Burden of illness associated with non-radiographic axial spondyloarthritis: a multiperspective European cross-sectional observational study

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Abstract

Objective

To assess the impact of non-radiographic axial spondyloarthritis (nr-axSpA) on patients and society based on real-world evidence from the Adelphi nr-axSpA Disease Specific Programme, a cross-sectional survey of rheumatologists and their patients in Germany, France, Spain, Italy and the UK.

Methods

Physicians completed patient record forms for the next two patients consulting with nr-axSpA (diagnosis at the physician's judgement); patients were invited to complete a patient self-completion form. Outcomes were assessed in responders and non-responders and those treated with and without biological agents.

Results

In total, 631 patients were included. Fulfilment of classification criteria varied across countries. Assessment of SpondyloArthritis international Society classification criteria were most commonly met; other criteria, including Amor and European Spondyloarthropathy Study Group criteria, were applied less frequently. Most German and UK patients had their condition classified without formal criteria. Despite being diagnosed with nr-axSpA, 13% of patients met the criteria for ankylosing spondylitis. EuroQol 5-Dimensions (3L) utility scores were lower in patients with nr-axSpA versus general population matched controls (0.776 vs. 0.884; p<0.001); non-responders to treatment had impaired activity (as measured by the Work Productivity and Activity Impairment questionnaire) of 47.4% versus 33.3% in responders (p<0.001). Clinical outcomes were consistently better in biological-treated versus -naïve patients. Average pretreatment pain levels were 6.6 and 6.2, respectively (p=0.072) but reduced to 2.5 and 4.0, respectively (p<0.001) at the time of the survey.

Conclusion

nr-axSpA was associated with a significant QoL and societal burden in this study of German, French, Spanish, Italian and UK patients. Treatment with biological agents was associated with improved QoL. Considerable variability in patients' clinical characteristics were observed across the countries studied and further education, aimed at improving awareness of the condition, may be needed.

Key words
quality of life, biological products

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Introduction

Spondyloarthritis (SpA) is the name of a heterogeneous group of rheumatic diseases sharing common clinical and genetic features, including ankylosing spondylitis (AS), reactive arthritis and psoriatic arthritis (1). SpA is peripheral if the limbs are predominantly affected and axial if the spine or sacroiliac joints are predominantly affected (2). Axial SpA (axSpA) is typically seen in younger patients (age at onset ≤45 years) and characterised by chronic inflammatory back pain (3). Classification of axSpA is based on the presence of sacroiliitis on imaging and other features associated with SpA, *e.g.* arthritis, uveitis, psoriasis, association with human leucocyte antigen (HLA)-B27 and family history of axSpA (3).

Radiographic sacroiliitis can occur relatively late in the axSpA disease course and many patients experience most symptoms long before radiological evidence of inflammation presents. Consequently, classification criteria were developed by the Assessment of SpondyloArthritis international Society (ASAS) to allow identification and treatment of patients with early disease, *i.e.* non-radiographic axial SpA (nr-axSpA) (3). Classification of nr-axSpA requires ASAS clinical criteria for axSpA without radiological evidence of sacroiliitis; however, evidence of active inflammation on magnetic resonance imaging that indicates sacroiliitis is an important feature. Patients with chronic back pain starting at age <45 years can also be classified as having nr-axSpA if they are HLA-B27 positive and have two more features characteristic of SpA (2–5).

Nr-axSpA is a chronic condition and imposes a considerable burden on patients, as well as on the healthcare system (both providers and payers) and society as a whole. Affected individuals may have compromised health-related quality of life (QoL), as a result of chronic pain, and poor work productivity. Although the burden has not been widely quantified because of the relatively recent classification of nr-axSpA, studies have demonstrated that patients with nr-axSpA have similarly compromised physical function as patients with AS (6). However, Bath Ankylosing Spondylitis Metrology Index scores – an indication of spine and hip mobility – were lower in patients with nr-axSpA, indicating less compromised spinal mobility, than in those with AS (6, 7).

Randomised controlled trials are of limited use in quantifying disease burden as they have minimal external validity, protocol-related costs associated with unrealistic treatment patterns and a non-representative patient population. Consequently, real-world evidence is an integral source of data relating to burden of disease. The Adelphi Real World Disease Specific Programmes (DSPs) are multinational, cross-sectional market-research surveys that generate data from current clinical practice to provide real-world evidence on a variety of diseases (8–11). Given the lack of currently available information about the impact of nr-axSpA on patients and society, we interrogated the Adelphi nr-axSpA DSP to provide an insight into this patient population.

Methods

Study design and populations

Data were extracted from the 2014 Adelphi nr-axSpA DSP – a survey of rheumatologists and their presenting patients. The DSP methodology was implemented as previously published (12), adapted to the nr-axSpA setting. Local fieldwork agencies recruited a geographically representative sample of eligible physicians who recruited patients presenting with nr-axSpA. Eligible physicians were rheumatologists seeing ≥2 patients with nr-axSpA in a typical month, to have qualified as rheumatologists between 1975–2010 and to be personally actively involved in patient drug management. Local teams telephoned doctors, described the requirements of the survey and checked eligibility using screening criteria; they then confirmed consent to take part. The physician survey was sent via an email link; patient self-completion forms were delivered in person by the recruiters. Physicians were paid according to fair market value for the time they spent completing the surveys.

Physicians completed patient record forms (PRFs) for the next two consecu-

tive patients consulting with nr-axSpA. The PRF captured patient demographics, severity of condition (physician's perception), pain level (where 1=none; 10=worst), disease progression (physician's perception), remission status, acute episodes (flares), concomitant conditions, current treatment, clinical results, diagnostics used, symptomatology (axial only or axial and peripheral disease; back pain; presence of sacroiliitis; joint inflammation; buttock pain; tendonitis; dactylitis; enthesitis; synovitis; syndesmosis; osteoporosis; uveitis; inflammatory bowel disease; psoriatic skin lesions; diarrhoea; family history of inflammatory disease) and consultation history. The nr-axSpA diagnosis was at the clinical judgement of the physician; no formal classification criteria were mandatory for inclusion in the survey.

Patients were invited to complete a patient self-completion form independently of the physician. This included the EuroQol 5-Dimensions three-level questionnaire (EQ-5D-3L) (13), which was completed by all patients, and the Work Productivity and Activity Impairment (WPAI) questionnaire (14), the work productivity questions being completed by employed patients and the activity impairment question by all patients.

Data collection was in accordance with European Pharmaceutical Market Research Association guidelines. Patients provided consent for de-identified and aggregated reporting of research findings. Data were de-identified according to Health Insurance Portability and Accountability Act regulations before receipt by Adelphi Real World.

Control data

A general population control group was used to contextualise findings from nr-axSpA patients. Control data were obtained from the 2012 Health Survey for England (HSfE), a cross-sectional health survey of 10 000 individuals representative of the English population (15). The HSfE collects many of the items collected in the DSP, eg demographic, clinical and subject-reported outcome data, including the EQ-5D-3L, enabling patient-to-control matching based on demographic and clinical covariates common to both datasets.

Objectives

The first objective was to understand the clinical and demographic characteristics of patients with nr-axSpA. We also wished to identify how patients are being diagnosed and classified in different European countries and to quantify the humanistic and societal burden of nr-axSpA from the patient's perspective. We also aimed to identify if there is an element of avoidable burden in patients with nr-axSpA.

Definitions

Patients were defined as responding to current treatment (conventional and disease-modifying anti-rheumatic drugs [DMARDs], including anti-tumour necrosis factor-alpha agents) if they met all of the following criteria: the physician was satisfied with the patient's current disease control; the patient was not currently experiencing an acute episode and there was either an improvement in physician-perceived severity since initiation of current therapy or the patient's disease remained mild or moderate between time points. Non-responders did not meet these criteria.

Biological-naïve biological-eligible candidates were those who had never received biological therapy (adalimumab [Humira], certolizumab pegol [Cimzia], etanercept [Enbrel], golimumab [Simponi] or infliximab [Remicade]) and were reported to be candidates for biological therapy by the physician. Biological-treated patients were those currently receiving biological therapy and on their current biological agent for ≥6 months, allowing sufficient time for optimal treatment effect.

Burden of disease was defined from the patient and societal perspectives. The burden perceived by patients (humanistic burden) was measured using EQ-5D-3L scores. The burden to society was measured in terms of lost productivity and activity impairment from the patient's perspective (societal burden). Avoidable burden was the extent to which burden of disease could be alleviated through treatment with a biological agent in biological-naïve biological-eligible patients. This was assessed by comparing outcomes in biological-treated *versus* biological-naïve biological-eligible patients.

Presenteeism was defined as the percentage of impairment at work/reduced effectiveness at work. Absenteeism was the proportion of time absent from work as a result of ill health (16).

The economic cost of productivity loss was the mean annual income of employed biological-naïve patients, multiplied by time from diagnosis to prescription and optimal effect of a biological agent in biological-treated patients, multiplied by the percentage difference in overall work impairment between biological-naïve and biological-treated patients.

Statistical analysis

Summary statistics were used to compare (a) different disease classification practices between countries; (b) patient demographic and clinical characteristics across countries and between responders/non-responders; and (c) biological-naïve biological-eligible patients *versus* patients currently receiving a biological agent in terms of clinical factors, such as physician-perceived disease severity, disease duration, remission status and physician-perceived disease progression, and outcomes. Univariate weighted regressions were performed to obtain *p*-values for comparisons between these two subgroups. Productivity loss in biological-naïve patients was calculated using the human capital method (17).

To ensure patients were representative of the patient population, the number of consultations in the last 12 months was used as an inverse probability weight. For patients managed for <12 months, imputation was used to estimate the expected 12-month consultation rate. This weighting affected means, standard deviations and percentages but was not used in multivariate analyses.

In order that meaningful conclusions could be drawn from the patient-perspective burden analysis, the sample size was increased by combining data from the 2014 nr-axSpA DSP with data from additional patients with nr-axSpA in the 2011 DSP (Fig. 1). This analy-

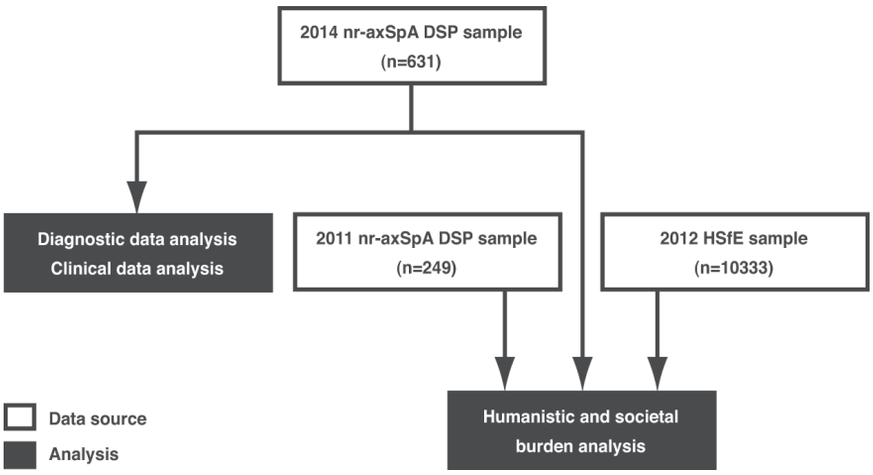

Fig. 1. Analysis sample diagram.
DSP: Disease Specific Programme; HSfE: Health Survey for England; nr-axSpA: non-radiographic axial spondyloarthritis.

sis was in two parts: (a) comparison of QoL in the nr-axSpA DSP sample *versus* the HSfE general population sample; and (b) comparison of QoL and productivity in responders and non-responders, both derived from the nr-axSpA DSP sample.

In the control group analysis, one-to-one propensity score matching with replacement was used to ensure patients with similar profiles in the study group and the control group were analysed (18); covariates included age, sex, body mass index, comorbidities, caregiver status and employment status. A genetic search algorithm was used to find optimal balance for covariates. DSP patients were matched to HSfE subjects and non-responders to responders. Balance diagnostics were assessed post-matching to ensure patients were adequately matched. Absolute standardised mean differences were used to assess balance; <10% post-matching is deemed acceptable (19). Outcomes were compared between the two matched groups; Abadie–Imbens standard errors (AI SEs) and corresponding test statistics (T-stat) and *p*-values were calculated. The AI SE was used as it takes into account the estimation of propensity scores.

Rosenbaum bounds provide a sensitivity analysis around the *p*-value associated with the treatment effect (20). Gamma (Γ) measures the degree of departure from random assignment of subgroup classification. The value of Γ at which the *p*-value is no longer significant quantifies how sensitive the *p*-value is to unobserved covariates. The higher the value of Γ, the less sensitive and more robust the results are to unobserved confounders.

All analyses were performed in Stata v. 13.1 or later (StataCorp LP, College Station, TX, USA) and R v. 3.1 or later (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

What characterises patients with nr-axSpA clinically and demographically?

Patient demographics and clinical characteristics are shown in Table I and Supplementary Table I. Physicians reported that the majority of patients (78%) had moderate or severe nr-axSpA at the time of diagnosis and were diagnosed for an average of 4 years. By the time of the survey, patients' disease severity was perceived to be milder than at diagnosis in all countries and 50% of patients were currently classed as being in remission. Almost all patients (94%) had inflammatory back or spinal pain at the time of diagnosis (Table II); this reduced to 57% by the time of the survey. Mean pain score was also lower at the time of the survey than at the time of diagnosis (3 *vs*. 6, respectively). Among the 68% of patients who had ever had an HLA-B27 test, 74% had a positive result.

Differences were observed between countries in clinical characteristics (Table I). The use of biological agents varied, ranging from 25% in Italy to 49% in France. The proportion of patients with severe disease at diagnosis was lowest in Italy (10%) and highest in France (24%); conversely, the proportion of patients in remission was lowest in Italy (18%) and highest in France (66%). Italian patients were most likely and German patients were least likely to have ever had an acute episode (31% *vs*. 19%, respectively); French patients had been in remission longest (19 months) and the time in remission was shortest in Italy (3 months). The proportion of patients with a positive HLA value from their most recent test was lowest in Italy (58%) and highest in France (84%).

Responders were more likely to be receiving biological therapy than non-responders (43% *vs*. 22%, respectively). In addition, 26% of patients (ranging from 15% in France and the UK to 48% in Italy) were receiving a traditional DMARD and this proportion was similar for responders and non-responders (28% *vs*. 26%, respectively).

How are patients diagnosed and classified in different countries?

Physicians reported using ASAS classification criteria in 52% of patients, ranging from 24% in Germany to 75% in Spain (Table II). The Amor criteria were most widely used in France (25% *vs*. 7% overall), whereas the European Spondyloarthropathy Study Group criteria were most widely used in Italy (16% *vs*. 6% overall). Patients were classified as having SpA without reference to formal criteria (Germany 75%, France 33%, Italy 34%, Spain 19% and the UK 52%).

In total, 13% of patients met the criteria for AS at diagnosis: inflammatory back pain; evidence of sacroiliitis identified by x-ray; and either unilateral sacroiliitis grade 3+ or bilateral sacroiliitis grade 2+. This proportion ranged from 35% in France to 4% in the UK. Patients fulfilling AS criteria were in more pain at diagnosis than those who did not (pain score 5.8 *vs*. 5.5, respectively) and were more likely to be perceived as having moderate/severe disease by their physician at diagnosis (91% *vs*. 75%, respectively).

Table I. Patient demographics and clinical characteristics.

Variable	France (n=124)	Germany (n=122)	Italy (n=127)	Spain (n=120)	UK (n=138)	All patients (n=631)	Responders (n=419)	Non-responders (n=156)
Age (years), mean (SD)	42.5 (9.9)	49.9 (15.1)	43.2 (10.7)	38.6 (11.3)	38.5 (11.4)	41.8 (12.0)	41.9 (11.7)	41.2 (12.7)
Age at onset (years), mean (SD)	33.5 (9.3)	44.7 (14.7)	38.8 (10.0)	32.3 (9.6)	30.5 (8.6)	35.0 (11.2)	35.1 (11.0)	34.8 (11.0)
Sex, n (%)								
Female	44 (26.0)	35 (23.4)	55 (42.5)	29 (26.0)	41 (27.3)	204 (29.6)	123 (27.8)	63 (33.4)
Male	80 (74.0)	87 (76.6)	72 (57.5)	91 (74.0)	97 (72.7)	427 (70.4)	296 (72.2)	93 (66.6)
BMI (kg/m^2), mean (SD)	24.6 (4.7)	25.7 (3.3)	23.9 (3.0)	25.1 (2.5)	24.9 (3.9)	24.7 (3.6)	24.6 (3.5)	25.2 (4.1)
Time since diagnosis was made (months), mean (SD)	75.8 (69.0)	43.8 (51.9)	36.1 (45.9)	40.8 (43.5)	58.6 (71.0)	51.6 (60.0)	55.7 (57.4)	41.8 (64.9)
Current treatment, n (%)								
Traditional DMARD	19 (14.6)	33 (22.9)	59 (48.5)	34 (29.9)	24 (14.7)	169 (25.8)	125 (28.1)	42 (25.9)
Biological agent	63 (48.5)	39 (30.9)	37 (24.8)	40 (31.3)	52 (42.0)	231 (36.1)	187 (43.2)	40 (22.5)
Disease severity at diagnosis								
Mild	12 (12.0)	23 (23.4)	48 (41.4)	22 (20.6)	16 (14.7)	121 (22.2)	95 (25.9)	11 (9.0)
Moderate	76 (63.6)	74 (65.8)	67 (48.6)	81 (67.5)	93 (65.7)	391 (62.0)	254 (59.6)	102 (67.7)
Severe	36 (24.4)	25 (10.8)	12 (10.0)	17 (12.0)	29 (19.6)	119 (15.9)	70 (14.5)	43 (23.3)
Current disease severity, n (%)								
Mild	85 (75.4)	70 (61.6)	95 (74.8)	88 (77.7)	87 (71.0)	425 (72.7)	350 (85.6)	37 (28.4)
Moderate	33 (21.6)	46 (33.9)	32 (25.2)	30 (20.0)	44 (26.2)	185 (24.9)	69 (14.4)	98 (60.4)
Severe	6 (3.0)	6 (4.5)	0	2 (2.3)	7 (2.8)	21 (2.4)	0	21 (11.2)
Current disease progression, n (%)								
Improving	43 (35.1)	30 (25.1)	38 (28.9)	39 (35.0)	27 (24.0)	177 (29.5)	148 (33.8)	21 (14.8)
Stable	60 (53.2)	62 (66.3)	72 (64.7)	59 (56.6)	72 (61.9)	325 (60.3)	259 (64.0)	48 (42.1)
Deteriorating slowly	6 (4.8)	8 (6.5)	4 (2.9)	8 (7.5)	16 (8.1)	42 (6.0)	10 (1.8)	31 (23.1)
Deteriorating rapidly	3 (1.5)	0	2 (2.0)	0	6 (2.7)	11 (1.5)	1 (0.3)	10 (6.4)
Unstable	9 (5.4)	3 (2.2)	2 (1.5)	2 (1.0)	7 (3.3)	23 (2.8)	1 (0.1)	22 (13.5)
Remission status								
In remission, n (%)	70 (66.2)	63 (48.8)	26 (18.2)	65 (60.3)	69 (56.2)	293 (49.8)	255 (62.2)	12 (5.6)
Time in remission (months), mean (SD)	18.9 (26.3)	14.4 (28.2)	2.5 (10.5)	10.0 (12.9)	16.0 (26.7)	12.3 (22.7)	15.7 (24.9)	0.5 (2.8)
Acute episodes, n (%)								
Ever experienced	44 (27.8)	27 (19.2)	37 (30.7)	32 (29.8)	35 (20.0)	175 (25.6)	100 (20.7)	70 (47.4)
Currently experiencing	13 (7.2)	1 (0.9)	4 (3.9)	1 (0.8)	9 (3.4)	28 (3.5)	0	26 (16.8)
Pain score at diagnosis [1=None; 10=Worst], mean (SD)	6.0 (1.9)	4.6 (1.7)	4.9 (2.4)	5.9 (1.7)	6.1 (1.9)	5.6 (2.0)	5.4 (2.1)	6.4 (1.7)
Current pain score [1=None; 10=Worst], mean (SD)	2.6 (1.9)	3.1 (1.7)	2.9 (1.7)	2.8 (1.9)	3.1 (2.2)	2.9 (1.9)	2.3 (1.4)	5.0 (2.0)
Findings currently present, n (%)								
IBP or spinal pain	69 (48.6)	83 (68.4)	81 (69.4)	55 (43.4)	81 (56.1)	369 (56.7)	198 (47.2)	135 (86.7)
Sacroiliitis (by x-ray)	38 (36.5)	38 (27.6)	13 (8.7)	14 (9.4)	16 (11.7)	119 (17.5)	81 (18.1)	30 (17.4)
Sacroiliitis (by MRI)	38 (26.5)	39 (32.8)	27 (20.4)	46 (39.8)	55 (40.7)	205 (32.4)	119 (29.8)	69 (43.1)
Alternating buttock pain	32 (22.7)	19 (14.2)	17 (14.6)	13 (7.9)	24 (14.1)	105 (14.7)	53 (11.0)	44 (28.3)
Enthesitis	8 (6.5)	8 (6.3)	9 (7.3)	8 (4.4)	26 (16.1)	59 (8.9)	24 (5.3)	28 (20.5)
None	16 (16.8)	18 (16.3)	16 (9.7)	32 (27.4)	24 (19.9)	106 (18.1)	92 (22.5)	1 (1.0)
Most recent CRP results (mg/L), n (%)								
≤ 5	82 (78.0)	58 (60.8)	78 (63.9)	78 (79.3)	72 (71.5)	368 (71.2)	258 (73.7)	77 (61.0)
> 5	25 (22.0)	38 (39.2)	34 (36.1)	24 (20.7)	40 (28.5)	161 (28.8)	94 (26.4)	54 (39.0)
Most recent HLA-B27 result, n (%)								
Negative	18 (16.3)	7 (25.1)	29 (42.3)	25 (24.0)	23 (24.6)	102 (26.1)	70 (25.8)	29 (28.5)
Positive	76 (83.7)	42 (074.9)	42 (57.7)	73 (76.1)	74 (75.4)	307 (73.9)	210 (74.3)	75 (71.5)

Data source: Adelphi 2014 nr-axSpA Disease Specific Programme. Percentages, means and standard deviations are weighted to adjust for design bias in the Disease Specific Programme methodology; frequencies are not weighted.

Responders met all of the following criteria: the physician reported being satisfied with the patient's current disease control; the patient was not currently experiencing an acute episode and there was either an improvement in severity since initiation of current therapy or the patient's disease remained mild or moderate between time points. Non-responders were defined as those who did not meet these criteria.

BMI: body mass index; COX-2: cyclo-oxygenase-2; CRP: C-reactive protein; DMARD: disease-modifying anti-rheumatic drug; HLA-B27: human leucocyte antigen B27; IBP: inflammatory back pain; MRI: magnetic resonance imaging; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation.

Table II. Diagnosis and classification of patients.

Variable, n (%)	France (n=124)	Germany (n=122)	Italy (n=127)	Spain (n=120)	UK (n=138)	All patients (n=631)
Spondyloarthropathy confirmation criteria						
Amor	32 (25.0)	0	2 (2.0)	9 (7.2)	1 (1.5)	44 (7.0)
ESSG	5 (4.9)	3 (2.4)	19 (16.2)	5 (3.9)	3 (2.3)	35 (6.1)
ASAS	60 (49.5)	37 (24.3)	74 (57.2)	92 (75.4)	74 (48.2)	337 (52.4)
None	40 (33.2)	83 (74.8)	44 (34.3)	20 (18.8)	64 (51.8)	251 (41.3)
Findings present at diagnosis						
IBP or spinal pain	119 (94.5)	111 (91.6)	113 (90.1)	117 (96.8)	132 (94.7)	592 (93.7)
Sacroiliitis (by x-ray)	48 (46.2)	46 (33.5)	18 (11.3)	22 (19.0)	22 (15.8)	156 (23.6)
Sacroiliitis (by MRI)	67 (51.7)	64 (53.1)	50 (34.6)	83 (70.0)	100 (72.9)	364 (57.5)
Alternating buttock pain	71 (55.1)	41 (29.2)	51 (39.1)	64 (49.8)	66 (45.0)	293 (44.5)
Enthesitis	27 (20.5)	13 (9.9)	21 (14.2)	35 (29.5)	43 (28.7)	139 (21.7)
Sacroiliitis by x-ray and/or MRI						
No	31 (20.6)	39 (35.6)	71 (61.9)	28 (20.8)	26 (18.4)	195 (30.9)
Yes	93 (79.4)	83 (64.4)	56 (38.1)	92 (79.2)	112 (81.6)	436 (69.1)
Satisfy ankylosing spondylitis criteria						
No	87 (64.6)	99 (87.7)	118 (95.3)	104 (86.1)	121 (96.4)	529 (86.8)
Yes	34 (35.4)	20 (12.3)	8 (4.8)	16 (13.9)	6 (3.6)	84 (13.2)

Data source: Adelphi 2014 nr-axSpA Disease Specific Programme. Percentages are weighted to adjust for design bias in the Disease Specific Programme methodology; frequencies are not weighted.
ASAS: Assessment of SpondyloArthritis international Society; ESSG: European Spondyloarthropathy Study Group; IBP: inflammatory back pain; MRI: magnetic resonance imaging.

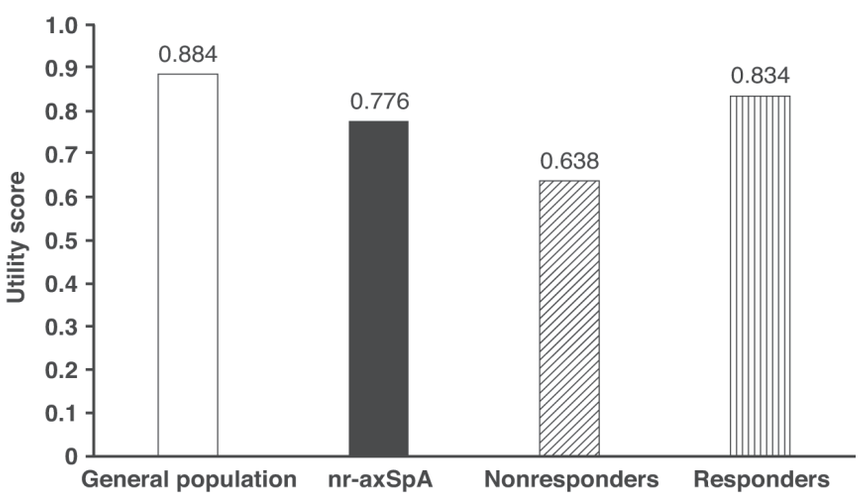

Fig. 2. EQ-5D utility scores after propensity score matching in the nr-axSpA population, in patients classed as responders and non-responders to treatment, and in the general population as represented by the Health Survey for England.
AI SE: Abadie–Imbens standard error; EQ-5D: EuroQol 5-Dimensions questionnaire; nr-axSpA: non-radiographic axial spondyloarthritis.
Data sources: Adelphi 2011 and 2014 nr-axSpA Disease Specific Programmes; Health Survey for England database (15). Higher scores represent better patient-perceived health state.
The difference between the Health Survey for England and Disease Specific Programme groups was statistically significant (p<0.001; AI SE 0.019; T-stat -5.702) based on the AI standard. The difference between responders and non-responders was also statistically significant (p<0.0001; AI SE 0.04; T-stat -4.62).
Responders met all of the following criteria: the physician reported being satisfied with the patient's current disease control; the patient was not currently experiencing an acute episode and there was either an improvement in severity since initiation of current therapy or the patient's disease remained mild or moderate between time points. Non-responders were defined as those who did not meet these criteria.

What is the patient-perceived humanistic burden of nr-axSpA?

Of the 880 DSP patients included in the multivariate analysis (DSP *vs*. HSfE), 187 DSP patients were matched to 187 controls from the HSfE sample. Health-related QoL, as measured using the EQ-5D-3L, was significantly worse in patients with nr-axSpA (0.776 and 0.884, respectively; Fig. 2). This difference of 0.108 was statistically significant (p<0.001) and exceeded the minimally important difference (MID) threshold of 0.074 (21). Adequate balance of the covariates was achieved (Supplementary Table II) and Rosenbaum sensitivity testing demonstrated that the p-value was moderately insensitive to change in magnitude of an unobserved confounding factor (Γ= 2.2).

In the responder *versus* non-responder EQ-5D-3L analysis, 67 non-responder patients were matched to 67 responder patients. The EQ-5D-3L utility score post-matching for non-responders was statistically significantly lower than that of responders (0.638 *vs*. 0.834, respectively; p<0.001; Fig. 2) and exceeded the EQ-5D-3L MID. Balance diagnostics indicated that adequate balance was achieved for all covariates (Supplementary Table III) and results were moderately insensitive to change in magnitude of an unobserved confounding factor (Γ=2.8).

What is the patient-perceived societal burden of nr-axSpA?

The responder *versus* non-responder activity impairment analysis was based on 62 matched pairs of patients. Non-responders had statistically significantly greater activity impairment than

responders (means: 47% *vs*. 33%, respectively; $p<0.001$; Fig. 3). The balance achieved was adequate (Supplementary Table IV) and results were moderately insensitive to change due to unobserved confounding factors (Γ=2.1).

Because of a low completion rate (n=116 in total), overall work impairment was analysed descriptively and not weighted. Non-responders had an overall work impairment of 53% (95% confidence interval: 44–61%), *versus* 20% (95% confidence interval: 16–25%) in responders (Fig. 3).

Is the burden of nr-axSpA avoidable?

Outcomes were consistently poorer in biological-naïve candidates *versus* biological-treated patients (Table III): 94% of biological-treated patients were classed as having moderate to severe disease at initiation of current treatment *versus* 92% of biological-naïve candidates ($p<0.001$). These figures had changed to 23% and 51%, respectively, by the time the survey was completed ($p<0.001$). Average physician-assessed pain scores at initiation of current treatment were 6.6 and 6.2 in biological-treated patients and biological-naïve candidates, respectively (p=0.072). By the time of the survey, pain scores had reduced to 2.5 for biological-treated patients and 4.0 for biological-naïve candidates ($p<0.001$). Biological-treated patients were more likely to be in remission than biological-naïve candidates (67% *vs*. 34%, respectively; $p<0.001$) and less likely to have experienced an acute episode in the last 12 months (12% *vs*. 36%, respectively; $p<0.001$).

Biological-naïve candidates reported greater presenteeism than biological-treated patients (mean 28% *vs*. 16%, respectively; p=0.037), overall work impairment (mean 37% *vs*. 19%; p=0.018) and activity impairment (mean 31% *vs*. 23%; p=0.045); however, the difference in absenteeism was not statistically significantly different (mean 10% *vs*. 9%; p=0.869). Mean EQ-5D-3L utility scores and mean EQ-visual analogue scale scores, collected at the time of the survey only, did not differ between the two cohorts.

Using the mean annual income of €30,171.83 in biological-naïve patients and a difference in overall work impairment of 18.4% between biological-naïve and -treated patients, the cost/patient from the employers' perspective was estimated at €5549.13/year. However, the mean time to optimal effect of biological agents in biological-treated patients was 48.1 months (42.1 months from diagnosis to initiation of treatment with a biological agent plus 6 months for the treatment to have an optimal effect), therefore, the cost of lost productivity to the employer for biological-naïve *versus* -treated patients was estimated at €22,222.38/patient.

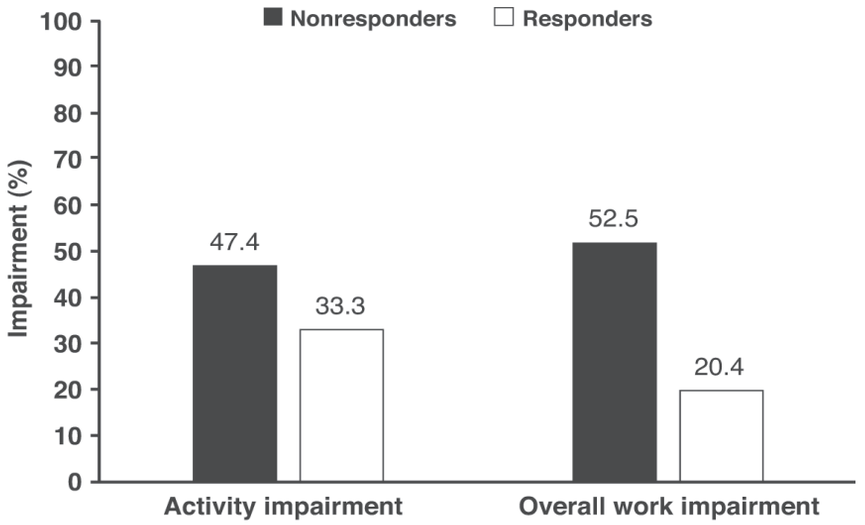

Fig. 3. Activity and work impairment after propensity score matching in patients classed as responders and non-responders to treatment.
AI SE: Abadie–Imbens standard error.
Data sources: Adelphi 2011 and 2014 nr-axSpA Disease Specific Programmes.
Higher scores indicate reduced ability to perform the activity. The difference in activity impairment was statistically significant ($p<0.001$; AI SE 3.84; T-stat 3.67); analysis of work impairment was descriptive because of a low completion rate.
Responders met all of the following criteria: the physician reported being satisfied with the patient's current disease control; the patient was not currently experiencing an acute episode and there was either an improvement in severity since initiation of current therapy or the patient's disease remained mild or moderate between time points. Non-responders were defined as those who did not meet these criteria.

Discussion

This analysis of the Adelphi Real World nr-axSpA DSP provides a multinational overview of the burden of nr-axSpA, a recently classified condition about which relatively little is known in terms of patient characteristics, treatment patterns and disease burden. This analysis was undertaken to address four key aspects of the disease: clinical and demographic characteristics of nr-axSpA; diagnosis and classification of patients; burden of disease on patients and society; and whether this burden is avoidable.

This analysis highlighted differences in patient clinical characteristics across the five countries. Italian patients appeared to have milder disease at diagnosis and less use of biological agents compared with patients in other countries. The proportion of patients who had ever experienced an acute episode was highest in Italy, however. In Germany and the UK, where the use of biological agents was common, the proportion of patients experiencing acute episodes was lowest and the time in remission longest, in line with the ESTHER, RAPID-axSpA and INFAST studies (22–24). Conversely, the proportion of patients in remission was lowest in Italy. Low remission rates were reported in Italian patients with lupus in a similar real-world study, suggesting that Italian rheumatologists may apply stricter criteria than other EU5 physicians (25). The relative novelty of nr-axSpA as a condition may have played a part in the between-country differences in the results seen, as variations in physician awareness of nr-axSpA as a distinct condition rather than a mild version of AS are likely to have

Table III. Comparison of biological-naïve biological candidates and biological-treated patients.

Variable	Biological-treated patients (n=187)	Biological-naïve candidates (n=123)	*p*-value
Time since diagnosis (months), mean (SD)	73.0 (62.4)	46.1 (62.2)	0.015
In remission, n (%)	120 (66.9)	43 (34.2)	<0.001
Acute episode, n (%)	30 (12.3)	47 (36.4)	<0.001
Currently experiencing acute episode, n (%)	6 (2.5)	16 (12.7)	0.001
Disease severity prior to current treatment, n (%)			<0.001
Mild	12 (6.3)	7 (8.4)	
Moderate	95 (50.7)	84 (75.6)	
Severe	80 (43.0)	32 (16.1)	
Current disease severity, n (%)			<0.001
Mild	140 (76.8)	56 (49.3)	
Moderate	41 (20.5)	59 (46.2)	
Severe	6 (2.7)	8 (4.5)	
Pain score prior to current treatment, mean (SD)	6.6 (2.0)	6.2 (1.8)	0.072
Current pain score, mean (SD)	2.5 (1.6)	4.0 (2.2)	<0.001
Disease progression prior to current treatment, n (%)			0.668
Improving	13 (5.8)	10 (6.5)	
Stable	27 (11.7)	17 (16.9)	
Deteriorating slowly	83 (41.9)	31 (36.2)	
Deteriorating rapidly	59 (22.3)	28 (18.4)	
Unstable	45 (18.3)	23 (22.0)	
Current disease progression, n (%)			0.001
Improving	66 (35.2)	30 (23.0)	
Stable	110 (60.0)	50 (52.7)	
Deteriorating slowly	7 (3.0)	12 (11.8)	
Deteriorating rapidly	1 (0.7)	7 (5.0)	
Unstable	2 (1.1)	10 (7.6)	
Patient-reported outcomes			
EQ-5D utility score, mean (SD)	0.820 (0.249)	0.806 (0.262)	0.827
EQ-VAS, mean (SD)	64.8 (25.6)	65.5 (19.2)	0.912
WPAI, % impairment, mean (SD)			
Absenteeism	8.7 (24.0)	10.0 (18.4)	0.869
Presenteeism	15.8 (20.5)	27.6 (16.7)	0.037
Overall work impairment	18.8 (26.0)	37.1 (18.8)	0.018
Activity impairment	22.5 (20.0)	31.4 (23.0)	0.045

Data source: Adelphi 2014 nr-axSpA Disease Specific Programme. Percentages, means and standard deviations are weighted to adjust for design bias in the Disease Specific Programme methodology; frequencies are not weighted. Biologic-treated patients had been receiving their current biologic for at least 6 months. Biologic-naïve patients had never received biologic treatment, yet were considered a candidate for biologic therapy by their physician.
EQ-5D: EuroQol 5-Dimensions questionnaire; SD: standard deviation; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment.

impacted on the types of patients recruited into the study. Further research is needed aimed at identifying the extent to which physicians' understanding of and ability to classify nr-axSpA has evolved since its introduction.

Although many physicians referred to ASAS or other formal classification criteria in diagnosing their patients, a considerable proportion of patients in all five countries were diagnosed without confirmation using classification criteria. Over one in ten of our patients fulfilled the criteria for AS, underlining the fact that nr-axSpA is a relatively new condition on the axSpA spectrum and physicians may not yet differentiate between those with or without radiographic signs of disease. Indeed, whether nr-axSpA and AS need to be differentiated in clinical practice has been questioned (26, 27). Correct treatment of symptoms, regardless of meeting classification criteria, is more important in easing the burden of this condition, unless a formal differentiation is needed for treatment or patient-related purposes (26).

We have demonstrated a humanistic burden in our patients with nr-axSpA, in agreement with other studies (28–31), which is similar to the burden observed in patients with axSpA. Our reference HSfE population did not have WPAI data; however, other sources suggest a typical overall work impairment of 3.47% for the general working-age public (32), notably lower than the 29.8% seen in our sample. Others have observed that indirect costs associated with AS and nr-axSpA account for a considerable proportion of the overall costs of the condition, with lost productivity accounting for most of the indirect costs (33-35); however, economic data on the treatment of this condition are limited at present.

When treatment responders and non-responders were compared, a higher proportion of responders had received biological agents. Responders had consistently better disease activity indicators including lower pain scores, were more likely to be in remission and less likely to have deteriorating disease than non-responders. This analysis suggests that more widespread use of biological agents could reduce the impact of nr-axSpA on patients eligible for these agents and on the healthcare systems. Cost-effectiveness studies on biological agents in nr-axSpA have not yet been published in full and these agents are not yet widely approved for use in patients with nr-axSpA.

Some limitations of this analysis should be considered. Rheumatologists selected the next two consulting patients with nr-axSpA. Physicians were not required to base their diagnosis on formal classification criteria or clinical test results, resulting in misdiagnosis in some cases and inclusion of patients with AS. Consequently the burden of nr-axSpA may have been overestimated in our population. Nonetheless, our analysis provides valuable insight into this poorly understood patient population. Randomised controlled trials may exclude patients based on age, comorbidities and prior therapies, and may not provide information that can be generalised to the nr-axSpA population. The value of observational databases in providing information on this patient group is questionable as appropriate International Statistical Classification

of Diseases and Related Health Problems codes will not be widely used and patients may not be correctly classified. Therefore, real-world data represent an important source of information in this setting.

This real-world study has demonstrated considerable variation in how patients with nr-axSpA are diagnosed and treated across five European countries, potentially highlighting a need for heightened awareness of this condition and its differentiation from AS among physicians. Nr-axSpA is associated with significant QoL impairment and high levels of work productivity loss compared with general population controls. Patients unresponsive to conventional therapies are especially burdened. Effective treatment with biological agents appears to be associated with improved outcomes and QoL; more widespread use of these agents may reduce the burden of nr-axSpA on patients and healthcare providers.

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