing data were rare, data were analysed as observed and imputation of missing data was not done. In a first exploratory step, multivariable linear regression models were used to identify associations between EQ-5D-3 L and demographic and clinical variables, namely age, gender, education (university or equivalent), body mass index (BMI), smoking status, current alcohol consumption ( $\geq 3$  units/day), overall work productivity loss, and current treatment [nonsteroidal anti-inflammatory drugs (NSAID), csDMARD and bDMARD]. Disease specific variables were also tested in these models, namely BASFI, ASDAS-CRP, HLA-B27 positivity, sacroiliitis on pelvic X-rays (i.e. radiographic sacroiliitis) and active sacroiliitis on MRI (according to the ASAS definition), for SpA patients, and positivity of rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA), presence of unequivocal radiographic erosion, DAS28-CRP-3v and MHAQ, for RA patients.

Subsequently, hierarchical multivariable analysis was conducted using the Chi-square Automatic Interaction Detector (CHAID) method, with EQ-5D-3 L as dependent variable [21]. The independent variables which were tested were the same as described above for the SpA and RA multivariable linear regression analyses. The CHAID method is a technique used to study the relationship between variables, automatically building a tree model which depicts how variables best merge to explain a defined dependent outcome. A decision tree like CHAID works by recursively partitioning the data based on input field values. The data partitions are called branches. The initial/parent branch (sometimes called the root) encompasses all data records. The parent branch is split into subsets, or child branches, based on the value of a particular input field. Each child branch can be further split into sub-branches, which can in turn be split again, and so on. At the lowest level of the tree are branches that have no more splits. Such branches are known as terminal branches (or leaves). We stipulated a minimum requirement of 20 cases to allow the creation of a parent branch and a minimum number of 10 cases to allow the creation of child branches. After setting up these criteria the results were purely analysis driven in this model. The significance values were adjusted using Bonferroni method. IBM SPSS Statistics (version 20) was used to conduct the statistical analysis.

## Results

### Study population

Data from 3984 SpA patients and 3920 RA patients were available. SpA patients were younger (mean age 43.6 vs. 56.3 years in RA) and more frequently male (65.0% vs 18.3% males in RA). In the SpA population, axial involvement was present in 85.0% of the patients and 59.7% had a history of peripheral joint disease (of which 86.2% had objective signs of synovitis confirmed by a rheumatologist on examination or by an imaging technique); the prevalence of radiographic sacroiliitis was 70.0% and active sacroiliitis on MRI (ASAS definition) was seen in 65.7% of the patients; HLA-B27 was positive in 72.4% of the patients. Regarding the RA population, the prevalence of seropositive disease was 80.7%, and unequivocal radiographic erosions were documented in 53.7% of RA patients (Table 1). Missing data were rare and are presented in Table 1.

### Multivariable analysis

In SpA, multivariable linear regression analysis showed a significant and independent association between HRQoL and BASFI (adjusted [adj]  $B = -0.006$ ; 95% confidence interval [CI] =  $-0.007$  to  $-0.005$ ), ASDAS-CRP (adjB =  $-0.052$ ; 95%CI =  $-0.071$  to  $-0.033$ ), work productivity loss

**Table 1**

Summary of clinical and demographic characteristics of the 7904 patients enrolled in the COMOSPA and COMORA studies.

Characteristics	SpA (n = 3984 patients)	n	RA (n = 3920 patients)	n
Age, years; mean (SD)	43.6 (13.9)	3932	56.3 (13.0)	3907
Male gender; n (%)	2588 (65.0)	3982	717 (18.3)	3908
University education; n (%)	1683 (42.4)	3972	941 (24.5)	3839
BMI, Kg/m <sup>2</sup> ; mean (SD)	26.1 (5.7)	3925	26.1 (5.5)	3731
Currently employed; n (%)	2325 (58.8)	3956	1225 (31.4)	3897
Current smoking; n (%)	914 (23.0)	3976	503 (13.2)	3814
Current alcohol intake ( $\geq 3$ units/day); n (%)	269 (6.8)	3966	99 (2.6)	3856
EQ-5D-3L <sup>*</sup> ; mean (SD)	0.6 (0.3)	3936	0.7 (0.3)	3864
Work productivity loss score (%)**; mean (SD)	30.5 (28.4)	2061	28.0 (27.9)	1051
NSAID intake during the last 3 months; n (%)	2678 (67.8)	3947	2002 (51.1)	3920
Current csDMARD; n (%)	1411 (35.4)	3984	3270 (83.4)	3919
Current bDMARD; n (%)	1522 (38.2)	3984	1275 (32.6)	3914
Seropositive for RF or ACPA; n (%)	NA	NA	3062 (80.7)	3793
Presence of erosions; n (%)	NA	NA	2030 (53.7)	3777
DAS28-CRP-3v score; mean (SD)	NA	NA	3.4 (1.5)	3625
MHAQ; mean (SD)	NA	NA	0.51 (0.57)	3862
BASFI; mean (SD)	30.2 (26.7)	3949	NA	NA
HLA-B27 positivity; n (%)	2217 (72.4)	3758	NA	NA
Radiographic sacroiliitis; n (%)	2539 (70.0)	3627	NA	NA
Active sacroiliitis on MRI; n (%)	1326 (65.7)	2017	NA	NA
ASDAS-CRP; mean (SD)	2.0 (1.1)	3675	NA	NA

\* EQ-5D-3 L using country value set when available or UK value set by default.

\*\* Work productivity loss score corresponding to overall work impairment, i.e. absenteeism plus presenteeism. Legend: ACPA, anti-citrullinated protein antibody; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; COMORA, COMOrbidities in Rheumatoid Arthritis; COMOSPA, COMOrbidities in SPondyloArthritis; DAS28-CRP-3v, Disease Activity Score 28-CRP- 3 variables; EQ-5D-3 L, EuroQOL-5 Dimension 3-level; MHAQ, Modified Health Assessment Questionnaire; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SpA, spondyloarthritis.

score (adjB =  $-0.002$ ; 95%CI =  $-0.003$  to  $-0.002$ ), current NSAID treatment (adjB =  $-0.052$ ; 95%CI =  $-0.083$  to  $-0.020$ ), current bDMARD treatment (adjB =  $-0.051$ ; 95%CI =  $-0.082$  to  $-0.021$ ), university education (adjB =  $-0.051$ ; 95%CI =  $-0.075$  to  $-0.027$ ) and radiographic sacroiliitis (adjB =  $0.035$ ; 95%CI =  $0.004$  to  $0.030$ ).

In RA, multivariable linear regression analysis showed a significant and independent association between HRQoL and MHAQ (adjB =  $-0.220$ ; 95%CI =  $-0.253$  to  $-0.188$ ), DAS28-CRP-3v (adjB =  $-0.027$ ; 95%CI =  $-0.036$  to  $-0.018$ ), work productivity loss score (adjB =  $-0.003$ ; 95%CI =  $-0.003$  to  $-0.002$ ), presence of radiographic erosions (adjB =  $-0.042$ ; 95%CI =  $-0.065$  to  $-0.020$ ), current alcohol consumption  $\geq 3$  units/day (adjB =  $0.012$ ; 95%CI =  $0.001$  to  $0.024$ ) and current csDMARD treatment (adjB =  $0.034$ ; 95%CI =  $0.001$  to  $0.066$ ) (Table 2).

### Decision tree model

The decision tree revealed BASFI and MHAQ as the first variables with the most discriminative power on HRQoL, in the SpA and RA models, respectively. After physical function, work productivity loss and disease activity (measured by ASDAS-CRP in SpA and by DAS28-CRP-3v in RA) were the next variables explaining HRQoL variation, followed by several other third level variables in both disease models: gender, NSAID intake during the last 3 months, current bDMARDs, university education and alcohol consumption. Other third level variables were significant for the SpA model only (age, radiographic sacroiliitis and active sacroiliitis on MRI, HLA-B27 positivity and current csDMARDs treatment) or for the RA model only (current smoking, BMI, positivity for RF or ACPA, and radiographic erosions) (Fig. 1). The stipulated minimum requirements for the creation of a parent branch and child branches (20 and 10 cases respectively) avoided the overfitting of data for SpA patients, as only 11 of the 43 child branches had less than 1% of the cases from the training population and all of them had more than 0.25% of cases from the training population. The same requirements also avoided the overfitting of data for RA patients, as only 13 of the 39 child branches had less than 1% of the cases from the training population and all of them had more than 0.25% of cases from the training population. [22,23]

## Discussion

Our study demonstrates a robust and consistent association between HRQoL, as assessed by EQ-5D-3 L, and physical function, disease activity and work productivity loss, both in populations with SpA and RA. These associations were demonstrated using two statistical approaches: multivariable linear regression analyses and hierarchical CHAID models, with the latest allowing stratification of the variables with the most discriminative power on HRQoL. Our study also suggests that there are several other disease specific factors playing an important role on HRQoL, namely current treatment and imaging abnormalities (for SpA: radiographic sacroiliitis and active sacroiliitis on MRI; for RA: the presence of erosions).

Both BASFI and MHAQ were negatively and significantly associated with HRQoL in the multivariable regression models i.e. higher BASFI/HAQ scores (worse function) were associated with lower EQ5D-3 L scores (worse HRQoL). The association between HRQoL and physical function has previously been described for both SpA [24,25] and RA patients [26,27].

We also report similar associations between HRQoL and work productivity loss and disease activity, for both conditions, i.e. increased work productivity loss and higher ASDAS/DAS28-CRP-3v scores (higher disease activity) were associated with lower EQ5D-3 L scores (HRQoL). Similar results have been previously reported, both in SpA [25,28-30] and RA patients.

The CHAID algorithm is a robust tool that allowed us to discriminate between subgroups of patients with different mean EQ-5D-3 L scores, based on a set of clinical and demographic variables. This analysis

**Table 2**

Multivariable linear regression analyses investigating the association between HRQoL (assessed by EQ-5D-3 L) and other demographic and clinical variables in patients with SpA and RA.

Characteristics	SpA Model Adjusted B* (95%CI)	p- value	RA Model Adjusted B* (95%CI)	p- value
Age	−0.001 (−0.002, 0.001)	0.319	0.000 (−0.001, 0.001)	0.521
Male gender	0.014 (−0.018, 0.045)	0.391	0.004 (−0.023, 0.030)	0.786
University education	−0.051 (−0.075, −0.027)	<0.001	0.002 (−0.013, 0.018)	0.763
BMI	−0.001 (−0.003, 0.002)	0.719	0.002 (0.000, 0.004)	0.092
Current smoking	−0.004 (−0.016, 0.007)	0.471	0.000 (−0.010, 0.011)	0.946
Current alcohol intake (≥3 units/day)	0.011 (−0.003, 0.025)	0.122	<b>0.012 (0.001, 0.024)</b>	<b>0.033</b>
Work productivity loss score**	−0.002 (−0.003, −0.002)	<0.001	−0.003 (−0.003, −0.002)	<0.001
NSAID intake (last 3 M)	−0.052 (−0.083, −0.020)	<b>0.001</b>	0.014 (−0.008, 0.036)	0.210
Current csDMARD	−0.009 (−0.040, 0.022)	0.586	<b>0.034 (0.001, 0.066)</b>	<b>0.045</b>
Current bDMARD	−0.051 (−0.082, −0.021)	<b>0.001</b>	−0.003 (−0.027, 0.021)	0.813
Seropositive for RF or ACPA	NA	NA	0.016 (−0.012, 0.043)	0.267
Presence of erosions	NA	NA	−0.042 (−0.065, −0.020)	<0.001
DAS28-CRP-3v	NA	NA	−0.027 (−0.036, −0.018)	<0.001
MHAQ	NA	NA	−0.220 (−0.253, −0.188)	<0.001
BASFI	−0.006 (−0.007, −0.005)	<0.001	NA	NA
ASDAS-CRP	−0.052 (−0.071, −0.033)	<0.001	NA	NA
HLA-B27 positive	0.002 (−0.031, 0.035)	0.911	NA	NA
Radiographic sacroiliitis	<b>0.035 (0.004, 0.066)</b>	<b>0.029</b>	NA	NA
Active sacroiliitis on MRI	−0.001 (−0.032, 0.030)	0.937	NA	NA

\* Unstandardized coefficients.

\*\* Work productivity loss score corresponding to overall work impairment, ie, absenteeism plus presenteeism. Significant associations highlighted in bold. Legend: ACPA, anti-citrullinated protein antibody; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS28-CRP-3v, Disease Activity Score 28-CRP-3 variables; EQ-5D-3 L, EuroQOL-5 Dimension 3-level; M, months; MHAQ, Modified Health Assessment Questionnaire; NA, not applicable. NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; RF, rheumatoid factor; SpA, spondyloarthritis.

allowed us to conclude that physical function measured by BASFI or MHAQ was the most important predictor of HRQoL. The relevance of physical function on QoL in RA has been previously suggested [27]. This method also determined which other variables contributed to differentiating patients' profiles regarding their level of HRQoL. After physical function, disease activity and work productivity loss were the next variables explaining EQ-5D-3 L, both for SpA and RA. A large number of third level variables were identified, some shared (gender, treatment with NSAIDs and bDMARDs, education and alcohol consumption) and other disease specific (radiographic sacroiliitis, active sacroiliitis on MRI, HLA-B27 positivity, positivity for RF or ACPA and the presence of erosions). There were also variables such as age, treatment with csDMARDs, current smoking and BMI which appeared as third level variables in just one of the disease models.

Inflammation, pain, stiffness, functional limitations, and work productivity loss characterize inflammatory joint diseases such as RA and SpA. We have shown that in RA and SpA, HRQoL is independently determined by disease activity, physical function, and work productivity loss. Strategies to preserve quality of life should therefore address these three health domains, and rheumatology healthcare teams should be proficient in their assessment as part of RA and SpA management, so that functional decrements and work productivity loss are also addressed as part of routine care (in addition to disease activity). This will translate in better HRQoL outcomes and increased patient perceived value of care.

Our study has limitations. Some potentially important determinants of HRQoL were not studied, namely psychological and societal factors such as the level of life satisfaction, the presence of healthy interpersonal relationships, feelings of self-worth and self-esteem, the person's total perceived degree of control in life and the presence of "positive or negative" personality traits [31]. In both databases, HRQoL was not assessed through other tools. Despite EQ-5D-3 L having some overlap with the functional dimension in such patients, it is an extensively validated index to assess HRQoL in rheumatic diseases and the preferred measure of health-related HRQoL in adults, according to NICE [15]. Furthermore, COMOSPA and COMORA initiatives provide a unique opportunity to analyze these diseases in parallel, as the comparable dimensions between both diseases were evaluated with similar tools.

In conclusion, physical function is a major contributor to HRQoL measured by EQ-5D in people with SpA and RA. Disease activity and work productivity loss also play critical roles in determining the level of HRQoL in these patients and are hierarchically superior to the contribution provided by other demographic and clinical variables.

## Contributors

PDC and PMM designed the study. PDC cleaned the database and performed the statistical analyses under the supervision of AM and PMM. PDC, EVS, and PMM drafted the first version of the manuscript. All those listed as authors read, commented on, and approved the final manuscript.

## Data availability statement

The data sets generated and/or analysed during the current study are not publicly available due to consent restrictions. Programming codes used for statistical analysis during the current study are available from the corresponding author upon reasonable request.

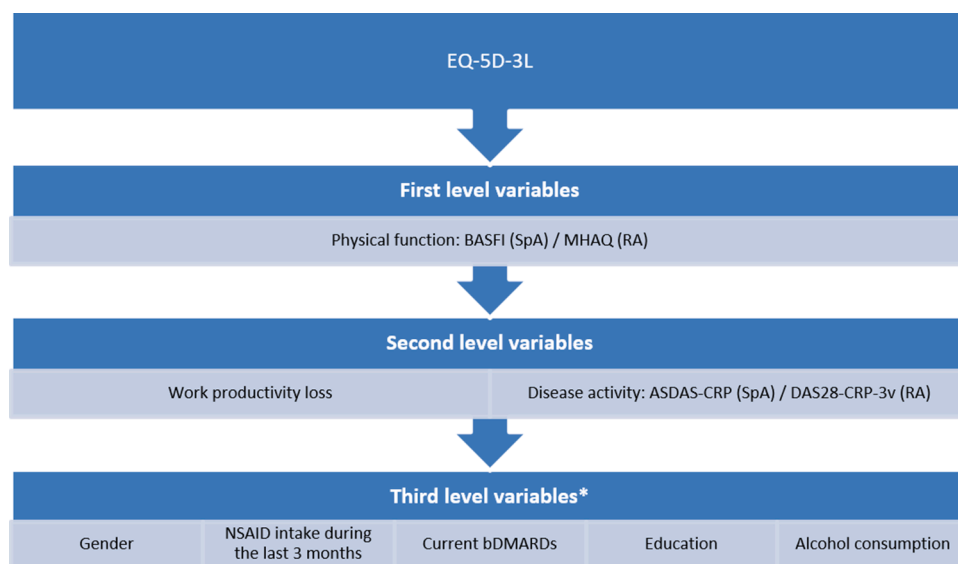
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Nothing to declare.

## Competing interests

PMM has received consulting/speaker's fees from Abbvie, BMS, Celgene, Galapagos, Janssen, MSD, Novartis, Pfizer, Roche and UCB.





**Fig. 1.** Hierarchical relationship of variables contributing to HRQoL in SpA and RA patients according to CHAID algorithm.

\*Other third level variables for SpA (age, sacroiliitis on pelvic X-Rays and on MRI, HLA-B27 positivity and current csDMARDs) and for RA (current smoking, BMI, positivity for RF or ACPA, and unequivocal radiographic erosion). Legend: ACPA, anti-citrullinated protein antibody; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS28-CRP-3v, Disease Activity Score 28-CRP-3 variables; EQ-5D-3 L, EuroQOL-5 Dimension 3-level; MHAQ, Modified Health Assessment Questionnaire; NSAID, nonsteroidal anti-inflammatory drug; HRQoL, health-related quality of life; RA, rheumatoid arthritis; RF, rheumatoid factor; SpA, spondyloarthritis.

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#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152086.

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