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Axial spondyloarthritis

Final validation of the hierarchical framework for outcomes in axial spondyloarthritis: longitudinal determinants of health-related quality of life

Augusta Ortolan [1,2,6], Désirée van der Heijde [2], Laure Gossec [3,4], Sofia Ramiro [4,5,*]

[1] *Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Department of Rheumatology, Rome, Italy*
[2] *Leiden University Medical Center, Department of Rheumatology, Leiden, The Netherlands*
[3] *INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Universite, Paris, France*
[4] *Hopital Universitaire Pitie Salpetriere, APHP, Rheumatology Department, Paris, France*
[5] *Zuyderland Medical Center, Department of Rheumatology, Heerlen, The Netherlands*
[6] *Università Cattolica del Sacro Cuore, Rome, Italy*

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ABSTRACT

Objectives: This study aims to study the framework describing the longitudinal association between disease activity and function (independent variables) and health-related quality of life (HRQoL, outcome) in axial spondyloarthritis (axSpA).

Methods: Patients with AxSpA (symptoms <3 years) from the Devenir des Spondylarthropathies Indifférenciées Récentes cohort were followed up for 10 years. The association of disease activity (ASDAS) and function (BASFI) with HRQoL (physical component summary [PCS] and mental component summary [MCS] of 36-item short-form health survey, ankylosing spondylitis quality of life [ASQoL]) was assessed. Multivariable generalised estimating equations models were built with PCS, MCS, or ASQoL as outcomes (higher PCS/MCS = better HRQoL, higher ASQoL = worse), and ASDAS and BASFI as main predictors. Standard and autoregressive (i.e., corrected for prior HRQoL) models were used. The impact of ASDAS vs BASFI on HRQoL was compared through standardised coefficients. Mediation analysis assessed whether the effect of ASDAS on HRQoL was mediated by BASFI. Confounders/effect modifiers (eg, contextual factors) were considered in all models.

Results: A total of 663 patients with axSpA (46% males, mean age 33.5 [8.6] years) were included. In standard and autoregressive multivariable models, significant associations for ASDAS and BASFI with HRQoL were found (beta coefficient [95% CI] for autoregressive models: PCS −2.93 [−3.28, −2.58]; −2.13 [−2.31, −1.96]), MCS (−2.38 [−2.91, −1.86]; −1.10 [−1.36, −0.84]), ASQoL (1.18 [1.02, 1.36]; 1.08 [0.99, 1.17]). A larger influence of BASFI, compared to ASDAS, on HRQoL was noted. Mediation analysis showed the ASDAS effect on HRQoL was mostly (~75%) mediated by BASFI, but a direct effect (~25%) also existed.

Conclusions: A validated longitudinal framework has been established for interpreting HRQoL: even correcting for contextual factors, disease activity consistently impacts HRQoL—primarily through functional impairment, but also directly. While HRQoL is an overarching outcome in axSpA, targeting low disease activity is crucial to optimise HRQoL.

*Correspondence to Dr. Sofia Ramiro, Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands.
E-mail address: sofiaramiro@gmail.com (S. Ramiro).
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WHAT IS ALREADY KNOWN ON THIS TOPIC

- Health-related quality of life (HRQoL) is a key outcome in axial spondyloarthritis (axSpA), known to depend on multiple factors, including disease activity and physical function. Previous cross-sectional studies in established radiographic axSpA suggested a hierarchical model where HRQoL is influenced by these domains.
- However, longitudinal confirmation of these relationships, especially across the full axSpA spectrum and in early disease, is still lacking. Furthermore, it is not known whether disease activity has a direct effect on HRQoL or mostly acts through alteration of physical function. Finally, the role of contextual factors has not been systematically explored.

WHAT THIS STUDY ADDS

- This study demonstrates that both disease activity and physical function are longitudinal determinants of HRQoL in patients with axSpA. It validates, over a 10-year follow-up, a hierarchical framework showing that HRQoL is influenced by disease activity both directly and indirectly through physical function.
- Additionally, functional impairment appears to exert a larger impact on HRQoL than disease activity itself. The longitudinal relationship among disease activity, function, and HRQoL, controlling for the relevant contextual factors (eg, gender, education, smoking), and extending to both radiographic and nonradiographic axSpA, is here demonstrated for the first time.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study confirms HRQoL as an overarching outcome in axSpA, depending longitudinally on various interrelated factors, with disease activity playing a key role.
- This study underscores the importance of persistently targeting low disease activity and preserving physical function throughout the disease course with the aim of optimising HRQoL.

INTRODUCTION

Health-related quality of life (HRQoL) in axial spondyloarthritis (axSpA) is a broad outcome influenced by multiple factors, including disease-related aspects, such as disease activity and physical function, as well as the patient's physical and social environment [1]. Previous studies in radiographic axSpA (r-axSpA, formerly ankylosing spondylitis) [2] have proposed a hierarchical model placing HRQoL at the top, as all other disease-related outcomes appear to contribute to it independently, to some extent (Supplementary Fig S1) [1].

This model was initially developed cross-sectionally in r-axSpA. More recently, longitudinal studies from the Devenir des Spondylarthropathies Indifférénciées Récentes (DESIR) cohort, including also nonradiographic axSpA (nr-axSpA), have confirmed several associations within this hierarchy. Specifically, a relationship over time between disease activity and spinal inflammation on one hand, and spinal mobility however, has been proven [3]. Moreover, disease activity over the axSpA course has been shown to be the main contributor of disability (i.e., loss of function), with spinal mobility becoming particularly relevant in advanced-stage disease [4]. What remains to be demonstrated is whether HRQoL truly depends on disease activity and physical function over the disease course (relationships with red lines in Supplementary Fig S1), and on their interaction with contextual factors. The importance of contextual factors has, in fact, been suggested by previous studies: maintaining low disease activity over time was associated with male sex, white-collar occupation, and higher education [5]. Cross-sectional analyses confirmed that disease activity and various non-disease-related factors contribute to HRQoL, though collectively accounting for only half of its variance [6]. Furthermore, it remains unclear whether these associations hold over time, in a longitudinal context.

In summary, the longitudinal relationship among disease activity, function, and HRQoL, across the whole spectrum of axSpA, particularly in earlier disease phases, and accounting for contextual factors, needs to be demonstrated. Thus, we set out to investigate these relationships in a representative axSpA population, including both r-axSpA and nr-axSpA.

Our primary aim was to investigate the longitudinal relationship between disease activity and physical function (independent variables) and HRQoL (dependent variable) over 10 years of follow-up. Our secondary aim was to determine which domain—disease activity or physical function—contributed more to HRQoL, and whether this contribution was direct or mediated, i.e., whether the impact of disease activity on HRQoL was direct or mediated through physical function.

METHODS

Patient population

Patients included in the DESIR cohort, diagnosed as axSpA by their treating rheumatologist, were included in the study. DESIR is an ongoing prospective observational and inception cohort involving 25 centres in France and enrolling patients with inflammatory back pain with a duration <3 years, and a high suspicion of axSpA (level of confidence ≥ 5 on a 0-10 scale), with a 10-year-long follow-up (NCT01648907) [7]. For the present study, only patients with a diagnosis of axSpA confirmed over the 10-year follow-up were considered. Patients' outcomes have been collected at baseline, every 6 months for the first 2 years, and yearly thereafter up to 10 years. The dataset used for this analysis was locked in November 2022. All patients provided signed informed consent before inclusion, and the study was approved by the French medical ethical committee.

Outcome: HRQoL

HRQoL was measured by different instruments, to verify consistency of the obtained results: the physical and mental component summary of the short form (36-item short-form health survey [SF-36]) (PCS, MCS) [8], a generic and multidimensional questionnaire, and the ankylosing spondylitis quality of life (ASQoL) questionnaire, more specific to axSpA [9]. SF-36 includes 36 questions assessing functional health and well-being, organised into 8 health domains, which contribute to PCS and MCS. Both are scored from 0 to 100, with higher scores indicating better health [10]. ASQoL is instead composed of 18 dichotomous items, with a total score ranging from 0 to 18, with higher scores indicating worse health [9].

Main independent variables: disease activity and function

The 2 main independent variables of interest, contributing to HRQoL (outcome), according to our hypothesis, were disease activity and function. Disease activity was primarily assessed by the Axial Spondyloarthritis Disease Activity Score (ASDAS),

which is the preferred measurement instrument according to the Assessment of SpondyloArthritis International Society (ASAS) core set, as it performs best in all the OMERACT filter 2.2 properties [11]. ASDAS is a weighted composite index including back pain (question #2 of the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]), peripheral pain (question #3 of the BASDAI), duration of morning stiffness (question #6 of the BASDAI), patient global assessment, and C-reactive protein (CRP). It gives a continuous score with higher values corresponding to worse disease activity, and has shown better validity and sensitivity to change than the other disease activity indices [11−13]. BASDAI and CRP were still taken into consideration as alternative measures of disease activity in a sensitivity analysis [14]. Physical function was assessed by Bath Ankylosing Spondylitis Functional Index (BASFI) [15], which ranges between 0 and 10, with higher scores indicating higher impairment in physical function.

Covariates: contextual factors

SpA features according to ASAS, personal and environmental factors, and therapy were considered as covariates (i.e., potential confounders or effect modifiers) in the relationship between ASDAS and BASFI, on one side, and HRQoL, on the other side. The following baseline covariates were used as time-fixed: sex, age (years), Human Leukocyte Antigen- B27 (HLA-B27) positivity, and positive baseline imaging (radiographic sacroiliitis according to modified New York Criteria or magnetic resonance imaging [MRI] sacroiliitis according to ASAS definition, according to central reading) [16,17]. Covariates that were collected at each follow-up point (time-varying covariates) were extra-musculoskeletal manifestations (psoriasis, inflammatory bowel disease [IBD], uveitis), peripheral manifestations (enthesitis, dactylitis, peripheral arthritis, enthesitis assessed by Maastricht Ankylosing Spondylitis Disease Activity score), body mass index (BMI, kg/m^2), smoking (current smoker vs nonsmoker), occupation (blue collar vs white collar), education (university education or equivalent yes/no), marital status (married/living together yes/no), parental status (number of children), use of nonsteroidal anti-inflammatory drugs (NSAIDs) (yes/no) or biological disease-modifying antirheumatic drugs (bDMARDs) (yes/no), comorbidities (simple comorbidity count, excluding depression due to its particular relationship with the outcome, especially MCS). Chronic comorbidities available in DESIR are lung disease, ischaemic heart disease, pericarditis, aortic insufficiency, other valvopathy, conduction system defects, cardiac insufficiency, stroke/transient ischaemic attack, cardiovascular accident, diabetes, upper gastrointestinal disease (ulcer, perforation, haemorrhage), and solid and lymphoproliferative neoplasm. To each of these comorbidities, a score of 1 was given if present (0-15).

Statistical analysis

The longitudinal association between disease activity, function, and HRQoL

Associations between the independent variables (ASDAS and BASFI) and the HRQoL outcomes over time were tested using generalised estimating equations (GEE) models: GEE is a technique suitable for modelling longitudinal data, as it makes use of all time points with information available, being relatively robust for missing data, and taking into account the intrasubject correlation across the various time points. The results are expressed in terms of the beta coefficient (which is an expression of the 'average' change in the units of outcome for a 1-unit increase of the independent variable) with its 95% CI. Among the GEE assumptions, it is required to specify a working correlation structure: in our case, the exchangeable correlation structure was selected, as it seemed to best fit the correlation structure between the outcomes at the various time points. First, univariable associations were investigated between ASDAS or BASFI as main independent variables and PCS, MCS, or ASQoL as outcome, each in a separate model. Since disease activity is known to influence function [18], we assessed whether there was an effect modification of the effect of BASFI on HRQoL by different levels of disease activity (ASDAS≥2.1 vs ASDAS < 2.1). Effect modification was considered to be potentially relevant if the interaction term was associated with the outcome with a $P <$ .15, in which case analyses would be stratified into different levels of the potential effect modifier, and clinical significance was judged, according to the different magnitude or direction of beta coefficients in the strata. In a further step, ASDAS and BASFI were considered together as main independent variables (so that each was adjusted for the other) in bivariable GEE models having PCS, MCS, or ASQoL as outcomes. Based on the literature and our hypotheses, the following covariates were tested as potential effect modifiers of the relationship between ASDAS or BASFI, on the one hand, and HRQoL, however: sex, HLA-B27, imaging at baseline (sacroiliitis modified New York, sacroiliitis MRI), occupation (blue collar vs white collar), smoking, NSAID-use, bDMARD-use, and comorbidity count [19−22].

The remaining contextual factors (age, psoriasis, IBD, uveitis, enthesitis, dactylitis, peripheral arthritis, BMI, smoking, education, marital status, parental status), as well as those shown not to be an effect modifier of the main relationships of interest, were tested as potential confounders. Confounders were considered to be relevant if the addition of the variable to the model led to a significant modification of the association between either ASDAS or BASFI and one of the HRQoL outcomes (variation of >10% of the coefficient). Furthermore, the univariable association between each of the covariates and each of the HRQoL outcomes was tested. These variables were included in the subsequent multivariable models if they were associated with the outcome with a P value <.1. Collinearity between covariates, as well as the opportunity to combine more variables into one (e.g., choosing between the variable grouping extramusculoskeletal manifestations or the single variables psoriasis, IBD, uveitis), were taken into consideration in the final covariate selection.

Multivariable models for the longitudinal relationship between disease activity, function, and HRQoL

Thereafter, three separate 'standard' GEE multivariable models were built, having PCS, MCS, or ASQoL as outcomes, ASDAS and BASFI as main independent variables, and all the covariates that had been found to be confounders, or significantly associated to the outcome in the univariable analysis, or that were considered to be important from a clinical point of view (sex, symptom duration, use of NSAIDS and bDMARDs were included *a priori*) [23−25]. To better identify the longitudinal effects, and to get more insight into the true longitudinal relationship between disease activity, function, and HRQoL, three 'autoregressive' GEE multivariable models GEE models were run: this means the models were adjusted for the outcome (ie, PCS, MCS, or ASQoL) at the previous time point (1 year earlier). For this analysis, visits at 6 and 18 months were dropped to ensure an equal lag between all timepoints. By comparing the autoregressive models with the standard models, we aimed to understand whether the associations were really present over

time, and not only cross-sectionally. Standard and autoregressive GEE multivariable models were also repeated with BASDAI and CRP instead of ASDAS as a sensitivity analysis.

Hypothesis about the magnitude and temporal structure of the influence of disease activity and function on HRQoL

To assess whether disease activity or function had a larger impact on HRQoL, we repeated the autoregressive GEE models using standardised coefficients, enabling comparison of effect sizes across variables with different scales. The computation applied to standardise each value of the independent variables of the models was standardised variable = (variable value − mean value)/SD. The obtained standardised variables were then used in the autoregressive models, thus obtaining standardised coefficients.

To explore whether disease activity influenced HRQoL through function or also independently, we conducted a mediation analysis. We hypothesised that ASDAS at a given time point affects BASFI (a), which in turn predicts HRQoL one year later (b), with a direct effect from ASDAS to HRQoL (c') also included for partial mediation (Fig 1A). The analysis used structural equation modelling, estimating both direct and indirect effects with maximum likelihood and 1000 bootstrap replications for robust SEs and 95% CIs. The indirect effect (a × b) was assessed via percentile-based bootstrap CI, preferred due to the non-normal distribution of indirect effects. The total effect (c) was the sum of direct (c') and indirect (a × b) effects (Fig 1A).

As a sensitivity analysis, we tested an alternative model where ASDAS at a given time point influenced BASFI 1 year later, which then predicted HRQoL at that same time.

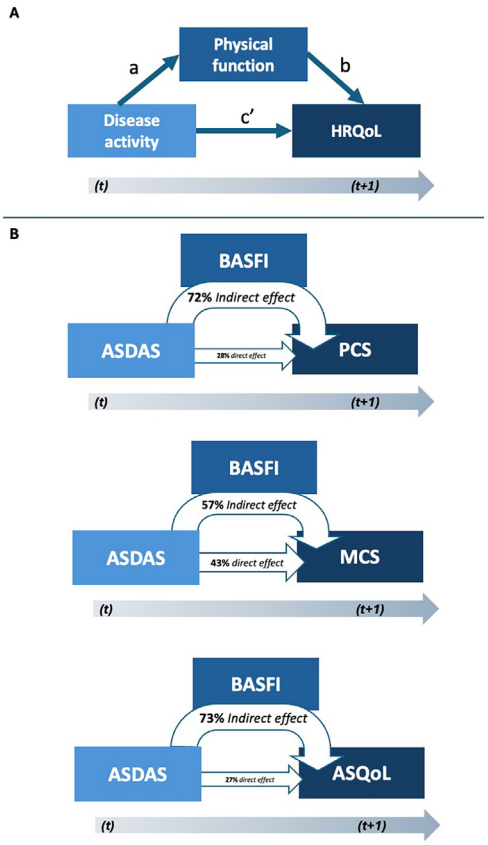

Figure 1. (A) Mediation hypothesis, general structure: the total effect (c) of disease activity (ASDAS) on HRQoL is the sum of a direct (c') and an indirect (a × b) effect, the latter mediated by BASFI. The timeline at the bottom of the figure indicates that a longitudinal relationship between BASDAI at a certain timepoint (t) and HRQoL at a following timepoint (t + 1) is assumed. (B) Mediation analysis, with actual estimation of direct and indirect effects. ASDAS, Axial Spondyloarthritis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; HRQoL, health-related quality of life; MCS, mental component summary; PCS, physical component summary.

RESULTS

A total of 663 patients with axSpA were analysed, of whom 306 (46%) were males, 392 (59%) were HLA-B27 positive, and 141 (22%) were classified as r-axSpA at baseline. At inclusion in the cohort, mean (SD) age was 33.5 (8.6) years, and mean symptom duration was 1.5 (0.9) years (Table 1). Mean values of PCS, MCS, and ASQoL at baseline were 39.3 (9.5), 40.3 (11.2), and 9.3 (4.9), respectively, and had very little variation over time except a slight amelioration in HRQoL (increase in PCS/MCS and decrease in ASQoL) from baseline to 6 months (Supplementary Table S1).

Table 1
Baseline characteristics of the population

Variables	N = 663
Male sex	306 (46%)
Age (y)	33.5 (8.6)
Symptom duration (y)	1.5 (0.9)
HLA-B27 positive	392 (59%)
University education or equivalent	390 (59%)
Married/living maritally	413 (62%)
Parental status (n of children)	
No children	283 (44%)
One child	126 (19%)
Two or more children	254 (35%)
Employed	570 (86%)
Blue-collar job	98 (17%)
Active smoking	257 (37%)
Psoriasis (ever)	115 (17%)
IBD (ever)	35 (5%)
Uveitis (ever)	64 (10%)
Dactylitis (ever)	96 (14%)
Radiographic sacroiliitis (mNY)	141 (22%)
MRI sacroiliitis (ASAS definition)	233 (37%)
ASDAS	2.6 (0.9)
BASDAI (0-10)	4.4 (2.0)
BASFI (0-10)	3.0 (2.3)
MASES (0-13)	4.3 (5.9)
Swollen joint count (0-28)	0.2 (0.8)
Tender joint count (0-53)	4.2 (8.3)
Body mass index (kg/m^2)	23.9 (4.1)
NSAIDs use	614 (92%)
csDMARDs use	93 (13%)
bDMARDs use	0 (0%)
Comorbidity count (0-15)	
No comorbidities	336 (48%)
One comorbidity	311 (44%)
Two or more comorbidities	49 (8%)

ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Axial Spondyloarthritis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HLA-B27, human leukocyte antigen B27; IBD, inflammatory bowel disease; MASES, Maastricht Ankylosing Spondylitis Disease Activity Score; MRI, magnetic resonance imaging; mNY, modified New York; NSAIDs, nonsteroidal anti-inflammatory drugs.

In the univariable analysis, ASDAS and BASFI were individually, strongly and significantly associated to PCS (beta −5.61 [95% CI: −5.80, −5.41] and −3.20 [−3.29, −3.11]), MCS (beta −3.99 [95% CI: −4.26, −3.71] and −2.06 [−2.20 −1.91], respectively), and ASQoL (beta 2.65 [2.55, 2.74] and 1.58 [1.53, 1.63]), with higher disease activity and higher functional disability associating to worse HRQoL scores. The interaction between disease activity and function was statistically significant, but when analysing function by disease activity strata, the effect of BASFI on the HRQoL outcomes was not substantially different between the strata, keeping effect sizes pointing in the same direction. Therefore, the interaction was not considered to be clinically relevant (Supplementary Table S2), so the models were not further stratified according to disease activity. In bivariable models, the association of ASDAS and BASFI, together as main independent variables, to PCS (−3.07 [95% CI: −3.32, −2.83] and −2.24 [−2.37, −2.11], respectively), MCS (beta −2.43 [95% CI: −2.84, −2.04] and 1.23 [−1.43, −1.03]), and ASQoL (1.35 [95% CI: 1.23, 1.48] and 1.16 [1.09, 1.22]) was confirmed.

When potential effect modifiers of the relationship between disease activity or function and HRQoL were considered, none of the contextual factors qualified as a clinically significant effect modifier. In other words, even when the interaction term had a $P < .15$, the beta coefficients for ASDAS or BASDAI in different strata of the covariate were not different enough to require separate models. Also, none of the remaining contextual factors qualified as confounders. Nonetheless, the univariable analysis between each contextual factor and the outcome was studied to select potentially relevant covariates to include in the multivariable models (Table 2).

Then, three different multivariable models having PCS, MCS, and AsQOL as outcome, and ASDAS and BASFI as main independent variables (across all models), along with the relevant covariates of Table 2 were then built, confirming the independent association between higher disease activity and higher functional impairment, on the one hand, and worse HRQoL however in the standard GEE model (Table 3).

For the autoregressive models, the univariable associations between each of the covariates and HRQoL were tested again, but this time correcting the models for the outcome at the previous time point (Supplementary Table S3). Then, the autoregressive multivariable models were built. The results of the models confirmed that indeed a higher disease activity and a worse function are major determinants for HRQoL outcomes, even when taking into consideration the strongest determinant of an outcome, which is the outcome in the previous time points, as well as taking other important covariates into account (Fig 2).

Results of the above models (standard and autoregressive models) were confirmed using BASDAI and CRP instead of ASDAS (Supplementary Tables S4 and S5). However, it has to be underlined that only BASDAI—and not CRP—was associated with PCS, MCS, and ASQoL. BASFI remained independently and strongly associated with all three HRQoL outcomes.

Moreover, when standardised variables were used in the autoregressive multivariable models, it was noted that standardised coefficients were consistently higher for BASFI than ASDAS, even though this was more evident for PCS and ASQoL rather than MCS (Table 4).

The results of the mediation analysis (Table 5) showed that, when PCS was considered as the key outcome, the total effect (direct and indirect) of ASDAS on PCS was −4.31, of which −1.22 being direct effect, and −3.09 indirect effect. Thus, the proportion of indirect (or mediated) effect was −3.09/−4.31, meaning that 72% of the effect of ASDAS on PCS was mediated by BASFI (Fig 1B). When MCS was considered as outcome, the

Table 2
Univariable associations with HRQoL outcomes

	PCS		MCS		ASQOL	
	Beta (95% CI)	*P* value	Beta (95% CI)	*P* value	Beta (95% CI)	*P* value
Male sex	4.17 (3.00, 5.35)	<.0001	2.55 (1.28, 3.82)	<.0001	−2.57 (−3.25, −1.90)	<.0001
Age (y)	−001 (−0.006, 0.003)	.67	−0.001 (−0.006, 0.005)	.80	0.0007 (−0.001, 0.003)	.54
HLA-B27 positive	3.61 (2.38, 4.83)	<.0001	2.59 (1.29, 3.88)	<.0001	−1.84 (−2.54, −1.13)	<.0001
Radiographic sacroiliitis (mNY)	1.70 (0.19, 3.20)	.027	0.59 (−0.97, 2.16)	.46	−0.59 (−1.46, 0.28)	.18
MRI sacroiliitis (ASAS definition)	2.31 (1.01, 3.61)	.001	1.15 (−0.20, 2.50)	.09	−1.15 (−1.90, −0.41)	.002
Psoriasis	0.84 (−0.04, 1.63)	.039	0.99 (0.04, 1.93)	.04	−0.99 (−1.40, −0.59)	<.001
IBD	−0.49 (−1.72, 0.75)	.44	−0.94 (−2.40, 0.53)	.21	−0.21 (−0.83, 0.41)	.51
Uveitis	−0.44 (−1.44, 0.56)	.39	1.69 (−0.51, 2.88)	.005	−0.58 (−1.08, −0.07)	.026
EMMs	0.11 (−0.55, 0.77)	.75	0.79 (−0.005, 1.59)	.048	−0.79 (−1.12, 0.45)	<.0001
MASES (0-13)	−0.09 (−0.12, −0.06)	<.0001	−0.06 (−0.09, −0.02)	.003	0.05 (0.03, 0.06)	<.0001
SJC (0-28)	−0.65 (−0.89, −0.40)	<.0001	−0.49 (−0.80, −0.19)	.002	0.25 (0.13, 0.36)	<.0001
Dactylitis	0.29 (−0.56, 1.15)	.50	1.38 (0.36, 2.40)	.008	−0.45 (−0.89, −0.01)	.045
Peripheral manifestations	−0.37 (−1.22, 0.48)	.39	−0.04 (−0.11, 0.10)	.92	−0.19 (−0.56, 0.17)	.30
BMI (kg/m^2)	−0.14 (−0.23, −0.05)	.002	−0.003 (−0.08, 0.14)	.95	0.02 (−0.02, 0.07)	.37
University education	3.84 (2.61, 5.07)	<.0001	3.57 (2.29, 4.86)	<.0001	−2.50 (−3.20, −1.81)	<.0001
Married/living maritally	−0.10 (−0.69, 0.50)	.75	0.53 (−0.19, 1.25)	.15	−0.001 (−0.30, 0.29)	.99
Parental status (n of children)	−0.04 (−0.36, 0.29)	.82	−0.12 (−0.50, 0.25)	.53	−0.13 (−0.30, 0.03)	.12
Blue-collar job	0.51 (−0.37, 1.37)	.25	−0.29 (−1.32, 0.73)	.57	0.04 (−0.39, 0.47)	.86
Active smoking	−0.55 (−1.13, 0.03)	.06	−1.45 (−2.16, −0.78)	<.0001	0.55 (0.26, 0.84)	<.0001
NSAIDs	−3.19 (−3.67, −2.72)	<.0001	−1.96 (−2.56, −1.37)	<.0001	1.72 (1.49, 1.95)	<.0001
bDMARDs	1.47 (0.92, 2.05)	<.0001	1.36 (0.67. 2.05)	<.0001	−1.24 (−1.52, −0.96)	<.0001
Comorbidity count (0-15)	−0.43 (−0.79, −0.08)	.016	0.28 (−0.15, 0.72)	.20	0.07 (−0.11, 0.25)	.44

ASAS, Assessment of SpondyloArthritis International Society; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; EMMs, extra musculoskeletal manifestations; HLA, human leukocyte antigen; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; MASES, Maastricht Ankylosing Spondylitis Disease Activity Score; MCS, mental component summary; mNY, modified New York; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; PCS, physical component summary; SJC, swollen joint count.

Table 3
'Standard' GEE multivariable models highlighting the associations between the main independent variables (disease activity and function) and the outcome (HRQoL) over time

	PCS N = 603 Beta (95% CI)	MCS N = 614 Beta (95% CI)	ASQOL N = 613 Beta (95% CI)
ASDAS	−3.01 (−3.27, −2.74)[a]	−2.74 (−3.16, −2.33)[a]	1.38 (1.25, 1.51)[a]
BASFI	−2.25 (−2.38, −2.12)[a]	−1.08 (−1.28, −0.87)[a]	1.10 (1.03, 1.16)[a]
Male sex	1.12 (0.40, 1.84)[a]	1.03 (−0.13, 2.21)	−1.23 (−1.65, −0.81)[a]
Age (y)	0.02 (−0.01, 0.05)	0.01 (−0.04, 0.06)	−0.02 (−0.04, −0.01)[a]
HLA-B27	0.67 (−0.07, 1.41)	0.78 (−0.41, 1.97)	−0.38 (−0.81, 0.05)
Radiographic sacroiliitis (mNY)	0.51 (−0.41, 1.44)	N/A	N/A
MRI sacroiliitis (ASAS definition)	0.74 (−0.04, 1.52)	0.59 (−0.60, 1.77)	−0.48 (−0.91, −0.05)[a]
Psoriasis	0.07 (−0.53, 0.68)	0.56 (−0.40, 1.53)	−0.22 (−0.54, 0.10)
IBD	N/A	N/A	N/A
Uveitis	N/A	0.85 (−0.38, 2.09)	−0.08 (−0.49, 0.33)
EMM	N/A	N/A	N/A
MASES (0-13)	−0.01 (−0.03, 0.01)	−0.01 (−0.03, 0.04)	0.01 (−0.002, 0.02)
SJC (0-28)	−0.01 (−0.23, 0.26)	−0.13 (−0.53, 0.26)	0.08 (−0.19, 0.03)
Dactylitis	N/A	0.10 (−0.97, 1.18)	0.18 (−0.18, 0.54)
Peripheral manifestations	N/A	N/A	N/A
BMI	0.08 (0.01, 0.15)[a]	N/A	N/A
University education	0.21 (−0.51, 0.95)	0.67 (−0.50, 1.85)	−0.62 (−1.04, −0.20)[a]
Married/living maritally	N/A	N/A	N/A
Parental status (n of children)	N/A	N/A	N/A
Blue-collar job	N/A	N/A	N/A
Active smoking	0.43 (−0.04, 0.91)	−1.04 (−1.79, −0.29)[a]	0.18 (−0.05, 0.43)
NSAIDs	−1.10 (−1.51, −0.70)[a]	−0.38 (−1.02, 0.26)	0.60 (0.40, 0.80)[a]
bDMARDs	−1.40 (−1.86, −0.95)[a]	−0.47 (−1.20, 0.25)	0.25 (0.02, 0.49)[a]
Comorbidity count (0-15)	−0.38 (−0.67, −0.09)[a]	N/A	N/A

ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Axial Spondyloarthritis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; EMMs, extramusculoskeletal manifestations; GEE, generalised estimating equation; HRQoL, health-related quality of life; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; MASES, Maastricht Ankylosing Spondylitis Disease Activity Score; MCS, mental component summary; mNY, modified New York; MRI, magnetic resonance imaging; N/A, not included in the final multivariable model due to collinearity with other variables, or because $P > .1$ at univariable analysis; NSAIDs, nonsteroidal anti-inflammatory drugs; PCS, physical component summary; SJC, swollen joint count.
[a] Indicates significant results ($P < .05$).

total effect was −3.64, with −1.55 of direct effect and −2.09 indirect effect, meaning 57% of the ASDAS effect on MCS was mediated by BASFI (Fig 1B). When ASQoL was considered as outcome, the total effect was 2.17 (0.59 direct and 1.58 indirect effect), meaning that 73% of the ASDAS effect on ASQoL was mediated by BASFI (Fig 1B). The mediation analysis carried out with the second hypothesis (ASDAS influencing BASFI one year later, in turn influencing HRQoL at that same time point) showed very similar results (Supplementary Table S6 and Supplementary Fig S2).

Following all these analyses, and taking into account the previously presented parts of the framework showing a longitudinal relationship, we were able to complete the longitudinal validation of the hierarchical model for outcomes in axSpA, where HRQoL is the overarching outcome, and finalise it (Fig 3).

DISCUSSION

This work provided a final explanatory framework to describe the longitudinal relationship between disease activity and function, on the one hand, and HRQoL, on the other hand, correcting for the main contextual factors. Our results allow us to interpret HRQoL as an overarching outcome in axSpA: in other words, an outcome that can be seen as a consequence of other aspects of the disease. We confirmed the existence of a relationship between the outcomes of interest, not only at a cross-sectional level in r-axSpA [1], but also over time, and including nr-axSpA as well, therefore, in the whole spectrum of axSpA. We also went further by providing a relative 'weight' of the effect that disease activity and function, respectively, exert on HRQoL, and by analysing the mediation path that links disease activity and HRQoL through functional impairment. Because disease activity and function are closely linked, both were modelled as independent variables, allowing mutual adjustment and testing of mediation pathways to clarify their distinct effects on HRQoL. Therefore, we were able to demonstrate that targeting low disease activity is crucial to optimise HRQoL and hereby provide a full explanatory model of outcomes in axSpA (Fig 3).

The longitudinal association between disease activity, function, and HRQoL might seem intuitive, but it is not to be taken for granted, as many factors can influence HRQoL [6]; thus, the importance of disease activity in determining HRQoL could be questioned. Instead, we were able to complete the validation of the model originally proposed at a cross-sectional level by Machado et al. [1], and complement previous studies which had already elucidated other longitudinal relationships in the model [3,26].

The issue of what explains HRQoL is not an easy one to tackle, as it has been shown, as mentioned, that several nondisease related characteristics—such as age, smoking, socioeconomic background, and education—can influence HRQoL [21,22,27,28]. While smoking is a potentially modifiable factor,

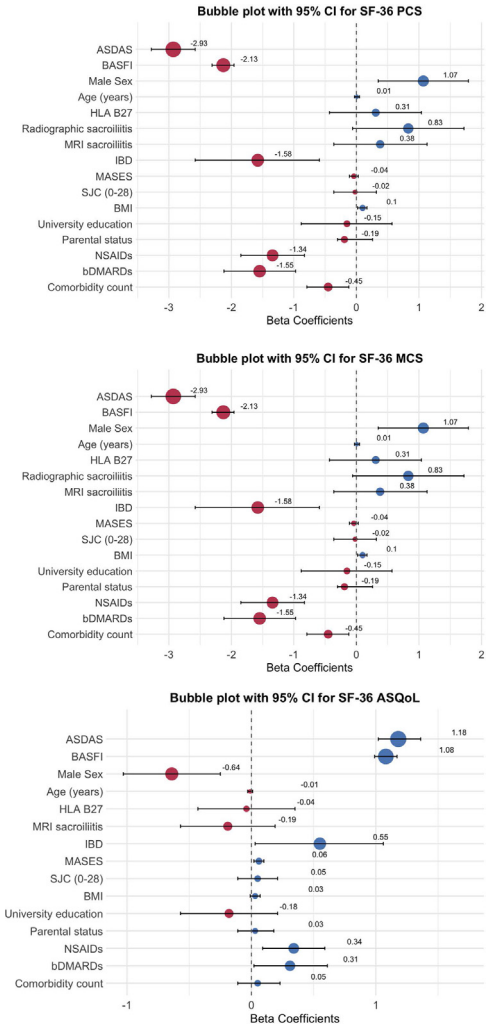

Figure 2. Longitudinal relationship between disease activity (ASDAS) and function (BASFI), on the one hand, and HRQoL outcomes (MCS, PCS, and ASQoL) on the other hand. Estimates reflect regression coefficients from autoregressive multivariable GEE models. Blue dots indicate positive regression coefficients, while red dots indicate negative regression coefficients. Independent variables ordered for comparison across models as main independent variables (ASDAS and BASFI), demographics, entry criteria of ASAS criteria, SpA features significant at univariable analysis, socioeconomic variables, therapy, comorbidity count. ASDAS, Axial Spondyloarthritis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; GEE, generalised estimating equation; HLA, human leukocyte antigen; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; MCS, mental component summary; MRI, magnetic resonance imaging; MASES, Maastricht Ankylosing Spondylitis Disease Activity Score; NSAIDs, nonsteroidal anti-inflammatory drugs; PCS, physical component summary; SF-36, 36-item short-form health survey; SJC, swollen joint count; SpA, spondyloarthritis.

the other factors are largely nonmodifiable or only minimally. This might lead to the perception that HRQoL is also scarcely modifiable, therefore potentially less of a priority for a therapeutic intervention. Our study considered disease-related and non-disease-related factors, both modifiable and non-modifiable, and came to the result that HRQoL is very largely and consistently influenced by disease activity and function in patients with axSpA, even when taking into account important confounders.

While acknowledging and confirming the role of non-disease-related factors such as sex, education, or comorbidities, our study highlighted how BASFI and ASDAS significantly impacted the physical and mental aspects of HRQoL. The fact that this relationship stands in a longitudinal way means that not only the current disease activity and function influence HRQoL [23,27–29], but that the entire course of the disease determines HRQoL over time. Translated into practice, this means we should not only aim at achieving remission or low disease activity at the beginning of the disease, but persistently over the axSpA course.

It is true, however, that most of the HRQoL improvement is achieved in the DESIR cohort over the first 6 months, with little variation over the following years [30]. It has also been previously reported that HRQoL seems to follow, over time, 2 types of trajectories: either the 'good HRQoL', with values of HRQoL close to the population norms, or the 'altered HRQoL', where, despite the initial improvement, HRQoL values seem to stay within the worst range [30]. It has been hypothesised that coping and personality traits (not collected in DESIR) might be at least partially responsible for the stable trajectory of HRQoL over time [30], especially considering that coping strategies have indeed been observed to be remarkably stable [31]. Rather than discourage intervention at later stages, though, this observation should prompt an investigation into how to better address HRQoL in the whole course of the disease of axSpA, to achieve the goal set from the 2022 ASAS-EULAR recommendations for axSpA management, which is maximising HRQoL [32]. It is reassuring to note how, compared to other causes of chronic back pain, patients with axSpA have, in fact, a higher likelihood of HRQoL improvement, once they are treated [33].

A further result of our study is that, between disease activity and function, the second seemed to have a higher impact on HRQoL: when standardised coefficients were compared, these were steadily higher for BASFI than for ASDAS. This was, however, less evident in the models with MCS as outcome, compared with models with PCS or ASQoL as outcomes, hinting at a more important association of functional ability with the physical aspects of HRQoL, rather than with the mental component. This outcome was—to some extent—expected, due to the fact that the definition of HRQoL refers to limitations and impairments that patients experience due to their disease [34,35]. Accordingly, in the mediation analysis, the majority of ASDAS's effect on HRQoL was mediated through BASFI. However, this does not necessarily imply that targeting function should take precedence over targeting disease activity. Physical function is largely influenced by disease activity, and functional impairment often results from previous periods of uncontrolled inflammation [36]. These considerations, together with the observation that ASDAS still exerts a meaningful direct effect on HRQoL, accounting for approximately one-quarter of the total effect (an even larger proportion in the case of MCS), suggest that effectively and persistently targeting disease activity remains the best strategy to prevent functional decline and to optimise HRQoL. Once substantial functional impairment has occurred, the potential for recovery is limited, which may contribute to the relative stability of HRQoL trajectories observed over time. Alongside disease activity, addressing functional aspects (eg, utilising specific measures such as physiotherapy) and psychological aspects can be very useful as a complementary measure [37].

It is worth underlining that the association between disease activity, function, and HRQoL was demonstrated to be robust by our results: it held consistently, with different HRQoL outcomes, over the entire axSpA spectrum, and it was confirmed by a sensitivity analysis with a different disease activity measure, BASDAI. This ensures the validity and the correct interpretation of our

Table 4
Autoregressive GEE multivariable models highlighting the associations between the main independent variables (disease activity and function) and the outcome (HRQoL) over time, with standardised beta coefficients

	PCS N = 509	MCS N = 551	ASQOL N = 510
	St. Beta (95%CI)	St. Beta (95%CI)	St.Beta (95%CI)
ASDAS	−2.81 (−3.15, −2.48)[a]	−2.29 (−2.80, −1.79)[a]	1.14 (0.98, 1.31)[a]
BASFI	−4.62 (−5.00, −4.24)[a]	−2.39 (−2.96, −1.82)[a]	2.34 (2.15, 2.53)[a]
Male sex	0.53 (0.17, 0.89)[a]	−0.18 (−0.70, 0.35)	−0.32 (−0.51, −0.13)[a]
Age	0.42 (−1.19, 2.02)	−0.73 (−3.08, 1.63)	−0.41 (−1.23, 0.43)
HLA B27	0.15 (−0.21, 0.51)	0.22 (−0.30, 0.74)	−0.02 (−0.21, 0.17)
Radiographic sacroiliitis (mNY)	0.34 (−0.03, 0.71)	N/A	N/A
MRI sacroiliitis (ASAS definition)	0.18 (−0.18, 0.55)	N/A	−0.09 (−0.27, 0.09)
Psoriasis	N/A	N/A	N/A
IBD	0.44 (−0.72, −0.16)[a]	−0,27 (−0.69, 0.15)	0.15 (0.01, 0.30)[a]
Uveitis	N/A	N/A	N/A
EMM	N/A	N/A	N/A
MASES (0-13)	−0.12 (−0.36, 0.12)	−0.15 (−0.50, 0.21)	0.20 (0.09, 0.32)[a]
SJC (0-28)	−0.01 (−0.26, 0.23)	N/A	0.03 (−0.08, 0.15)
Dactylitis	N/A	N/A	N/A
Peripheral manifestations	N/A	N/A	N/A
BMI	0.42 (0.09, 0.75)[a]	0.25 (−0.23, 0.73)	−0.12 (−0.29, 0.05)
University education	−0.07 (−0.45, 0.28)	−0.12 (−0.64, 0.40)	−0.09 (−0.28, 0.10)
Married/living maritally	N/A	0.71 (0.29, 1.14)[a]	
Parental status (n of children)	−0.02 (−0.37, 0.32)	−0.28 (−0.82, 0.27)	0,04 (−0.14, 0.22)
Blue-collar job	N/A	N/A	N/A
Active smoking	0.27 (0.01, 0.53)[a]	−0,30 (−0.69, 0.10)	N/A
NSAIDs	−0.60 (−0.83, −0.12)[a]	0,05 (−0.29, 0.39)	0.15 (0.04, 0.27)[a]
bDMARDs	−0.74 (−1.02, −0.46)[a]	−0,44 (−0.85, −0.04)[a]	0.15 (0.01, 0.29)[a]
Comorbidity count (0-15)	−0.48 (−0.83, −0.12)[a]	N/A	0.05 (−0.12, 0.23)

ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Axial Spondyloarthritis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; EMMs, extra musculoskeletal manifestations; GEE, generalised estimating equation; HRQoL, health-related quality of life; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; MASES, Maastricht Ankylosing Spondylitis Disease Activity Score; MCS, mental component summary; mNY, modified New York; MRI, magnetic resonance imaging; N/A, not included in the final multivariable model due to collinearity with other variables, or because $P > .1$ at univariable analysis; NSAIDs, nonsteroidal anti-inflammatory drugs; PCS, physical component summary; SJC, swollen joint count.
[a] Indicates significant results ($P < .05$).

Table 5
Mediation analysis considering a direct and indirect (mediated by function, BASFI) effect of disease activity (ASDAS) on HRQoL

Analysed paths	Coefficients	95% CI
Models with PCS as outcome[a]		
ASDAS → BASFI	1.49	(1.43, 1.56)
BASFI → PCS	−2.07	(−2.26, −1.87)
ASDAS → PCS (direct effect)	−1.22	(−1.65, −0.80)
ASDAS → BASFI → PCS (indirect)	−3.09	(−3.38, −2.80)
Models with MCS as outcome[b]		
ASDAS → BASFI	1.58	(1.52, 1.64)
BASFI → MCS	−1.32	(−1.57, −1.07)
ASDAS → MCS (direct effect)	−1.55	(−2.11, −1.00)
ASDAS → BASFI → MCS (indirect effect)	−2.09	(−2.50, −1.71)
Models with ASQoL as outcome[c]		
ASDAS → BASFI	1.38	(1.31, 1.46)
BASFI → ASQoL	1.14	(1.03, 1.25)
ASDAS → ASQoL (direct effect)	0.59	(0.36, 0.82)
ASDAS → BASFI → ASQoL (indirect effect)	1.58	(1.41, 1.75)

ASDAS, Axial Spondyloarthritis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; MASES, Maastricht Ankylosing Spondylitis Disease Activity Score; MCS, mental component summary; NSAIDs, nonsteroidal anti-inflammatory drugs; PCS, physical component summary.
Models (all analysed paths) adjusted for significant covariates in the multivariable autoregressive model.
[a] Adjusted for sex, IBD, BMI, NSAID use, bDMARDs use, and comorbidity count.
[b] Adjusted for marital/social status and bDMARDs use.
[c] Adjusted for sex, IBD, MASES, NSAIDs use, and bDMARDs use.

findings. Notably, in the model where BASDAI and CRP replaced the ASDAS, CRP was not associated with HRQoL, but this should not be a reason for concern, nor be interpreted as a contrasting result. In fact, in the DESIR cohort (much like in axSpA in general), less than 30% of the subjects had an elevated CRP at baseline, and it is very well-known how CRP, albeit prognostically very relevant, is infrequently abnormal [38].

Limitations of our study include, first, the fact that DESIR is an observational cohort, having therefore missing data (up to 30% of baseline patients had missing data over 10 years, as expected in long-term follow-ups). However, we used GEE as a method of analysis because it can handle missing data, as its estimates are relatively robust [39]. Second, we could not analyse the impact of variables that are unavailable in DESIR, such as fibromyalgia/widespread pain, or socioeconomic deprivation, and that can influence HRQoL [27,28,40]. Using surrogates such as MCS ≤ 38/50 for depression [41] or a score ≥8 on 3 out of the first 5 BASDAI questions for fibromyalgia [42] was not feasible in our case due to the risk of circular reasoning: the same variables would have been used as both independent and outcome variables in the case of depression and MCS, or duplicated as independent variables in the case of extreme BASDAI values and fibromyalgia. Nevertheless, since the association between disease activity, function, and HRQoL was quite consistent, it is unlikely that the addition of these factors would fundamentally alter the framework. However, we acknowledge that these aspects are clinically relevant and could modulate the

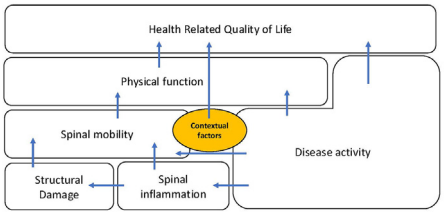

Figure 3. Hierarchical relationship between disease outcomes in axSpA (modified from Machado et al. Ann Rheum Dis 2011). Each domain is presented as a separate box. The final model includes HRQoL as an overarching outcome, depending longitudinally on disease activity and function (which, in turn, are also influenced by other outcomes). All confirmed associations are represented as solid arrows (both confirmed by previous studies and the present study). Contextual factors are positioned centrally, reflecting their potential role as confounders or effect modifiers across all these associations. AxSpA, axial spondyloarthritis; HRQoL, health-related quality of life.

magnitude of associations within the model. Third, a conceptual limitation is the use of patient reported outcomes (PROs) to define physical function and HRQoL: because it is well-known that PROs tend to correlate, the association could have a different magnitude if more 'objective' measurement instruments were used [43]. This is, however, purely hypothetical, as we used measurement instruments indicated as core outcomes in axSpA [44]. Strengths of the present study are the use of different outcome measures to corroborate the robustness of findings, the long follow-up time, and the considerable sample size.

In conclusion, our study establishes a validated framework clarifying how disease activity and function drive HRQoL in axSpA. HRQoL can thus be regarded as an overarching outcome, and achieving low disease activity is crucial to optimise it. This framework, both robust and generalisable, offers a valuable basis for interpreting future studies.

Competing interests

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: DvdH reports a relationship with AbbVie Inc that includes consulting or advisory. DvdH reports a relationship with Alfasigma SpA that includes consulting or advisory. DvdH reports a relationship with Argenx BV that includes consulting or advisory. DvdH reports a relationship with Bristol-Myers Squibb Company that includes consulting or advisory. DvdH reports a relationship with Eli Lilly and Company that includes consulting or advisory. DvdH reports a relationship with Grey Wolf Therapeutics Limited that includes consulting or advisory. DvdH reports a relationship with Janssen Pharmaceuticals Inc that includes consulting or advisory. DvdH reports a relationship with Novartis that includes consulting or advisory. DvdH reports a relationship with Pfizer Inc that includes consulting or advisory. DvdH reports a relationship with Takeda Pharmaceuticals International AG that includes consulting or advisory. DvdH reports a relationship with UCB Pharma SA that includes consulting or advisory. SR reports a relationship with AbbVie Inc that includes consulting or advisory and funding grants. SR reports a relationship with Alfasigma SpA that includes consulting or advisory and funding grants. SR reports a relationship with Merck Sharp & Dohme Corp that includes consulting or advisory and funding grants. SR reports a relationship with Novartis Pharmaceuticals Corporation that includes funding grants and speaking, and lecture fees. SR reports a relationship with Pfizer Inc that includes consulting or advisory and funding grants. SR reports a relationship with UCB Pharma SA that includes funding grants and speaking, and lecture fees. SR reports a relationship with Eli Lilly and Company that includes consulting or advisory and speaking and lecture fees. SR reports a relationship with Janssen Pharmaceuticals Inc that includes consulting or advisory. LG reports a relationship with AbbVie Inc that includes consulting or advisory and funding grants. LG reports a relationship with Biogen Inc that includes: funding grants. LG reports a relationship with Amgen Inc that includes consulting or advisory. LG reports a relationship with Bristol-Myers Squibb Company that includes consulting or advisory. LG reports a relationship with Celltrion Pharm, Inc. that includes consulting or advisory. LG reports a relationship with Janssen Pharmaceuticals Inc that includes consulting or advisory. LG reports a relationship with Eli Lilly and Company that includes consulting or advisory and funding grants. LG reports a relationship with Merck Sharp & Dohme Corp that includes consulting or advisory. LG reports a relationship with Novartis that includes consulting or advisory and funding grants. LG reports a relationship with Pfizer Inc that includes consulting or advisory. LG reports a relationship with Sandoz Inc that includes consulting or advisory. LG reports a relationship with UCB Pharma SA that includes consulting or advisory. AO reports a relationship with AbbVie Inc that includes consulting or advisory. AO reports a relationship with Johnson & Johnson MedTech that includes consulting or advisory. AO reports a relationship with Eli Lilly and Company that includes consulting or advisory. AO reports a relationship with Novartis Pharmaceuticals Corporation that includes consulting or advisory. AO reports a relationship with UCB Pharma SA that includes consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Augusta Ortolan: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Désirée van der Heijde:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Conceptualization. **Laure Gossec:** Writing – review & editing, Validation, Supervision, Methodology, Data curation. **Sofia Ramiro:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

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Patient consent for publication

Written inform consent was signed by all patients prior to the study inclusion.

Ethics approval

This study was approved by Comité de protection des personnes CCP Ile de France III, Number 2457, EUDRACT number 2007- A00608-45.

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Orcid

Augusta Ortolan: http://orcid.org/0000-0002-3131-0939
Désirée van der Heijde: http://orcid.org/0000-0002-5781-158X
Laure Gossec: http://orcid.org/0000-0002-4528-310X
Sofia Ramiro: http://orcid.org/0000-0002-8899-9087

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