Social economic costs of ankylosing spondylitis in Spain

M. Merino[1], O. Braçe[2], A. González-Domínguez[1], Á. Hidalgo-Vega[3,4], M. Garrido-Cumbrera[2,5], J. Gratacós[6]

[1]Weber, Madrid, Spain; [2]Health & Territory Research (HTR), Universidad de Sevilla, Spain; [3]Universidad de Castilla-La Mancha, Toledo, Spain; [4]Fundación Weber, Madrid, Spain; [5]Spanish Federation of Spondyloarthritis Associations (CEADE), Fuenlabrada, Spain; [6]Rheumatology Department, University Hospital Parc Taulí, 13PT Research Institute (UAB), Sabadell, Barcelona; Medicine Department (UAB), Barcelona, Spain.

Abstract

Objective

Ankylosing spondylitis (AS) is a disease associated with a high number of comorbidities, chronic pain, functional disability, and resource consumption. The aim of this study was to estimate the burden of AS in Spain.

Methods

A questionnaire, designed for the development of the "Atlas of Axial Spondyloarthritis in Spain 2017" cross-sectional study, was distributed to patients in 2016. This questionnaire was used to collect relevant sociodemographic and clinical information on patients with AS, as well as to identify resource consumption and patient work productivity losses related to AS within the previous 12 months of survey completion. Subsequently, direct costs were estimated with the bottom-up method and work productivity losses with the human capital method. Economic burden was estimated by subgroups, taking into account the degree of disease activity and the psychological status.

Results

The study sample comprised 578 patients with AS: mean age was 46.0±11.0 years, 52.9% were males, and 35.8% had a university-level education. Mean disease duration and diagnostic delay were 13.4±11.3 and 8.4±7.6 years, respectively, and mean Bath Ankylosing Spondylitis Disease Activity Index was 5.4±2.1. The estimated median annual cost per patient with AS was 5,402.4, with an average annual cost per patient of 11,462.3 euros, of which 61.1% (6,999.8 euros) were attributed to direct health care costs, 5.3% (611.3 euros) to direct non-health care costs, and 33.6% (3,851.2 euros) to work productivity losses.

Conclusion

AS poses a significant burden for the Spanish National Health System and society.

Key words

ankylosing spondylitis, burden of illness, health care costs, cost analysis

María Merino, MSc
Olta Braçe, PhD
Almudena González-Domínguez, MSc
Álvaro Hidalgo-Vega, PhD
Marco Garrido-Cumbrera, PhD
Jordi Gratacós, MD, PhD

Please address correspondence to:
María Merino,
Weber,
Calle Moreto 17,
28014 Madrid, Spain.
E-mail: maria.merino@weber.org.es

Received on November 3, 2019; accepted in revised form on April 27, 2020.

Funding: this study was supported by Novartis Spain, whose participation was limited to sponsoring the project.

Competing interests: M. Merino and A. González-Domínguez are employees of Weber, a company that received fees from Novartis Spain to develop this study. M. Garrido-Cumbrera and O. Braçe are employees of Universidad de Sevilla, a company that received fees from Novartis Spain to develop this study. J. Gratacós has received honoraria as chairman or lecturer in meetings for MSD, Pfizer, AbbVie, Janssen Cilag, Novartis, Celgene and Lilly, and as consultant in advisory boards for Pfizer, AbbVie, Janssen Cilag, Novartis, Gilead, Celgene and Lilly. A. Hidalgo-Vega has declared no competing interests.

Introduction

Ankylosing spondylitis (AS) is a chronic, inflammatory, rheumatic disease (1, 2) primarily affecting the sacroiliac and intervertebral joints which leads to a reduction in spinal mobility (3,4). Accordingly, patients with AS endure disability and pain which further result in functional limitations and reduced quality of life (4-6). Consequently, AS has been associated with an increase in medical care use, formal and informal care, and a reduction in patients' labour productivity (7).

As a disabling disease, AS has been associated with significant direct (drugs, medical visits, hospitalisations, home assistance, and complementary treatments) and indirect costs (work productivity loss and disability) (8). These costs provide objective data which have been previously used to identify which factors are associated to high costs, facilitating strategies to reduce costs and identifying subgroups of patients who contribute unreasonably to raising costs and who could benefit from specific interventions (5). Therefore, estimating the burden of AS may be essential to establish priorities and evaluate new therapeutic approaches to this disease.

The "Atlas of Axial Spondyloarthritis in Spain 2017" (hereafter Atlas 2017) (9, 10) is part of a national initiative, promoted by the Spanish Federation of Spondyloarthritis Associations (CEADE), that seeks to better understand the current state of people suffering from axial spondyloarthritis. The Atlas 2017 was developed using an integrative approach based on scientific evidence, expert knowledge, and patient opinion. The purpose of the present study was to estimate the burden of AS from the Atlas 2017 study, taking the disease activity level and psychological status into account.

Materials and methods

Design and participants

The Atlas 2017 (9, 10) was a cross-sectional study in which unselected patients with axial spondyloarthritis in Spain voluntarily and anonymously filled out an online, self-administered questionnaire. This questionnaire, which was specifically designed for the Atlas 2017 study through expert opinion and the scientific literature, was distributed by CEADE between January and May 2016 using a non-probability sampling method. A total of 680 valid questionnaires were collected. For the present analysis, only those patients who had AS were considered, which is equivalent to a total of 578 patients (85% of the total sample). Inclusion criteria were: having a diagnosis of AS at least 12 months prior to the survey, being older than 18 years, and residing in Spain. Due to the type of study, no clinical research ethical committee approval was required. Nevertheless, the present study conforms with the ethical principles of the Declaration of Helsinki.

Variables

Costs associated to AS were identified through the Atlas 2017 patient questionnaire. This questionnaire included sociodemographic data, information on diagnosis, consumption of health care resources (medical visits, medical tests, emergencies, hospitalisation, and medication) and non-health care resources (complementary treatments, rehabilitative therapies, and physical activity), and patient work productivity losses related to AS within the previous 12 months of survey completion.

In addition, patients completed four additional assessments, two of which had been previously validated: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to determine the degree of disease activity (11), and the 12-item General Health Questionnaire (GHQ-12) to determine the psychological status of patients (12). The two other scales used were specifically created for the Atlas 2017 (9, 10): the Functional Limitation Index, and the Spinal Stiffness Index. The Functional Limitation Index was generated by adding up individual non-weighted scores of functional limitations associated with 18 different activities of daily living (dressing, grooming, bathing, tying shoelaces, moving around the home, stairs, getting to/out of bed, toilet, shopping, preparing meals, eating, cleaning, walking, using public transportation, going to the doctor, driving, physical

exercise, and sexual relations). Scores ranged from 0 to 3 (0, no functional limitation; 1, low; 2, medium; and 3, high) allowing for a total score between 0 and 54. Thus, a global functional limitation value between 0 and 17 would imply low, between 18 and 35 moderate, and between 36 and 54 high functional limitation. The Cronbach alpha value obtained for this scale was 0.964, guaranteeing its reliability as an instrument for assessing functional limitation. The Spinal Stiffness Index was based on the Assessment of SpondyloArthritis International Society (ASAS) concept of spinal stiffness which is defined by intensity and duration upon awakening (13). Accordingly, the questionnaire included one item to assess the degree of spinal stiffness experienced by patients, distinguishing between the three spinal regions: cervical, thoracic, and lumbar regions. The index resulted from adding up individual unweighted scores of rigidity for each region on a scale of 0 to 9, where a value of 0 would imply no stiffness, between 1 and 3 light stiffness, between 4 and 5 moderate stiffness, and between 6 and 9 significant stiffness. The Cronbach alpha obtained for this scale was 0.850, which confirms the reliability of this scale for the assessment of spinal stiffness.

Costs

Direct Health Care Costs (DHC), those incurred by the National Health System and/or patients/families; Direct Non-Health Care Costs (DNHC), out of pocket expenditures borne by patients/families; and indirect costs (IC), cost equivalence of the patients' productivity losses, were estimated following the traditional methodology of cost-of-illness studies (14, 15). Overall, costs were estimated from a societal perspective, including all available direct and indirect costs associated with AS within the previous 12 months of the survey. Moreover, all direct costs were estimated using the bottom-up cost method (16), while work productivity losses were estimated using the human capital approach. Costs with reference year prior to 2015 were updated using the Spanish Medical Consumer Price Index for health care costs and the Spanish General Consumer Price Index for other costs (17).

a) *Direct health care costs*

DHC related to AS included medical visits and tests; outpatient and hospital emergencies; use of an ambulance for emergency medical transportation; hospital admissions; and medication, including pharmacological and administration cost.

Regarding pharmacological costs, recommended daily doses were extracted from the Summary of Product Characteristics for each drug (18), and prices were obtained from the database of medicines of the General Council of Official Colleges of Pharmacists of Spain (19). If not specified, daily doses for anti-inflammatory drugs (NSAIDs) and disease-modifying drugs (DMARDs) were extracted from the World Health Organization recommendations on defined daily doses (20). Moreover, the cost of NSAIDs and DMARDs was calculated from the estimated dose multiplied by the cost per milligram (22) and the administration time reported by each patient.

Regarding biological drugs, for patients reporting less than one year of treatment with certolizumab pegol, infliximab, infliximab biosimilar, and/or secukinumab, the induction period of each drug was taken into account (18). In these cases, the optimisation of vials was not taken into account, considering that the remains of all the vials were discarded. For intravenously administered infliximab and infliximab biosimilars, an administration cost of 62.4 euros was imputed. This value was obtained from a study measuring the average time in hospital during the day for each infliximab administration (178.29 minutes) as well as the cost per minute (0.35 euros updated to 2015) (21). Similarly, for subcutaneously administered adalimumab, certolizumab pegol, etanercept, golimumab and secukinumab, the cost of a nursing visit was imputed as the first administration is carried out by the nursing staff, who in turn train the patient for subsequent self-administration. Moreover, the costs for the administration of biological drugs were estimated from the scientific literature as cost per minute of stay at the day hospital (21).

The cost of healthcare resources used by patients, other than medication, was calculated by multiplying resource quantities by their unit cost. The prices for visits, tests, and emergencies were obtained from public prices of the official bulletins available for each of the Autonomous Communities of Spain (22-42). Given the large price variability between the different Autonomous Communities, the median was used. Furthermore, the price of hospitalisation was obtained from the statistical website of the Ministry of Health, Social Services, and Equality. According to the International Classification of Diseases (ICD), the ICD9MC 720.0 code corresponding to "Ankylosing Spondylitis" was considered (43).

b) *Direct non-health care costs*

DNHC included the use of complementary treatments (such as acupuncture or homeopathy), rehabilitation, and physical activity associated with AS. The costs of complementary treatments were calculated by multiplying the number of monthly sessions reported by the patient by their unit price, and extrapolated to 12 months in order to obtain annual costs. Monthly expenditure on rehabilitation therapies and physical activity was self-reported by the patient, and extrapolated to 12 months. Costs with reference year prior to 2015 were updated using the Spanish General Consumer Price Index (18).

c) *Indirect costs*

IC included patient work productivity losses in the form of absenteeism due to medical visits, sick leave, and hospitalisations, as well as early retirement and unemployment related to AS (according to the patients' self-reported information). Work productivity losses were measured using the human capital method, by which work time lost as a result of illness is valued at the market wage. Therefore, IC were estimated as the average wages incurred by the patient due to AS. The wage data were extracted from the Spanish National Statistics Institute (44, 45). Regarding employees and patients on temporary sick

leave, the average wage was assigned according to gender and occupational level. For the remaining employment situations, the average wage was imputed according to gender and the average number of hours worked in a year.
The total cost associated to AS included the sum of DHC, DNHC, and IC per patient and year in Spain in 2015.

Statistical analysis

Descriptive statistics (number of valid cases, mean, standard deviation (SD), median, and interquartile range [IQR]) were calculated for continuous variables, and frequencies and percentages were calculated for categorical variables. Additionally, costs were compared between levels of disease activity (BASDAI score <4 or low inflammation *vs*. BASDAI ≥4 or high inflammation) and risk of psychological distress (GHQ-12 score <3 or low risk versus GHQ-12 score ≥3 or high risk). Non-parametric techniques (Mann-Whitney U-test) were used after assessment of sample distribution.
For exploratory purposes, several multiple linear regressions were calculated to predict costs within typologies (total costs, DHC, DNHC, and IC) based on the following control variables: age (in years), sex, marital status, education level, employment status, being a member of a patient association related to AS, time from diagnosis (in years), diagnostic delay (in years), GHQ-12 groups (0: <3 or low risk of psychological distress; 1: ≥3 or high risk of psychological distress), BASDAI groups (0: <4 or low inflammation; 1: ≥4 or high inflammation), and use of biological drugs.
Due to agreements between hospitals and providers in the Spanish National Health System, the actual cost of biological treatments may differ from official market prices. Likewise, use of vials in day hospital clinical practice may be optimised by arranging appointments for several patients on the same day, thus taking full advantage of the contents of the vials. For this reason, a sensitivity analysis was carried out to estimate the treatment and administration costs of biological drugs, that more closely resemble the reality of clinical practice, based on criteria established by the scientific committee of the Atlas 2017 (10). As a result, in the estimated alternative scenario, the pharmacological cost has been reduced by 30%, optimisation of vials has been applied, and in those patients who have been on treatment for more than a year, drug administration time has been optimised to 50% of the half-life of the drug (*e.g.* one week has been increased to 10 days).
Statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS v. 22.

Table I. Socio-demographic and clinical characteristics of the sample.

Variables	Valid n.	mean (SD) / median (IQR) or %
Socio-demographic		
Age (years)	578	46.0 (11.0) / 45.0 (38.0-54.0)
Male	578	52.9
Married	578	72.5
University-level education	578	35.8
Employed	578	57.5
Patient association membership	578	47.1
Diagnosis		
Disease duration (years)	472	13.4 (11.3) / 11.0 (4.0-20.0)
Age at first symptoms (years)	471	23.8 (8.5) / 24.0 (18.0-29.0)
Age at diagnosis (years)	472	32.2 (9.5) / 32.0 (26.0-38.0)
Diagnostic delay (years)	469	8.4 (7.6) / 6.0 (2.0-12.0)
HLA-B27 test positive	445	76.9
Family member diagnosed with AS	407	43.5
Spinal stiffness		
Cervical (% moderate-severe)	446	46.2
Thoracic (% moderate-severe)	435	44.1
Lumbar (% moderate-severe)	455	63.3
Functional Limitation Index (0-54)	515	41.9 (10.0) / 44.0 (35.0-51.0)
Disease Activity		
BASDAI score (0-10)	376	5.4 (2.1) / 5.7 (4.1-6.9)
BASDAI score ≥4*	376	75.8
Comorbidity		
Self-reported Depression	268	30.6
Self-reported Anxiety	268	42.2
GHQ-12 score (0-12)	406	5.5 (4.4) / 5.0 (1.0-10.0)
GHQ score ≥3†	406	64.0
Treatment		
NSAID	578	57.1
DMARD	578	21.8
Biological treatment	578	37.2

*High disease activity, †Risk of psychological distress.
ADL: activities of daily living; AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DMARD: disease-modifying anti-rheumatic drug; GHQ-12: 12-item General Health Questionnaire de Goldberg; HLA-B27: human leucocyte antigen B27; IQR: interquartile range; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation.

Results

The total sample included 578 patients across the 17 Autonomous Communities of Spain. Table I shows sociodemographic and clinical characteristics of the sample.
The estimated average annual cost per patient with AS in 2015 was 11,462.3 (± 13,745.5) euros and was distributed as follows: DHC accounted for 61.1%, IC for 33.6%, and DNHC for 5.3% of the average annual cost. Accordingly, average annual DHC per patient was 6,999.8 (± 9,216.8) euros; of these, medication accounted for the largest amount (64.6%), followed by medical visits (13.3%), hospital admissions (12.7%), medical tests (6.0%), and visits to the emergency room (3.3%). Moreover, the average annual IC per patient, attributable exclusively to AS, was 3,851.2 (± 8,484.0) euros. Finally, the lowest average annual cost per patient corresponded to DNHC and was 611.3 (± 1,276.5) euros (Table II).
Table III shows the annual costs per patient according to BASDAI groups (<4 *vs*. ≥4) and GHQ-12 groups (<3 *vs*. ≥3). All cost typologies, except for the

Table II. Annual costs per patient (2015 euros).

Cost typology	Mean (SD)	Median (IQR)	Relative sub-category cost (%)	Relative total cost (%)
Direct health care cost	**6,999.8 (9,216.8)**	**1,789.2 (219.6-14,298.8)**	**100%**	**61.10%**
Health care professional	**930.4 (1,503.2)**	**471.1 (78.5-1,064.4)**	**13.30%**	**8.10%**
Rheumatologist	244.7 (293.7)	156.9 (0-313.8)		
General practitioner	187.4 (522.2)	39.6 (0-198.1)		
Nurse	49.6 (200.4)	0 (0-0)		
Orthopaedic specialist	38.8 (156.8)	0 (0-0)		
Physiotherapist	132.1 (399.4)	0 (0-62.5)		
Ophthalmologist	62.8 (170.1)	0 (0-78.5)		
Pulmonologist	13.6 (59.7)	0 (0-0)		
Cardiologist	13.8 (60.0)	0 (0-0)		
Psychologist / Psychiatrist	156.5 (780.6)	0 (0-0)		
Other	31.1 (172.3)	0 (0-0)		
Medical tests	**422.5 (561.2)**	**271.8 (0-554.9)**	**6.00%**	**3.70%**
Radiography	64.7 (116.6)	0 (0-88.1)		
Magnetic resonance	106.7 (241.6)	0 (0-183.6)		
Ultrasound	16.8 (53.1)	0 (0-0)		
Scintigraphy	12.8 (56.8)	0 (0-0)		
Computed tomography	3.5 (21.7)	0 (0-0)		
Blood test	186.2 (229.4)	122.8 (0-245.5)		
Urine test	24.5 (36.9)	13.1 (0-39.4)		
Other	7.3 (48.1)	0 (0-0)		
Visits to the emergency unit	**232.7 (617.2)**	**0 (0-184.7)**	**3.30%**	**2.00%**
Ambulance	8 (101.4)	0 (0-0)		
Home emergency	4.3 (41.2)	0 (0-0)		
Outpatient emergencies	93.9 (434.4)	0 (0-0)		
Hospital emergencies	126.5 (351.8)	0 (0-0)		
Hospital admissions	**890.3 (4,455.2)**	**0 (0-0)**	**12.70%**	**7.80%**
Medication	**4,523.9 (6,720.2)**	**38.6 (24.6-12,840.7)**	**64.60%**	**39.50%**
NSAID	33.6 (77.1)	0 (0-20.5)		
DMARD	4.3 (13.6)	0 (0-0)		
Biological therapy	4,445.6 (6,676.4)	0 (0-12,840.7)		
Biological therapy administration	40.4 (90.0)	24.6 (24.6-24.6)		
Direct non-health care cost	**611.3 (1,276.5)**	**0 (0-720)**	**100%**	**5.30%**
Rehabilitative therapies / physical activity	558 (1,201.4)	0 (0-720)		
Complementary therapies	53.4 (324.8)	0 (0-0)		
Indirect cost*	**3,851.2 (8,484.0)**	**0 (0-514)**	**100%**	**33.60%**
Total cost patient/year	**11,462.3 (13,745.5)**	**5,402.4 (666.2-17,780.1)**	**-**	**100%**

All costs have been rounded to the nearest tenth. Relative costs were calculated from mean values.
*All cases were included: zero cost (0 euros) has been assigned to patients over 65 years of age (retirement) and to work productivity losses that were not a consequence of AS.
AS: ankylosing spondylitis; DMARD: disease-modifying anti-rheumatic drug; IQR: interquartile range; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation.

DNHC, showed statistically significant differences between BASDAI groups ($p<0.05$), showing a progressive rise in cost from low to high disease activity. Regarding GHQ-12, all cost typologies showed statistically significant differences between groups (<3 *vs.* ≥3) ($p<0.05$), with higher costs associated with higher risk of psychological distress.

The sensitivity analysis yielded a total cost of 9,317.5 euros per patient/year. Furthermore, biological treatment costs could be reduced by 48% relative to the reference case. Thus, DHC would amount to 4,855 euros per patient/year, with 49% of costs attributed to medication (Table IV).

Table V shows the results for the regression analyses performed. Significant regression equations to predict costs within cost typologies were found. Higher total costs were associated with the use of biological drugs, not being employed, and a higher disease activity (BASDAI ≥4), with an R^2 of 0.391. Moreover, higher DHC were associated with the use of biological drugs and a high risk of psychological distress (GHQ-12 ≥3), with an R^2 of 0.599. Corresponding significant models were found for DNHC and IC, but with a lower R^2: 0.035 and 0.174, respectively.

Discussion

The present study estimated that the average annual cost per patient with AS in 2015 amounted to 11,462.3 euros. The majority of this cost was attributed to DHC (61.1%), with outpatient and pharmacy costs being key contributors. As in previous studies (5,46), outpatient care and medications were the major contributors to the direct costs of AS. However, pharmacy costs doubled those reported by Kobelt *et al*. (2008). This could be explained by the increase in the use of biological therapies, which are the most expensive treatments for AS. In fact, AS is associated with direct and indirect costs that have generally increased dramatically since the introduction of anti-TNF therapy (8).

Regarding the level of disease activity and risk of psychological distress, patients with an active disease and higher risk of psychological distress generated higher total costs than those with a controlled disease and at low risk of psychological stress (+50% and +20%, respectively). Moreover, patients with greater disease activity doubled associated IC (+100%) as a result of labour productivity losses. In fact, loss of productivity due to occupational disability is considered a major burden for both families and society (47, 48). Furthermore, patients at high risk of psychological distress increased DNHC considerably (+60%) compared with those with a lower risk. Therefore, an adequate control of AS that includes the evaluation of psychological aspects associated with the disease could be very useful to reduce costs. This is of great interest as an optimally treated patient, with adequate pharmacological treatment and complementary therapies, may reduce the IC derived from the loss of work productivity and disability.

Compared with Kobelt *et al*. (2008), the present study observed considerably greater pharmacological costs associated with AS, yet much lower costs attributed to labour productivity losses. More specifically, the present study observed 56% less IC with respect to that estimated in 2005. This may indicate an

Table III. Annual costs per patient according to BASDAI and GHQ-12 groups (2015 euros).

Cost typology		BASDAI		GHQ-12		Total
		<4 (low inflammation)	≥4 (high inflammation)	<3 (low risk)	≥3 (high risk)	
	Valid N	91	376	146	260	578
Direct health care cost	Mean (SD)	7,592 (7,854.8)*	9,706.9 (9,592.8)*	8,146.8 (8,318.5)*	9,772.9 (9,503.9)*	6,999.8 (9,216.8)
	Median (IQR)	2,527 (701.5-15,304.4)	6,566.8 (1,237.3-15,604.6)	4,978 (729.6-15,402.2)	6,753.5 (1,286.5-15,647.4)	1,789.2 (219.6-14,298.8)
Direct non-health care cost	Mean (SD)	557.3 (1,069.8)	768 (1,390.3)	493.6 (987.9)*	807.2 (1,412.9)*	611.3 (1,276.5)
	Median (IQR)	0 (0-840)	240 (0-1,200)	0 (0-600)	300 (0-1200)	0 (0-720)
Indirect cost	Mean (SD)	2,426.5 (7,449.2)*	5,104.8 (9,355.6)*	3,927.2 (9,063.6)*	4,512.3 (8,759.6)*	3,851.2 (8,484.0)
	Median (IQR)	0 (0-0)	0 (0-4,368)	0 (0-180.1)	0 (0-3,602.6)	0 (0-514)
Total cost	Mean (SD)	10,575.8 (10,592.9)*	15,579.7 (14,376.8)*	12,567.6 (12,768.1)*	15,092.5 (13,864.7)*	11,462.3 (13,745.5)
	Median (IQR)	6,788.8 (1,158.9-16,302.2)	14,446.6 (2,342.7-22,930.4)	13,201.6 (1,315.7-17,906.9)	13,996.5 (2,631.4-21,648.2)	5,402.4 (666.2-17,780.1)

All costs have been rounded to the nearest tenth. *Statistically significant differences between categories of BASDAI and GHQ-12 ($p<0.05$).
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DHC: Direct health care costs; DNHC: Direct non-health care costs; GHQ-12: 12-item General Health Questionnaire; IC: Indirect costs; IQR: interquartile range; SD: standard deviation.

Table IV. Comparison of annual costs: reference case *vs*. sensitivity analysis (2015 euros).

Cost typology	Reference case		Sensitivity analysis	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Direct health care cost	6,999.8 (9,216.8)	1,789.2 (219.6-14,298.8)	4,855 (6,922)	1,789.2 (219.6-8,000.6)
Direct non-health care cost	611.3 (1,276.5)	0 (0-720)	611.3 (1,276.5)	0 (0-720)
Indirect cost*	3,851.2 (8,484)	0 (0-514)	3,851.2 (8,484)	0 (0-514)
Total cost patient/year	11,462.3 (13,745.5)	5,402.4 (666.2-17,780.1)	9,317.5 (12,125.1)	5,200.4 (666.2-11,931.1)

Notes: All costs have been rounded to the nearest tenth. *All cases were included: zero cost (0 euros) has been assigned to patients over 65 years of age (age of retirement) and to work productivity losses that were not a consequence of AS.
SD: standard deviation; IQR: interquartile range.

Table V. Multiple linear regression results.

Models	Explanatory variables	Predictors	Unstandardised B coefficient	Standardised B coefficient	95% confidence interval	*p*-value
1	Total cost	Use of biological drugs	14,786.744	0.539	(12,586.452 – 16,987.036)	0.000
		Employment status	7,169.343	0.257	(4,931.297 – 9,407.388)	0.000
		BASDAI groups	3,973.979	0.124	(1,395.799 – 6,552.159)	0.003
2	Direct health care cost	Use of biological drugs	14,262.776	0.771	(13,062.283 – 15,463.269)	0.000
		GHQ-12 groups	1,772.766	0.092	(519.219 – 3,026.312)	0.006
3	Direct non-health care cost	Intercept	730.264		(453.217 – 1,007.31)	0.000
		Education level	-383.523	-0.140	(-659.766 – -107.281)	0.007
		GHQ-12 groups	366.651	0.132	(87.361 – 645.941)	0.010
4	Indirect cost	Employment status	7,015.012	0.384	(5,308.34 – 8,721.684)	0.000
		BASDAI groups	2,346.874	0.112	(367.624 – 4,326.123)	0.020
		Gender	-1,892.679	-0.105	(-3,590.348 – -195.009)	0.029

Corresponding R^2 are 0.391 (model 1), 0.599 (model 2), 0.035 (model 3), and 0.174 (model 4). Dependant variables included: age (in years), sex (0: male; 1: female), marital status (0: married; 1: others), education level (0: university; 1: others), employment status (0: working/temporary leave; 1: not working), being a member of a patient association related to AS (0: no; 1: yes), time from diagnosis (in years), diagnostic delay (in years), GHQ-12 groups (0: <3 or low risk of psychological distress; 1: ≥3 or high risk of psychological distress), BASDAI groups (0: <4 or low inflammation; 1: ≥4 or high inflammation), and use of biological drugs (0: no; 1: yes).

increase in labour productivity of patients with AS, possibly associated to current use and efficacy of biological treatments as well as reductions in diagnostic delay or greater access to complementary treatments, among others. Results highlight how well-treated patients, not only improve their quality of life as observed in previous studies (49, 50), but may also reduce their social dependence and elicit savings for the health care system.

Strengths and limitations

This study has several limitations. The questionnaire used in the present study was designed for the Atlas 2017 to collect clinical characteristics of AS and its impact on patients' psychological health, activities of the daily living, and occupational and social life. Hence, relevant information on costs related to transportation (medical visits, tests, emergencies, and other health care services), professional and informal care, or household adaptations (as a consequence of their physical limitations)

were not recorded. Moreover, not all IC could be identified through the questionnaire. Accordingly, previous studies have attributed 50% of the total costs to IC. Moreover, patients with advanced AS may incur significant out-of-pocket expenses to cover informal care and housing accommodations (51). Another aspect which was not addressed by the questionnaire was patients' adherence to treatment. In this regard, around 20% of irregularities in treatment-related appointments have been reported, and reducing them may further reduce pharmacological treatment related costs.

The present study underlines the importance of understanding the economic burden of AS, including relationships between costs and different disease domains. Specifically, the use of biological drugs, a high disease activity, and risk of psychological distress were associated with higher costs. This would help policy decision making relative to the establishment of preventive measures, which may further improve AS management while reducing total disease costs.

Acknowledgements

We thank the Spanish Federation of Spondyloarthritis Associations (CEADE) for its collaboration in this project, as well as the patients who gave their time to participate in the survey.

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