# A systematic literature review of the economic impact of ankylosing spondylitis

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*Received and accepted on October 1, 2012.*

*Clin Exp Rheumatol 2012; 30 (Suppl. 73): S136-S141.*



**Key words:** ankylosing spondylitis, loss of productivity, quality of life, costs, review

*Competing interests: none declared.*

**ABSTRACT**

*This article reviews the last decade studies on the economic impact of ankylosing spondylitis (AS). Interestingly, a common observation is that in AS indirect costs are higher than the use of direct healthcare resources.*

*Country, age, gender, and severity of the diseases impact on per patient annual costs AS related.*

*Different payment and reimbursement regimes may impact on the amount and distribution of indirect costs. The differences observed among countries on absolute and relative (compared with direct costs) amounts of indirect costs can be explained with the capability of a country of actually measure productivity losses and indirect costs. Low indirect costs without other indicators should not be considered as a sign of efficiency in AS care, but may be due to an underestimation of AS-related costs; as a consequence, indirect costs may be a net loss for patients that nobody can repay.*

*A private insurance reimbursement regime has the highest capability of inducing players to define, select and actually identify indirect costs better than in different reimbursement regimes. Therefore indirect costs may become very high in case of private insurance regimes because of their more detailed identification.*

## Introduction

Ankylosing spondylitis (AS) is a rheumatic disease with a socio-economic impact for the patient, the healthcare system and the society. This disease determines an increased healthcare utilisation, formal and informal care, and a reduced productivity or working ability of patients. The impact of AS on patient's life is meaningful from a clinical as well as an economic point of view but also in terms of quality of life. In fact, literature data show that AS patients are worried mainly about work ability, social relationships and family life. From the economic perspective, the main cost driver is represented by decreased physical function (1).

The objective of this systematic literature review is to establish the economic impact of AS. The review is based on papers published over the last decade and is designed in accordance with the recommendations of the Centre for Reviews and Dissemination (2) and of the Cochrane Collaboration (3), thereby using an established rigorous and reproducible methodology. A protocol was developed to define review questions.

## Methods

Published studies in English were searched using the main electronic database, PubMed MEDLINE. The search was performed for the period January 2002–September 3, 2012. The search strategy is as follows: ((“economics”[Subheading] OR “economics”[All Fields] OR “cost”[All Fields] OR “costs and cost analysis”[MeSH Terms] OR (“costs”[All Fields] AND “cost”[All Fields] AND “analysis”[All Fields]) OR “costs and cost analysis”[All Fields]) AND (“spondylitis, ankylosing”[MeSH Terms] OR (“spondylitis”[All Fields] AND “ankylosing”[All Fields])OR “ankylosing spondylitis”[All Fields] OR (“ankylosing”[All Fields]AND “spondylitis”[All Fields]))) AND ((“2002/01/01”[PDAT]: “2012/09/03”-[PDAT]) AND “humans”[MeSH Terms] AND English[lang] AND “adult”[MeSH Terms]).

The publications were assessed for inclusion by a 3-step process:

i. titles and abstracts of all identified studies were assessed by one reviewer and checked by a second reviewer;

ii. full texts of relevant articles were then obtained and inclusion criteria applied independently by two reviewers. Possible discords between reviewers were resolved by consensus;

iii. data were extracted by one reviewer and then checked by a second reviewer.

*Inclusion criteria*
In the study protocol the reviewers selected publications from the mentioned database as follows:
*Period*: Jan. 2002–Sep. 3, 2012
*Language:* English
*Studies:* all articles related to economic analysis
*Patients:* adult ≥18
*Outcomes:* direct costs, indirect costs, and quality of life costs

*Exclusion criteria*
The studies not published in English and all papers published before 2002 have been excluded from this review. Conferences proceedings, case reports, reviews, systematic reviews, letters and commentaries were also excluded.

**Results**
As of September 3, 2012, 68 articles were extracted by the search procedure. These were reduced to 50 articles after title scrutiny. After abstract review, 22 publications were included in the analysis. These 22 publications were examined and assessed for eligibility. On reading the full text copies, 15 publications were considered relevant to the review (Fig. 1). Two reviewers read and examined the full text of these publications.
None of the articles provided a full economic evaluation (Cost Minimisation Analysis, Cost Effectiveness Analysis, Cost Utility Analysis and Cost Benefit Analysis). The review (see Table I for more details) is based on 6 studies from The Netherlands (4-9), 2 from UK (10, 11), 1 from USA (12), 1 from Sweden (13), 1 from Spain (14), 1 from Tunisia (15), 1 from Hong Kong (16), 1 from Brazil (17), 1 from Germany (18).
Four articles are prospective (4, 5, 6, 12), 4 are retrospective (10, 14, 15, 16), 4 are observational (9, 11, 13, 17), 1 study reports data coming from randomised trials (7), 1 study presents data deriving from a longitudinal study (8), 1 article does not specify (18). 9 studies analyse direct and indirect costs (7, 11-18); 3 articles report only direct costs (6, 8, 10), 2 studies report only indirect costs (4, 9), 1 article reports healthcare and non-healthcare costs, and income loss due to days of absence from work

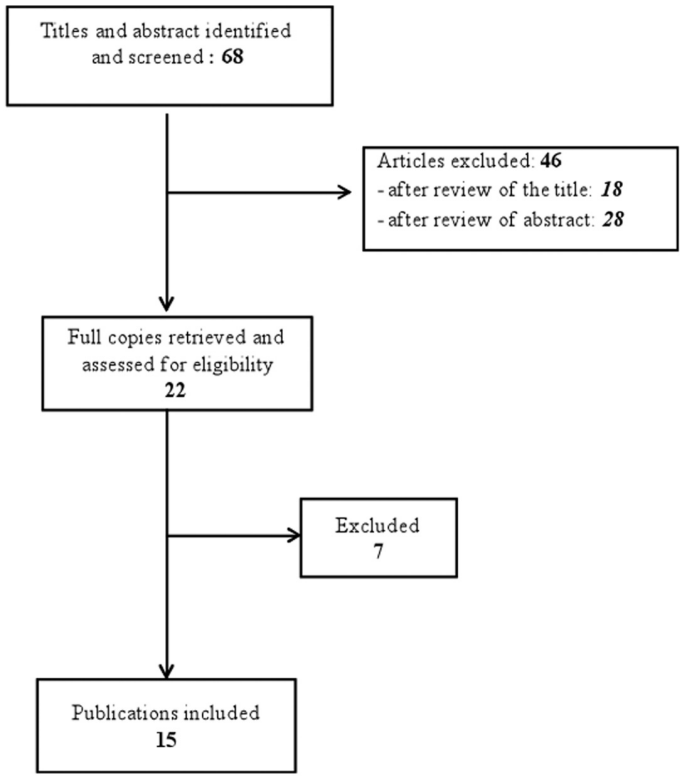


**Fig. 1.** PRISMA flow diagram for cost studies in AS.

adopting the patient's perspective (5). Of the 7 articles excluded, 2 studies compare pharmacological treatments (19, 20), 2 studies are review (21, 22), and 3 articles do not include costs (23, 24, 25).

*The burden of AS and its societal costs*
The studies included in the economic review present direct, indirect and quality of life costs related to AS.
The studies that analyse direct and indirect costs report very different values but all agree on the fact that the societal impact of AS is mainly related to non direct medical cost.
The importance of indirect costs is shown in different studies. Ward *et al*. (12) observed in a study assessing the composition, distribution and drivers of societal costs of AS, that, while annual AS related direct costs in the first year amount to $1,775 *vs*. $2,674 of direct health costs for all causes, indirect costs are about $4,945.
In the first year, AS-related and all cause costs for total outpatient care are in a ratio of 1 to 1.25; total hospital care of 1 to 2.7; diagnostic testing of 1 to 1.056; medication of 1 to 1.4.
Over a period of 5 years, cumulative AS related costs per patient are $31,766 with an average per year of $6,353, of these $23,418 are represented by indirect costs.
The most important predictor for high costs both in the first and in the fifth year is functional disability. Women have a higher probability than men to have high cumulative healthcare costs (gender factors matter in producing high cumulative heath costs).
Similarly Younes *et al*. (15) evaluated the impact of AS and its cost drivers through a retrospective study conducted in Tunisia on 50 AS Patients followed over the period March-September 2006.
With respect to direct medical costs they calculate €266.295 per patient per year. This result includes, among others, €107.218 for systemic medications, €1.369 for local treatments (*i.e*. intra-articular glucocorticoid therapy), €3.648 for osmic acid synovectomy therapy, €18.811 for physical therapy, €13.661 for surgery, €80.28 and €18.75 for inpatient and outpatient care, respectively, and €23.906 of cost of radiographs. Indirect costs are near €279.625 per year per patient overall,

**Table I.** Direct and indirect costs in the last decade literature (in $2012).

| Author | Year | Country | Currency | | $2012 Actualized[1] | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Annual costs per AS patient | | | |
| | | | | | Annual direct costs | Annual indirect costs | Tot. | |
| Ward | 2002 | US | US$ 2009 | First year | 1873.26 | 5278.21 | 7151.46 | |
| | | | | Cumulative (5 year) | 8909.44 | 24995.96 | 33905.41 | |
| | | | | Mean on 5 year | 1781.89 | 4999.19 | 6781.08 | |
| Younes et al. | 2009 | Tunisia | EU€ 2006 | | 448.06 | 470.49 | 918.55 | |
| Boonen et al. | 2010 | The Netherlands | EU€ 2008 | | | 3386.58 | | |
| Strombeck et al. | 2010 | Sweden | US$ 2007 | 3 years | 18939.69 | 21259.87 | 40199.56 | |
| | | | | 1 year | 6313.23 | 7086.62 | 13399.85 | |
| Torres et al. | 2010 | Brazil | US$ 2004 | | 3094.23 | 3793.38 | 6887.61 | |
| Zhu et al. | 2008 | Hong Kong | US$ 2006 | | 4330.74 | 6996 | 11326.74 | |
| Boonen et al. | 2002 | The Netherlands | € 1998 | | Human capital disability costs | Human capital absence costs | Human capital total costs | |
| | | | | The Netherlands | 14334.2 | 1206.5 | 15540.7 | |
| | | | | France | 4465.55 | 525.73 | 4991.27 | |
| | | | | Belgium | 4150.18 | 388.61 | 4538.79 | |
| | | | | | Annual direct costs | Annual indirect costs | Tot. | |
| Rafia et al.[2] | 2012 | UK | £ 2008 | | 3360.54 | 4279.56 | 7640.1 | |
| Kobelt et al. | 2008 | Spain | € 2005 | | 20979.42 | 10646.07 | 31625.49 | |
| Ara et al. | 2008 | UK | £ 2004 | BASDAI | | | | |
| | | | | <4.0 | 2068.5 | | | |
| | | | | 4.0–6.0 | 3239.75 | | | |
| | | | | >6.0 | 6724.55 | | | |
| Boonen et al. | 2003a | The Netherlands | €1998 | | Patient's healthcare costs | Patient's non-healthcare costs | Tot. | |
| | | | | The Netherlands | 189.94 | 493.59 | 683.53 | |
| | | | | France | 172.11 | 222.18 | 394.29 | |
| | | | | Belgium | 488.03 | 161.58 | 649.61 | |
| | | | | | | | | By a finantial point of view |
| Boonen et al. | 2003b | The Netherlands | €1998 | | Direct health cost | Direct non-health costs | Direct Costs | |
| | | | | The Netherlands | 3123.37 | 671.49 | 3794.86 | 2838.45 |
| | | | | France | 3229.46 | 791.72 | 4021.18 | 2193.66 |
| | | | | Belgium | 2591.84 | 359.43 | 2951.27 | 1551.48 |
| Boonen et al. | 2005 | The Netherlands. France. Belgium[3] | €2002 | | Direct costs | Indirect costs (productiivy losses) | Tot. | |
| | | | | FM | 8313.85 | 4081.58 | 12395.43 | |
| | | | | CLBP | 8875.4 | 4662.17 | 13537.57 | |
| | | | | **AS** | 3764.31 | 1322.98 | 5087.3 | |
| Huscher et al.[4] | 2006 | Germany | €2005 | | | | | |
| | | | | RA | 5345.44 | 16126.84; 4677.83 | 23134.71; 11685.71 | |
| | | | | **AS** | 4148.16 | 14552.77;5219.29 | 19991.01; 10657.53 | |
| | | | | PsA | 3561.37 | 11715.3; 3571.25 | 16384.25; 8240.21 | |
| | | | | SLE | 5855.01 | 16598.76;4920.45 | 21319.50; 9641.19 | |
| Verstappen et al. | 2007 | The Netherlands | €2003 | RA | 7884.15 | | | |
| | | | | **AS** | 3927.58 | | | |

1 Actualization computed by means of annual CPIs. Source: Global-Rates.com. In case of Turchia. annual CPIs from World Bank and IMS for 2012 (February) CPI. In case of Hong Kong 2007-20011 CPIs from World Bank. 2012 CPI from Census & Statistics Department. Hang Seng Bank

2 Costs as the mean of costs among different severity of AS. Annual costs (AC) calculated on the original three months costs (3MC) as AC=4*3MC

3 CPI actualization rate equals to 1.21 as the mean of Belgium. France and The Netherland's rates

4 HCA; FCA methods

AS: Ankylosing Spondylitis; FM: fibromyalgia; CLBP: Chronic low back pain; RA: Rheumatoid arthritis; PsA: Psoriatic Arthritis ; SLE: systemic lupus erythematosus

on average, about €1165.5 per patient on sick leave and €411.375 per working patient.

Analysing factors affecting direct medical costs, these authors observe that, with increasing disease duration, the major cost drivers are represented by worse quality of life, while no correlation was found between costs, age, and sex.

With respect to indirect costs, the probability of job absence for an employee with AS appears higher for patient aged 40 year old or more, married, and suffering by AS for 10 years and more.

Boonen *et al*. (9) evaluated the impact (in terms of sick leave and presenteeism) of AS on work productivity in The Netherlands. The authors evaluated the impact of age, disease duration from diagnosis, sex, education, manual or non-manual profession; having partial work disability impact on the probability of sick-leave, presenteeism, restriction in unpaid work and need for help for unpaid tasks.

These authors observe that 73% (80% in term of days) of cases of sick leave were associated with AS.

This means €1451 for friction costs AS-related (€1982 for men and €257 for women) and €967 as the cost of extra hours to compensate for inefficient work (€1078 for men and €717 for women).

Other studies have evaluated in detail direct medical costs for employed people with AS. Strombeck *et al*. (13) assessed the incremental cost for AS employees with respect to the general population, from a public payer perspective. The analysis is focused on AS patients aged <66 years in 2007, followed between 1993 and 2006, and living in Southern Sweden. The study involves 116 patients (97 men and 19 women), of these, during the 3-year follow up period, 25 were treated with TNF inhibitors.

Health care costs related with AS were $37095 *vs*. $11071 for no AS employees.

Splitting the costs, the authors calculate $3277 *vs*. $1023 on average of total direct costs for AS and no AS patient, respectively; $3277 *vs*. $1023 for inpatient care; $4299 *vs*. $1754, respectively for care delivered by physicians; $658 *vs*. $226 for physiotherapy; $8479 *vs*. $979 for pharmacological therapy. Sickness benefit and work disability amount to $5982 *vs*. $ 2131 and $13636 *vs*. $3774, respectively. In detail, anti TNF drug treatment amounts to $31859.

Reducing the variability of the costs (excluding the 5% of patients with the lowest and highest costs), Strombeck *et al*. (13) observe that the three-year total costs for AS and non AS employees shift from $37095 to $34876 *vs*. $11071 to $7427, respectively.

Comparing a subset of AS treated with TNF inhibitors with respect to not treated patients, these authors also show that the 3 year period costs for TNF drugs are about $31,859. However the sickness compensation and in general indirect costs (*e.g*. days lost, cost of sickness compensation *i.e*. disability pension) are lower for patients treated with TNF inhibitors. The 3-year total costs for treated patients (two times the 3-year costs associated non treated patients) mainly depend on drug costs.

As a general conclusion of their contribute, these authors claim that costs for the public payers associated with AS are about 3 times higher than the costs for the general population. They also attest that indirect costs are the most important driver of total costs.

Similar results were obtained in different countries by Torres *et al*. (17) and Zhu *et al*. (16).

Torres *et al*. (17) examined total annual direct and indirect costs related to Brazilian AS patients. In this study, direct and indirect costs per patient per year are $2065.15 and $2531.76, respectively. As observed, annual direct and indirect costs weight 45% and 55% of total costs, respectively. Similarly, Zhu *et al*. (16) affirm that the major cost driver is represented by indirect costs as of an annual total cost amounting to $9120 62% is represented by indirect costs.

The important impact of AS in terms of work disability, sick leave, and loss of productivity is underlined by Boonen *et al*. (4) comparing data from The Netherlands, France, and Belgium. The days of sick leave per working patient per year are higher in The Netherlands compared with France and Belgium (18.5 days *vs*. 6.0 and 9.2). Applying the *Friction Cost Method* to patients with paid work, the mean costs per patient per year are higher in The Netherlands versus France and Belgium, respectively €1257 *versus* €428 and €476. Considering the absence from paid work and productivity costs for all patients (The Netherlands: 130, France: 53, Belgium: 26), the days absent from paid work for all patients are 8.2, 4.5, and 5.3, respectively in The Netherlands, in France, and in Belgium. Friction costs for all patients are €557 in The Netherlands, €324 in France, and €274 in Belgium. The costs with *Human Capital Approach* amount to €8862 in The Netherlands, €3188 in France, and €3609 in Belgium. The study highlights the differences among the countries that may be attributed to different organisational systems of social security.

A recent study of Rafia *et al*. (11) evaluates the amount of healthcare resources consumed, productivity losses AS-related and the relationship between the severity of AS and total costs.

The study recruits 1000 AS patient from registries of Secondary Care Rheumatology in the UK through two postal questionnaires in the interval of three months. Direct costs AS related are due to medications, disease-modifying anti-rheumatic drugs and anti-TNF drugs, length of hospitalisations, outpatients and General Practitioner (GP) visits, physiotherapy and hydrotherapy treatments.

Over a three-month period, direct and indirect costs AS-related sum £1330.56 and £4839.70, respectively. Differences are observed when patients are subdivided on the basis of disease severity, in fact direct costs for patients with low and high severity of AS are £305.63 *vs*. £595.41, respectively.

With respect to indirect costs, the monetary quantification of productivity losses is £1,014.56 and £ 4148.05, for low and high severity.

The leitmotif shared by this article and the above analysed is that AS severity and non medical indirect costs play a fundamental role in the societal costs of AS in terms of productivity losses. Kobelt *et al*. (14) also observed an increase

of costs related to disease severity as measured with BASDAI and BASFI (Bath AS functional and disease activity indexes): costs increase from €4260 at BASFI of 1 to €78300 at BASFI of 10; and from €11600 at BASDAI of 1 to €18900 at BASDAI of 10. The authors estimate that the total annual costs per patient amount to €20328 of which 66.3% is represented by direct costs. The major direct costs are related with patients' out-of-pocket costs (investments and informal care), 43.5% of the direct costs.

The study of Ara *et al*. (10), which compares the direct healthcare costs subdividing the patients according to disease severity in moderate (BASDAI <4.0/ BASFI <4.0), severe (BASDAI 4.0-6.0/ BASFI 4.0-6.0), and very severe (BASDAI≥6.0)/BASFI ≥6.0), affirms that the annual cost per patient increases according to BASDAI and BASFI scores, and reports that in the very severe group the direct cost is much higher and is partly due to the increased need for physiotherapy. In this study costs range between £1072 and £3485 according to BASDAI, and between £1010 and £3544 according to BASFI.

Interestingly, when AS is compared with other rheumatic diseases (7, 8, 18), such as fibromyalgia (FM) and chronic low back pain (CLBP), direct medical costs are similar whereas direct non medical costs show important differences among diseases.

While direct AS related costs are lower than in FM, but higher than in CLBP, indirect costs associated to AS are lower than those in FM and in CLBP (7).

In the study of Verstappen *et al*. (8), mean total direct costs of AS are lower respect to rheumatoid arthritis costs. With respect to Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Systemic Lupus Erythematosus (SLE), AS presents the third higher direct costs but the lower indirect costs (18) and SLE occupies the first position for direct costs related to hospitalisations.

The evaluation of healthcare and non healthcare costs from patient's perspective shows another interesting aspect: overall mean total annual costs amount to €1795 per patient of which 76% is represented by income loss (5). The higher patient's cost is observed in The Netherlands compared with France and Belgium (€2172 *vs*. €1286 and €988). An interesting result is represented by the 1.25 hours consumed by the patient each day due to the disease.

Quality of life (QoL) represents another important outcome treated by Boonen *et al*. (5), Kobelt *et al*. (14), and Zhu *et al*. (16). In the study of Boonen *et al*. (5), the QoL evaluated with EuroQol questionnaire does not present differences between the countries but after adjusting for socio-demographic and disease characteristics it is worse in France and in Belgium than in The Netherlands. QoL is influenced by many factors such as lower education, presence of peripheral arthritis, worse physical function, and higher disease activity.

Similarly, a reduced QoL is shown by Kobelt *et al*. (14) and Zhu *et al*. (16), particularly in general health and vitality.

## Discussion and conclusions

As many other rheumatic diseases, AS has high medical and societal costs and the relative weight of AS related costs on the all cause related costs is extraordinary large (26-32).

Indirect costs associated with days of absence from work (and the relative productivity losses) are the most important determinant of total costs and are related with the high patients' functional limitations due to AS.

This fact may also partly explain the association between total costs and the severity of the disease.

Table I summarises the direct and indirect costs evaluated in different countries and periods (actualised at $2012) according to the consumer price index.

It has to be noted that different payments and reimbursement regimes may impact on the amount and distribution of indirect costs (31).

For instance, in the US system, characterised by a predominant private insurance reimbursement mechanism, indirect costs AS related result three times higher than direct costs. On the contrary, in those countries in which a public reimbursement regime prevails, direct and indirect costs are more comparable.

A possible explanation for these different results may reside in the capability of a country of actually measuring productivity losses and indirect costs, and of compensating those losses.

From a public payer point of view, low indirect costs without other indicators could be due to an underestimation of this cost dimension rather than being a sign of efficiency in AS care. As a consequence, indirect costs may be a net loss for patients that nobody can repay. On the contrary, a private insurance reimbursement regime can induce players to better define, select and actually identify indirect costs. Future studies and analysis are required to test this hypothesis as well as to evaluate in detail – and in an international comparative way – the burden of AS (33).

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