

EXTENDED REPORT

Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries

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Objective: To assess direct costs associated with ankylosing spondylitis (AS). To determine which variables, including country, predict costs.

Methods: 216 patients with AS from the Netherlands, France, and Belgium participated in a two year observational study and filled in bimonthly economic questionnaires. Disease related healthcare resource use was measured and direct costs were calculated from a societal perspective (true cost estimates) and from a financial perspective (country-specific tariffs). Predictors of costs were assessed using Cox's regression analysis.

Results: 209 patients provided sufficient data for cost analysis. Mean annual societal direct costs for each patient were €2640, of which 82% were direct healthcare costs. In univariate analysis costs were higher in the Netherlands than in Belgium, but this difference disappeared after adjusting for baseline differences in patients' characteristics among countries. Longer disease duration, lower education, worse physical function, and higher disease activity were predictors of costs. Mean annual direct costs from a financial perspective were €2122, €1402, and €941 per patient in the Netherlands, France, and Belgium, respectively. For each country, costs from a financial perspective were significantly lower than costs from a societal perspective.

Conclusion: Direct costs for AS are substantial in three European countries but not significantly different after adjusting for baseline characteristics among countries. Worse physical function and higher disease activity are important determinants of costs, suggesting better disease control might reduce the costs of AS. The difference in costs from a societal and financial perspective emphasises the importance of an economic analysis.

Cost of illness (COI) studies can contribute to a more complete understanding of the impact of a disease. The results can be used to identify which cost categories contribute most to the total costs of the disease, to explore determinants of costs, and to compare costs of different diseases. In addition, data can be imputed in cost-effectiveness or cost-utility models. In national policy making, results can be helpful to set priorities for research and treatment options.^{1–5} There is an increasing interest in international comparisons of healthcare expenditure, because it is recognised that the costs of a disease can vary importantly among countries. Apart from telling what is known about the costs of the disease, cross-country comparisons potentially allow assessment of a country's performance in containing costs. From a methodological point of view, international comparative studies can contribute to the formulation of methods of generalising cost studies from one country to another. Despite the growing attention on cost studies, in the rheumatic diseases also, few data exist on the direct costs of ankylosing spondylitis (AS).^{6,7} This is surprising because the disease occurs not infrequently, with an estimated prevalence varying from 0.08 to 0.8%,^{8,9} starts at early age (usually in the third decade), and has important consequences on physical function.^{10–13} In 1997 and 1998 we performed a prospective burden of illness study in AS in three countries: the Netherlands, France, and Belgium. These European countries share scientific standards in medical care and have comparable economic prosperity. There are, however, differences in the organisation of health care and in medical culture. We have already reported the productivity costs and the contribu-

tion of differences in social security systems to variation in these costs.¹⁴ Here, we compare the direct costs related to AS. Costs were calculated from the classic societal but also from the financial point of view. In the societal perspective, all costs are relevant, irrespective of who pays them, whereas in the financial perspective only the costs born by the official healthcare payer are relevant. In this international comparative study, the financial perspective allows an estimation of the economic burden of the disease for each country's healthcare payers. Finally, determinants of costs, including the country providing the care, were explored.

PATIENTS AND METHODS

Patients

Patients were obtained from the rheumatology departments of four hospitals in three countries, the University Hospital Maastricht and the Maasland Ziekenhuis Sittard in the Netherlands, L'Hôpital Universitaire Cochin Paris in France and the University Hospital Gent in Belgium. In Maastricht and Sittard, patients with the diagnosis AS according to the Dutch Standard Diagnostic Register were selected, while in

Abbreviations: ANOVA, analysis of variance; AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; COI, cost of illness; CT, computed tomography; DMARD, disease modifying antirheumatic drug; HR, hazard ratio; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis

Paris and Gent consecutive outpatients were included within an agreed and limited period of time. All patients had radiological sacroiliitis according to the modified New York criteria for AS. The hospitals of Maastricht, Paris, and Gent have a regional and referral (academic) function. Sittard is a regional hospital cooperating in research projects with the University Hospital Maastricht. Traditionally, in all three countries patients with a chronic rheumatic disease are referred to a rheumatologist. Patients were included between September 1996 and March 1997 and have been followed up for two years.

Questionnaires

At baseline and every six months patients underwent a clinical examination and completed questionnaires comprising (a) sociodemographics, including (changes in) professional and working status; (b) disease characteristics, including AS related comorbidity and AS-specific physical function measured by the Bath Ankylosing Spondylitis Functional Index (BASFI; range 0–10; higher values indicating worse function)¹⁰; and (c) an economic questionnaire asking about aids and appliances purchased, adaptations at home, spa treatments, and financial contributions to health related organisations in the past six months. Every two months patients completed the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), measuring AS-specific disease activity (range 0–10; higher values indicating higher disease activity),¹⁵ and an economic questionnaire asking about the number of visits to all kinds of healthcare providers, kinds and doses of drugs used, numbers and kinds of technical procedures performed, numbers of days of inpatient care, number of days absent from paid work, and number of weekly hours of formal and informal household care received because of AS in the past two months. The economic questionnaires concerned resource use or costs related to AS and were developed for this study, using examples from other cost studies in rheumatic disease as a guide.^{16–18} Because of the international character of the study, questionnaires were adapted for each country's language, educational system, national currency, and health insurance system. For the statistical analysis the educational level was dichotomised into more than 12 years formal education as opposed to 12 years or less. The presence of peripheral arthritis was defined as the presence at baseline of at least one swollen joint out of 44 possible joints (including the shoulders) assessed by the doctor,¹⁹ and inflammatory bowel disease (IBD) was defined as self reported presence at baseline of IBD for which a visit to the specialist had been necessary in the year preceding entry into the study.

Financing and organisation of health care

The three countries have had an obligatory health insurance system since the middle of the 20th century, reflecting essentially a Bismarkian model. Differences can be noted in the macroeconomic sources which finance health care (including patient out of pocket contributions), in remuneration of the healthcare providers, in the financing of hospital care, and in regulations for access to secondary care. These differences are described in Appendix 1 of the online version of this article.

AS related healthcare resource use

Direct healthcare resource use

Direct healthcare resource use because of AS, including the extraspinal manifestations, comprised (a) the number of visits to the general practitioner, specialist (rheumatologist and other specialists), alternative medicine practitioner, physiotherapist, and other paramedical care providers (rheumatology nurse practitioner, ergotherapist, social worker, or

psychotherapist); (b) the number of days of inpatient care (emergency department, hospital, and rehabilitation clinic); (c) the number of technical procedures performed (venal punctures, conventional radiographic examinations, and all other technical procedures, including computed tomography (CT) scan, magnetic resonance imaging, ultrasound, all types of endoscopies, joint aspirates, fundoscopic examinations, preoperative electrocardiograms, spirometry, etc); (d) all drugs taken in tablets per day and number of prescriptions purchased; (e) number and duration of spa treatments; (f) number and type of assistive devices; (g) number of adaptations at the house or at the work place; and (h) the weekly number of hours of formal home care. Because the questionnaires asked only about the number of venal punctures and number of radiographic sessions, without specifying which examinations were performed, we did a small additional investigation among the rheumatologists of the different participating centres to ask them about their routine practice when ordering specific laboratory tests or conventional radiographic examinations in different types of patients with AS (with and without extraspinal manifestations; with and without non-steroidal anti-inflammatory drug (NSAID) treatment; with and without disease modifying antirheumatic drug (DMARD) treatment). The country-specific practice was then used to specify the type of laboratory examinations for each venal puncture and the type of conventional radiographic films for each session.

Direct non-healthcare resource use

Direct non-healthcare resource use because of AS or its extraspinal manifestations included (a) number of times a swimming or exercise group was attended; (b) renewals of memberships to AS societies or healthcare providing organisations; (c) weekly number of hours of informal care by (paid) private household help or unpaid help from family or friends; and (d) kind of transport and distance to all healthcare providers (in- and outpatient).

At the start of the study patients were told verbally how to complete the economic questionnaire, especially how to distinguish between AS related and AS non-related resource use. Self reported healthcare resource use was not ascertained by comparison with other data sources.

Sources of costs

Costs were calculated first from a societal perspective and next from a financial perspective. In the societal perspective all cost categories are relevant to the total costs. In the financial perspective, only costs for a specific payer are relevant. For each perspective, the appropriate unit cost for each resource has to be determined.

When considering the *societal perspective*, the unit cost has to reflect the true cost of the resource. The market price is the best reflection of the true costs but is not available for most healthcare resources. It is well known that the tariffs (or charges) of most healthcare provisions (especially visits to healthcare providers, inpatient care, and technical procedures) are by no means a reflection of the true cost. In France and Belgium, calculations of true costs for healthcare provisions have been performed for only a very limited number of resources and were insufficient for our analysis. In the scope of our study, it was not feasible to perform true cost calculations for each single healthcare resource in each country. In the Netherlands, true costs of almost all resources were available and it was decided to apply these to the country-specific healthcare resource use. The costs were not converted to national values for the other countries by using healthcare purchasing parities because their validity is still insufficient.²⁰ Moreover, choosing this approach, the differences in costs among countries in the societal perspective

reflect differences in healthcare resource use among countries. In the Netherlands, the recent "Guidelines for Pharmacoeconomic evaluations"²¹ provide estimates of the true cost for a large number of healthcare provisions. The method for calculating the true cost includes immediately attributable (such as materials) and non-immediately attributable (such as overheads) cost components and uses national averages for the cost components. For admissions to hospital and visits to specialists separate calculations for peripheral and university hospitals were made. For technical procedures, however, the guideline refers still to the Dutch tariffs. Fortunately, the financial and economic department of the University Hospital Maastricht has performed true cost calculations for such procedures since 1997, which are updated yearly. Comparable to the cost accounting method in the Dutch guidelines, calculations include immediately attributable and non-immediately attributable cost components. True costs of alternative medicine were not available in the guideline, but were derived from a Dutch study on the costs of alternative medicine.²² For cost valuation of drugs, the patients had insufficiently reported the number of prescriptions purchased at the pharmacy (reflecting the true expenditures for drugs). Therefore, the number of prescriptions purchased was estimated from the daily doses of each drug recorded by the patient in the cost questionnaire. The official Dutch drug price was used to calculate the unit cost for each drug or tablet.^{23, 24} In addition, for each prescribed item (with a maximal prescription period of three months) an additional fee of €4.64 has to be paid to the pharmacists (prescription rule), which was included in the total costs of drugs. In the Netherlands, generic prescribing is stimulated by imposing a fixed maximal reimbursable price for each cluster of drugs (such as the cluster NSAIDs). The pharmacist is likely to provide the cheapest product within the cluster because he can keep the difference between the wholesale price and the reimbursable price. Therefore, in our analyses, we used the lowest cost price when multiple prices for drugs were available. For drugs prescribed in France and Belgium, we used the price of the Dutch generic drug, if the generic drug was marketed in the Netherlands. When a drug prescribed in France or Belgium was not available in the Netherlands, a substitute from a similar class of drugs was sought. For costs of spa therapy, aids and appliance or adaptations in the house and costs of private household, the costs mentioned by the patients in the questionnaires were used. If these were missing, we used the cost of a similar resource from a patient from the same country. Following the Dutch guideline, formal care was valued at €17.25 per hour and informal care at €7.95. Transport costs were valued at €0.11 per km (variable price per kilometre) for private or public transport and €1.30 per km for transport by taxi or special transport for chronically ill patients. Parking costs were valued at €1.14 per ticket.

When considering the *financial perspective*, a broad healthcare payer's point of view was chosen in order to provide the most complete estimate of the economic burden of the disease for the (national) healthcare payer. This included expenditures by health insurance companies, government, municipality, and special funds for patients with chronic diseases. The official country-specific tariffs²⁵⁻²⁸ or other sources if applicable and country-specific drug prices^{23, 24, 29, 30} were used. Tariffs or prices were corrected for patient out of pocket contributions. In the Netherlands, differences for some tariffs between the private and public insured patients were taken into account. Also, during the second year of the study, all patients in the Netherlands had an obligatory out of pocket contribution of the first €46.60 a year for use of medical resources included in the basic coverage packet which was therefore subtracted from the total cost if applicable. In the Netherlands and France, but not in Belgium, pharmacists are allowed to substitute a brand drug by the cheaper generic drug. In Belgium, several specific regulations for calculating the tariffs for some

technical procedures such as consultancy honoraria, fixed honoraria for each group of procedures (independent of the number of tests), and regulations concerning the possibility of combining procedures of a similar type had to be considered, as well as the maximum amount of copayment for drugs.

Costs within the two years' observation were averaged and the unit cost for the year 1998 was applied without discounting for the resource use in 1997. Where applicable, taxes were included. All costs were expressed in the euro currency of 31 December 31 1998. One euro was fixed to equal NLG 2.20, FF 6.56, and BEF 40.34. At the same date, €1.00 was worth \$1.17.

The sources of the unit cost for each resource for the societal and financial perspective among the countries are available in Appendix 2 of the online version of this article.

Statistical analyses

Results are analysed for patients who completed two years of follow up and filled out at least nine of the 12 bimonthly questionnaires. For missing values of healthcare resource use in these questionnaires, the mean of the completed questionnaires of the same patient was imputed. Demographic and disease characteristics are presented using descriptive statistics, and differences among countries are assessed by χ^2 for proportions and analysis of variance (ANOVA) for continuous variables. For healthcare resource use, firstly, the proportions of patients who had used this resource over the study period were assessed; next, the mean annual number of units of each particular resource was averaged over all patients; and finally, the annual costs for each resource were averaged over all patients. Because costs were skewed, medians and ranges are also presented to reflect the distribution of the costs. To compare unadjusted differences in healthcare use or costs among the three countries, univariate analyses were performed using χ^2 (for proportions of patients who had used that resource) or bootstrapping with 10 000 replications (for the number of resources or costs). Bootstraps were also performed to compare the costs from a societal and financial perspective within each country.³¹

To assess determinants of costs, Cox's proportional hazard regression analyses were performed with costs as dependent variable. Several sociodemographic and disease characteristics were chosen as independent variables: gender, age, disease duration since diagnosis, educational level (dichotomised into ≤ 12 years and > 12 years of formal education), presence of baseline peripheral arthritis, presence of baseline inflammatory bowel disease, baseline BASFI, baseline BASDAI, and country (dummy). Because our primary interest was to assess differences in costs among countries, the dummy variable country was entered in a first bloc and all other independent variables in a second bloc using a backward likelihood elimination technique. Interactions between the final variables of each model and the dummy country were sought by entering the main effects and the interaction terms simultaneously in the model. Interactions between IBD and France as the country could not be explored because none of the French patients had IBD. Cox's proportional hazard regression analysis is a semiparametric statistical method and was chosen because costs had a skewed distribution. Hazard ratios (HRs) > 1 indicate that high values of the independent variable are associated with a worse outcome (higher costs). An HR of 1.5 for a dichotomous variable refers to a 1.5 increase in (median) costs.

All regression analyses were repeated by eliminating patients with extreme values and by including and excluding patients with extraspinal disease. Sample size calculations were not computed before the start of the study, firstly, because no data on costs in AS were available to serve as a basis for the calculation and, secondly, because the aim of the study was primarily explorative. Moreover, the method used to calculate sample sizes in economic studies is much debated. Bootstraps were performed in Excel, and all other procedures in SPSS 9.0.

Table 1 Characteristics of patients completing the study

	Total (n=209)	The Netherlands (n=130)	France (n=53)	Belgium (n=26)
Male (%)	70	71	68	73
Age (years), mean (range)*	43.1 (18–77)	45.6 (23–77)	37.4 (19–67)	41.9 (18–74)
Education ≤12 years (%)*	72	83	48	65
Disease duration (years), mean (SD)	11.1 (8.9)	11.9 (9.2)	9.2 (7.4)	10.8 (10.3)
IBD (%)*	7	10	0	8
Peripheral arthritis (%)	25	29	26	9
BASFI baseline, mean (SD)*	3.3 (2.6)	3.9 (2.4)	2.5 (2.9)	2.6 (2.3)
BASDAI baseline, mean (SD)	3.3 (2.1)	3.7 (2.1)	2.8 (2.3)	3.1 (1.9)

*p Value for difference among countries <0.05 (tested by χ^2 for proportions and ANOVA for continuous variables).

IBD, inflammatory bowel disease; BASFI, Bath Ankylosing Spondylitis Functional Index (range 0–10, higher values indicating worse function); BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (range 0–10, higher values indicating higher disease activity).

RESULTS

Patients

In total 216 (135 Dutch, 54 French, and 27 Belgian) patients with AS fulfilled the modified New York criteria and started the study. In the course of the follow up five Dutch, one French and one Belgian patient dropped out. Table 1 presents, for each country separately, the sociodemographic characteristics of the 209 patients who completed the study. Comparison shows that Dutch patients were older, had on average a lower educational level, and reported worse physical function (BASFI). None of the French patients had concomitant inflammatory bowel disease. Of the Dutch patients, 77% had public insurance and 23% private. Of the French patients, 72% had 100% reimbursement of direct medical costs by the Sécurité Sociale. None of the Belgian patients had a special reimbursement status. To determine the national generalisability of the study group, the characteristics of the Dutch sample were compared with the characteristics of a large cross sectional national sample (n=658) from the same register³²; no differences were noted in sociodemographic and disease characteristics. For the French and Belgian patients no comparative national data were available from registers or published cross sectional studies. All patients who completed the follow up had filled out at least nine of the 12 questionnaires. The proportion of patients with a missing

bimonthly questionnaire was 84% and the proportion of missing (or incomplete) questionnaires was 10%. Of all missing questionnaires, 25% were missing at random because at a specific time, the bimonthly questionnaire was not presented to 62% of the patients because of an administrative error. Patients with one or more non-random missing questionnaire were more often younger and working men with a higher educational level, but their disease characteristics did not differ from those without a missing questionnaire.

Health resource use and costs

Table 2 presents the proportions of patients who had used a specific resource, the annual average number of units per patient used for each resource, and the associated annual societal costs in euros per patient. The average annual direct costs were €2640 (median €1242) per patient. Direct healthcare costs accounted for 82% of the total direct costs and direct non-healthcare costs for 18%. In decreasing order of importance, the largest contributors to the total direct costs were inpatient care (overall 27% (admissions to hospital 18%, visits to emergency department 8%, and costs of rehabilitation clinic 1%)), combined formal and informal care (22%), physiotherapy (13%), drugs (13%), and technical procedures (8%). Reasons for admission to hospital during the course of the study were active AS for 12 out of 28 patients admitted to

Table 2 Annual healthcare resource use and costs (euros) per patient (n=209)

Type of resource (category)	% Patients*	Annual units per patient		Annual societal costs per patient (€)		% Of mean costs
		Mean [median]	Mean (SD)	Median (range)		
General practitioner	64	1.9 [0.5] visits	32 (57)	9 [0–469]	1.2	
Specialists	77	2.7 [1.1] visits	186 (240)	105 [0–1832]	7.0	
Physiotherapy†	60	19.1 [6.25] visits	350 (496)	116 [0–2585]	13.2	
Other healthcare providers‡	21	0.4 [0] visits	21 (68)	0 [0–596]	0.8	
Drugs	95	1.4 [1] kind of drugs	331 (376)	206 [0–2390]	12.5	
Inpatient care§	24	2.3 [0] days	701 (2561)	0 [0–23671]	26.6	
Technical examinations	90	5.8 [3.6] examinations	200 (423)	53 [0–4484]	7.6	
Aids and adaptations	19	0.19 [0] aids	133 (746)	0 [0–9863]	5.0	
Formal home care	4	12.6 [75.1] hours	218 (1280)	0 [0–14369]	8.3	
All direct healthcare costs (€)			2172 (3598)	1002 (0–27531) (CI 729 to 2658)**	82	
Swimming and exercise group¶	56	12.0 [3.3] sessions				
Financial contributions to societies	65		41 (47)	14.88 [0–132]	1.5	
Informal household help	14	44.32 [0] hours	353 (1476)	0 [0–14891]	13.4	
Transportation	100	530 [196] km	74 (110)	32.03 [0–763.51]	2.8	
All direct non-healthcare costs (€)			468 (1490)	104 (0–14965) (CI 292 to 659)**	18	
Total direct costs (€)			2640 (4305)	1242 (5–32393) (CI 2105 to 3263)**	100	

*Proportion of patients in the course of the two years of the study; †includes also the costs of spa treatment for two French patients and one Dutch patient; ‡includes visits to rheumatology nurse, social worker, and psychotherapist; §includes admissions to hospital, attendance at emergency department, and (day care) admissions to rehabilitation day clinic; ¶the costs for attending swimming and exercise groups are included in the financial contributions to patient societies; **CI assessed by 95% method of 10 000 bootstrapped replications.

Table 3 Comparison among countries of the annual healthcare resource use and annual societal costs per patient

Resource categories	Annual health resource use per patient; mean [median]			Annual costs in € per patient; mean [median] (% of total)		
	The Netherlands (n=130)	France (n=53)	Belgium (n=26)	The Netherlands	France	Belgium
General practitioner†	1.4 [0.5] visits	2.2 [1.0] visits	4.0 [1.1] visits	23 [42] (0.8%)	36 [51] (1.5%)	66 [106] (4%)
All specialists	2.6 [1.5] visits	2.6 [1.0] visits	3.3 [2.7] visits	181 [105] (6.4%)	181 [70] (7%)	219 [189] (12%)
Rheumatologist‡	1.7 [1] visits	1.6 [0.5] visits	2.6 [2.4] visits	118 [76] (4%)	114 [34] (4%)	184 [168] (10%)
Physiotherapist§	18.3 [6.5] visits	17.4 [4.4] visits	26.6 [14.3] visits	330 [116] (12%)	338 [85] (13%)	472 [254] (26%)
Other care providers††	0.4 [0] visits	0.6 [0] visits	0.1 [0] visits	22 [0] (0.8%)	28 [0] (1%)	3 [0] (0.2%)
Drugs*‡	1.2 [1] kind of drugs	2.0 [2] kind of drugs	1.4 [1] kind of drugs	282 [151] (10%)	465 [371] (18%)	306 [229] (17%)
Technical procedures	4.5 [2.7] examinations	4.1 [2.5] examinations	4.6 [5.6] examinations	204 [45] (7%)	152 [53] (6%)	278 [114] (16%)
Inpatient care¶†	2.6 [0] days	2.7 [0] days	0.3 [0] days	800 [0] (28%)	759 [0] (30%)	85 [0] (4.7%)
Aids and adaptations*†	0.3 aids	0.1 aids	0.02 aids	199 [0] (7%)	37 [0] (1%)	4 [0] (0.2%)
Formal home care	17.1 [0] hours	3.9 [0] hours	8.0 [0] hours	295 [0] (10%)	68 [0] (3%)	218 [0] (12%)
All healthcare costs (€)				2335 [1025] (82%) (CI 1774 to 2962)**	2064 [983] (80%) (CI 1120 to 3405)**	1572 [1122] (88%) (CI 1084 to 2200)**
Swim and exercise group	16 [4.8] sessions	6 [1] sessions	5 [0.75] sessions			
Contributions*††				51 [0] (2%)	14 [0] (0.5%)	6.0 [0] (0.3%)
Informal household care	46 [0] hours	54 [0] hours	14 [0] hours	369 [0] (13%)	429 [0] (17%)	111.0 [0] (6%)
Transportation	528 [175] km	451 [96] km	777 [407] km	74 [31] (7%)	62 [24] (2%)	101 [57] (6%)
All non-healthcare costs† (€)				502 [131] (18%) (CI 314 to 760)**	506 [62] (20%) (CI 101 to 1187)**	218 [63] (12%) (CI 72 to 405)**
Total direct costs† (€)				2837 [1267] (100%) (CI 2200 to 3506)**	2570 [1078] (100%) (CI 1262 to 4415)**	1790 [1161] (100%) (CI 1140 to 2572)**

*Bootstrapped difference between the Netherlands and France statistically significant; †bootstrapped difference between the Netherlands and Belgium statistically significant; ‡bootstrapped difference between France and Belgium statistically significant; §includes costs of spa therapy for one Dutch patient and two French patients; ¶includes admissions to hospital, attendance at emergency department and (day care) admissions to rehabilitation day clinic; **confidence interval (CI) assessed by 95% method of 10 000 bootstrapped replications.

hospital, arthroscopy or joint replacement for six patients, active IBD for eight patients, IBD related bowel surgery in one patient and AS related cataract surgery in one patient. In addition, one patient was admitted to a rehabilitation hospital because of paraplegia after spinal fracture.

Table 3 illustrates the differences in resource use and costs among countries, and table 4 provides details on the use of the different kinds of drugs among the countries. In univariate analysis, bootstrap showed that the societal direct non-healthcare costs and total direct costs were higher in the Netherlands than in Belgium. There were clear differences among countries for several subcategories of costs, reaching statistical significance for costs of visits to general practitioners, rheumatologists, visits to other care providers, drugs, inpatient care, aids and appliances, and financial contributions to patient societies. Resource use of all outpatient care combined (visits to all care providers and technical procedures) and associated costs were higher in the Belgian patients (€1038 per patient per year compared with €738 and €737 in the Netherlands and France, respectively), but this difference was offset by lower costs of inpatient care in the Belgian patients. In contrast with both other countries (day care), rehabilitation facilities, included in the category inpatient care, are not available in Belgium for patients with

AS. French patients had remarkably higher drug costs. This could be explained by an overall higher use of drugs, especially of painkillers and (more expensive) gastroprotective drugs (table 4). Also, a large proportion of patients were prescribed a particular NSAID (meloxicam) that was relatively new at the time of the study and more expensive (no generic substitute) than the regularly prescribed drugs. Of all patients regularly using an NSAID, 32% of French patients used meloxicam compared with 14% and 9% of Dutch and Belgian patients, respectively. Costs for aids and adaptations and for contributions to patient societies were significantly higher in the Netherlands than in both other countries.

When interpreting the costs from a financial perspective (table 5), it is clear that some cost categories disappear from the analyses because no external payer exists. For all countries, costs from a financial perspective were significantly lower than costs from a societal perspective. For several cost categories the ranking of the countries for a particular cost category changed. For example, costs of visits to the specialists and the physiotherapists were highest for Belgium in the societal perspective while they were the lowest in the financial perspective. Drug cost in the financial perspective for Belgium were significantly lower than in the societal perspective. This discrepancy can be explained mainly by the large patient contribution for drugs in that country.

Determinants of costs

Table 6 presents the determinants of the total direct costs from a societal perspective. After adjusting for baseline variables, there were no longer any significant differences in the total direct societal costs among the countries. Patients with longer disease duration, lower educational level, worse physical function, and higher disease activity had higher costs. In addition, societal costs tended to be somewhat higher for female patients, who incurred €3439 (median €1522) direct societal costs compared with €2318 (median €1126) for male patients. This could be attributed entirely to the higher costs of formal

Table 4 Proportion of patient using drugs at baseline

	The Netherlands (%)	France (%)	Belgium (%)	p Value*
Analgesics	9	25	7	0.03
NSAIDs	75	89	85	0.6
DMARDs	6	21	33	<0.0001
Gastroprotective drugs	14	38	7	0.003
Corticosteroids	0.75	4	2	0.08
Treatment for uveitis†	6	15	4	0.03

*p Value for overall difference among the countries assessed by χ^2 ; †proportion of patients treated for uveitis in the course of the study.

Table 5 Comparison among countries of annual costs in euros per patient from a financial point of view

	The Netherlands; €/pt/yr: Mean [median] (% of costs)	France; €/pt/yr: Mean [median] (% of costs)	Belgium; €/pt/yr: Mean [median] (% of costs)
General practitioner*†	19 [18] (0.8%)	36 [17] (2.5%)	43 [12] (5%)
All specialists	59 [48] (3%)	55 [23] (4%)	45 [35] (5%)
Rheumatologists†	47 [49] (2%)	36 [11] (2.5%)	34 [31] (2%)
Physiotherapy§	326 [116] (15%)	383 [109] (27%)	305 [164] (19%)
Other care providers	0.21 [0] (-)	7 [0] (1%)	1 [0] (0.1%)
Drugs*‡	282 [150] (13%)	416 [374] (30%)	217 [168] (23%)
All technical examinations	159 [80] (8%)	114 [46] (8%)	139 [90] (8%)
Inpatient care¶††	836 [0] (39%)	362 [0] (26%)	57 [0] (6%)
Aids and adaptations*†	135 [0] (6%)	12 [0] (0.8%)	4 [0] (0.5%)
Formal care*	339 [0] (16%)	16 [0] (1%)	131 [0] (14%)
Transportation*‡‡	13 [0] (0.2%)	2 [0] (0.2%)	0 [0] (-)
Total direct costs† (€)	2122 [747] (95% CI 1545 to 2772) (100%)	1402 [989] (95% CI 952 to 1969) (100%)	941 [631] (95% CI 591 to 1390) (100%)

*Bootstrapped difference between the Netherlands and France statistically significant; †bootstrapped difference between the Netherlands and Belgium statistically significant; ‡bootstrapped difference between France and Belgium statistically significant; §includes costs of spa therapy for one Dutch patient and two French patients; ¶includes admissions to hospital, attendance at emergency department and admissions to rehabilitation day clinic.

and informal home care ($p < 0.0001$) and for aids and adaptations ($p = 0.04$) for female patients. This was seen in all countries. For all other cost categories, female patients tended to have lower healthcare resource use and costs, despite similar disease characteristics as male patients.

In patients with a lower educational level (≤ 12 years) total direct costs were €2830 (median €1152) compared with 2146 (median €942) in those with a higher educational level. Resource use and costs were higher for all cost categories in patients with a lower educational level. In univariate analysis this was significant for costs for physiotherapy ($p = 0.002$), costs for "other" healthcare providers (including rheumatology nurse, psychotherapist, and social worker) ($p = 0.04$), all non-healthcare costs ($p = 0.001$), and almost significant for costs of aids and adaptations ($p = 0.09$).

Although patients with lower educational level had a similar incidence of extraspinal disease manifestations as patients with a higher educational level, they reported worse physical function (BASFI 3.81 v 2.07; $p < 0.0001$) and higher disease activity (BASDAI 3.63 v 2.47; $p < 0.0001$). Disease activity at entry into the study was the most important predictor of direct societal costs. Patients with a baseline BASDAI lower than four incurred €1468 (median €1053) societal costs as opposed to €4722 (median €2513) in patients with baseline BASDAI equal to or higher than four. Extraspinal disease manifestations were no independent predictors of direct costs, but their effect was fully explained by higher disease activity and worse physical function. Total annual direct societal costs per patient in those without extraspinal disease was €1798 (median €1063) compared with €4499 (median €1971) in those with extraspinal disease. Detailed differences in costs between male and female patients, patients with low or high

education, patients with low and high disease activity, and patients with and without extraspinal manifestations can be seen in Appendix 3 of the online version of the article.

No interactions between country and the other determinants of the final model could be detected, indicating that all determinants act similarly in each country separately. When repeating the analyses after exclusion of five patients (three Dutch and two French patients) with extreme high costs, the results of the regression models did not change.

Interestingly, determinants of costs from a financial perspective were somewhat different. Female gender did not contribute to this model, reflecting the fact that the costs for (in-)formal care are mainly paid out of pocket by the patients. Higher age (HR=1.01; 95% CI 1.01 to 1.03), lower educational level (HR=1.78; 95% CI 1.29 to 2.56), poor physical function (BASFI) (HR=1.09; 95% CI 1.01 to 1.18), and high disease activity (BASDAI) (HR=1.14; 95% CI 1.03 to 1.25) remained associated with higher costs from a financial perspective. In addition, IBD (HR=1.89; 95% CI 1.09 to 3.23) was associated with higher costs. Total direct healthcare costs (financial perspective) in patients with extraspinal disease manifestations were €3027 per patient per year (median €1340) as opposed to €1237 (median €561) for patients without extraspinal disease. It is important to note that for all the subcategories of costs the differences among the countries observed in univariate analyses did not change significantly in the multivariate analyses. No interactions between country and the other determinants of the explanatory model were detected.

A separate regression was performed with costs of drugs as outcome. Also in multivariate analyses drug costs remained significantly higher in France (HR=2.38; 95% CI 1.69 to 4.00) and Belgium (HR=1.89; 95% CI 1.16 to 3.12) than in the

Table 6 Determinants of total direct annual costs from societal perspective assessed by Cox's regression analysis

	HR (95% CI)*	p Value
France as opposed to the Netherlands	0.99 (0.68 to 1.47)	0.75
Belgium as opposed to the Netherlands	0.93 (0.56 to 1.52)	0.77
Belgium as opposed to France	0.93 (0.54 to 1.56)	0.77
Female gender	1.33 (0.09 to 1.85)	0.09
Disease duration in years	1.03 (1.02 to 1.05)	0.002
Education (≤ 12 years)	1.49 (1.04 to 2.17)	0.03
BASFI baseline	1.10 (1.01 to 1.19)	0.03
BASDAI baseline	1.27 (1.12 to 1.41)	<0.0001

*HRs <1 indicate higher costs.
BASFI, Bath Ankylosing Spondylitis Functional Index (range 0–10, higher values indicating worse function);
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (range 0–10, higher values indicating higher disease activity).

Netherlands. Not surprisingly, longer disease duration (HR=1.02; 95% CI 1.01 to 1.04), presence of IBD (HR=4.67; 95% CI 2.50 to 9.01), peripheral arthritis (HR=1.49; 95% CI 1.03 to 2.17), and higher disease activity (BASDAI) (HR=1.15; 95% CI 1.06 to 1.25) contributed to higher drug costs. The analyses for drug costs from a financial perspective provided comparable results (not shown separately).

Comparison with national expenditure

Accepting in the population of the three countries a minimal point prevalence of patients with AS who are under the supervision of a rheumatologist of 0.08% in each country³³ and population sizes of 15.5 million for the Netherlands, 57.4 million for France, and 10.2 million for Belgium,³⁴ then the number of patients with AS in each country would be 11 250 patients in the Netherlands, 43 062 in France, and 7646 in Belgium. Assuming that the cross sectional study sample would be representative for the national group of patients with AS, the total annual expenditures would be €23.88 million in the Netherlands, €60.38 million in France, and €7.20 million in Belgium. This represents 0.83‰, 0.51‰, and 0.39‰ of the total national expenditure on healthcare for the Netherlands, France, and Belgium, respectively. In 1998 the proportion of the gross national product spent on healthcare was 8.6% in the Netherlands, 9.6% in France, and 8.8% in Belgium and the annual healthcare expenditures per capita €1840 in the Netherlands, €2036 in France, and €1826 in Belgium.³⁵

The differences among the countries in healthcare consumption for subcategories of costs among patients could also be seen at a national level. According to the OECD figures in 1996 the annual number of doctor visits in the Netherlands was 5.7 per inhabitant, compared with 6.5 per inhabitant in France, and 8.0 in Belgium. In 1998 the mean annual days of inpatient care were 3.6 per inhabitant in the Netherlands, 2.5 in France, and 2.1 in Belgium. The availability of CT scans in 1993 (no other comparative data on national availability of technical procedures could be found) was 9.0 per million inhabitants in the Netherlands, 7.5 per million in France, and 16.0 per million in Belgium. Total expenditure for drugs in 1996 was €198 per inhabitant (30% of the volume of generic prescribing) in the Netherlands and €361 per inhabitant (3% of the volume of generic prescribing) in France (figure for Belgium not available).³⁵

DISCUSSION

In this prospective COI study of prevalent direct costs related to AS in three European countries, we calculated costs from a societal and financial perspective. The mean annual societal direct costs were €2640 (median €1242) per patient. Inpatient care was the most important cost driver, being 27% of the total direct costs. Remarkable was the high contribution of costs for physiotherapy (13%) and costs for formal and informal home care (22%) to the total direct costs, reflecting the importance of exercise in the treatment of this disease but also the important disability in performing activities of daily living. For several (sub-)categories of costs, there were interesting differences among the countries. Costs for ambulatory medical care, including visits to general practitioners, specialists, and physiotherapists, as well as costs of technical procedures were substantially higher in Belgium. The higher costs of drugs in France can partly be explained by the higher proportion of patients who receive (more expensive) gastro-protective and disease modifying drugs and partly because the majority of patients were prescribed a relatively new and more expensive NSAID (meloxicam). For the Netherlands, the high participation in group exercise organised by the patient society, the high costs for aids and appliances, and the higher use of formal and informal care combined is striking.

The differences we noted in our study reflect partly the national differences in healthcare use. In Belgium the number of visits to healthcare providers and the availability of medical technical procedures is higher than in both other countries, the Netherlands have a high number of days in hospital for each inhabitant, and in France the national expenditure on drugs per capita is high.³⁵ Explaining differences among countries remains controversial but cannot be attributed to the design of the present study. The care oriented healthcare, the gatekeeper role of the general practitioner, and a more important fraction of payment on capitation basis in the Netherlands compared with cure orientation, unlimited access to healthcare, and fee for service payment system in both other countries, all contribute to the observed differences. The design of this study does not allow the differences among the systems (for example, a comparison of outpatient and inpatient care) to be related to the relative effectiveness of the systems.

Whereas the societal perspective reflects accurately the true economic burden of the illness to the society, the financial perspective provides additional information on the costs for a specific payer, in our case the official national healthcare payers. To our knowledge, this COI study is the first to compare the societal and financial perspective in patients with rheumatic diseases. Within each country, the costs from a financial perspective were significantly lower than from a societal perspective. This illustrates the importance of the choice of perspective and use of the appropriate unit costs in cost studies. Interestingly, for several cost categories the ranking of countries according to the magnitude of the costs changed when comparing costs from a societal perspective as opposed to a financial perspective. Differences between true costs and tariffs, but also the level of patient out of pocket costs (such as specifically in the Belgian patients), explain the differences in costs from both perspectives. Projecting the costs from financial perspective to the national health expenditures showed that 0.83‰, 0.51‰, and 0.39‰ of the total healthcare budget in 1998 was spent by the official healthcare payer on AS in the Netherlands, France, and Belgium, respectively. It would have been interesting to know the distribution of the national healthcare budget over different diseases (including musculoskeletal diseases), but this information was only available for the Netherlands (6% for musculoskeletal diseases).

Longer disease duration, worse physical function, and higher disease activity, but also lower educational level, were determinants of higher total direct costs from a societal perspective. In addition, female gender tended to be associated with higher costs, but this could be entirely attributed to the higher costs for formal and informal care and costs for aids and adaptations. Worse health status, despite comparable severity of disease among patients from lower social classes, was seen in other rheumatic diseases.³⁶⁻⁴² Differences in health perception and coping styles are advocated as contributors to healthcare use but were not examined during the collection of data on costs. Disease activity at baseline was the most important predictor of direct societal costs. Considering the new treatment options of AS by biological agents, it will be important to know if the beneficial effect of these treatments on disease activity and function will reduce the lifetime patient costs and provide acceptable cost-effectiveness and cost-utility ratios.

Previously we published the productivity costs by the human capital approach as well as by the friction cost method in these patients.⁴³ Using the human capital approach (€6812 per patient per year; median €90), the total mean annual costs of AS amount to €9452 per patient per year and the indirect costs would be 72% of the total costs. Using the friction cost method (€465 per patient per year; median €0), the total mean annual costs would be €3105 per patient per year, 16% of which due to indirect costs. Although the human capital

approach may overestimate the true societal costs, this method more accurately reflects the economic burden of disease because not only sick leave but also chronic work disability is captured in a monetary value.⁴⁴

We found two reported COI studies in AS.^{6,7} In a retrospective prevalence based study among 172 French patients with AS, annual AS related mean direct healthcare costs for the years 1978 and 1979 were €2686 per patient per year (adjusted to 1998 values using the consumer price index and expressed in euros using 31 December 1998 currency) compared with the €2064 per patient per year in the present French study. Although comparison should be made cautiously, the decrease over time in the average number of days in hospital, which dropped from six days per patient per year in 1978 to 2.7 days in the present cohort, may explain this difference.⁶ A recent publication on a prospective study in 241 American patients with AS, reported mean annual direct AS related costs of €1493 (median €951) per patient (converted using 31 December 1998 currency).⁷ Indirect costs assessed by the human capital approach amount to 47% and 74% of the total AS related costs in the French and American study, respectively, compared with 72% of total costs in our COI study. The French study used disability benefits (and not true societal costs) as the basis on which to calculate the productivity costs, whereas in the American study and in our study the premorbid income (reflecting the true societal production loss) was estimated to value production loss. Both, the French and American study confirmed that worse physical function was associated with higher costs.

In a systematic review, Cooper reported the results of 16 prevalent COI studies in rheumatoid arthritis (RA) and costs were adjusted by using 1996 consumer price indices.⁴⁵ Twelve studies in the review provided data on direct costs and, together with two more recent reports,^{38,46} showed mean annual direct costs per patient ranging from €1626 to €6155, with costs higher than €9832 in one publication. Results of our study in AS fall in the lower range of costs reported for RA. In addition to direct costs, six COI studies in RA reported productivity costs, assessed by the human capital approach.^{45,46} Productivity costs contributed 30–66% to the total costs, compared with 72–74% in AS. Comparability of COI studies is limited, because economic evaluations still lack standardisation, especially in the methods used to collect data on resource use, and methods used to assess the costs of each resource, methods used to analyse and report costs, and methods used to adjust for differential timing of the studies. It should be realised that all these studies assessed the prevalent costs of illness. Because AS usually starts at an earlier age than RA, the lifetime costs of AS may well be higher than those of RA. To estimate the lifetime costs of AS, it will be necessary to assess the incidence costs of the disease (including the costs of the diagnostic phase as measured in an inception cohort).

Our study has several limitations. Patient samples were obtained from hospitals and not the community. Therefore, costs are representative for patients followed up by a hospital based rheumatologist. Also, rheumatologists in the three participating centres have an academic affiliation. Possibly, differences in provision of medical care are greater among rheumatologists in peripheral care centres or private practice, where market considerations have a more important role. In addition, Dutch patients were sampled from a register while in both other countries consecutive outpatients were included. It is unlikely that this explains the higher costs in the Netherlands because it was shown that register based samples usually have less severe disease,⁴⁷ whereas our Dutch patients had worse physical function and higher disease activity. For the Dutch patients we were able to show that this subgroup was representative for the national group of patients with AS under the care of a rheumatologist, but for the French and Belgian patients with AS no national data were available.

Furthermore, data were collected through bimonthly (for resources frequently used) and biannual (for resources used less often) questionnaires, but were not ascertained by other data sources. In health economics no validation studies have yet been performed to validate the acceptable recall period for healthcare use in economic questionnaires.⁴⁸ Missing values for resource use in the bimonthly economic questionnaires were replaced by the mean of the other values for the same patient, but no sensitivity analyses with other methods have been performed. Only AS related costs were calculated. Therefore, no conclusions can be drawn about the degree to which these costs are additional to healthcare costs of an age and gender adjusted population without chronic disease. Ward showed in the American study that for 50% of patients, direct costs attributed to AS accounted for 90% of all-cause direct costs and for 66% of patients, direct costs attributed to AS accounted for 75% of all-cause direct costs.⁷

Another methodological choice of our analysis is that resource use of two observation years was averaged and valued with costs of the second observation year without discounting. However, over two years no important changes in prices or tariffs occurred.

Most importantly, our study comprised only 209 patients, with, especially in the Belgian group, only a small number of patients. Feasibility and methodology of sample size calculations in economic analyses are debated. Important arguments for the validity of the study results are that (a) the three study groups seem to be a reliable sample of what might be expected in samples of patients with AS and that (b) differences in reported healthcare resource use among the countries reflect the national differences in resource use. A major problem for the international comparison, was the absence of true costs for healthcare resources, which are required to calculate the societal perspective. We turned this problem into an advantage by applying the Dutch true unit costs, to the country-specific healthcare resource use. This allowed us to compare directly healthcare resource use. Of course, we should be careful in stating that the societal costs as calculated for France and Belgium reflect the true societal costs. Not only differences in local practice patterns but also differences in wages for healthcare providers and differences in capital for healthcare (overhead) would cause differences in true costs. However, it is not likely that these would differ greatly among three European countries with comparable economic prosperity.

Only a few studies have compared resource use and direct costs of rheumatic diseases among countries. For 752 patients with systemic lupus erythematosus from the United Kingdom, Canada, and America significant differences in several cost categories were observed, but not in the overall direct costs.^{49,50}

In conclusion, direct costs due to AS are considerable from a societal and financial perspective and the cost of hospitalisation is the major cost driver. Prevalent societal costs fall within the range of costs reported for RA, but lifetime costs of AS may well be higher than those of RA because of the usual earlier age at onset of the disease. High disease activity is a strong determinant of costs. Among three European countries, there are differences in several categories of costs. The higher discrepancy between direct costs from a societal and financial perspective in Belgium suggests higher patient contributions in this country.

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Three appendices can be found on the website at <http://www.annrheumdis.com/supplemental>

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Appendix 1

Financing and organisation of healthcare in The Netherlands, France and Belgium.

The three countries have an obligatory health insurance system since the middle of the 20th century, reflecting essentially a Bismarkian model.

In The Netherlands, chronic in-patient care (elderly, psychiatric patients and handicapped) is financed through taxes and amounts to 10.25% of the gross wage of employees (AWBZ). Ambulatory and acute in-patient care is financed through premiums to health insurance companies. For people with a lower income, a public insurance system exists. These premiums are 7.4% of the gross wage (5.85% paid by the employer and 1.55% by the employee). People with a higher income, have a private insurance with higher premiums. The Dutch law obliges the many competing health insurance companies to guarantee a basic insurance package against a uniform premium (approximately € 1,036 per year for one individual). In the Netherlands, two thirds of the population are public insured and one third private. For provisions included in the basic insurance package there is no or minimal patient contribution for public as well as for privately insured patients. For healthcare provisions not reimbursed, reinsurance is possible for all subjects through an additional (private) insurance. Premiums, risks covered and level of coverage differ greatly among kind of insurance chosen and among the health insurance companies. Approximately 90% of Dutch subjects have some kind of additional health insurance. Patients with chronic diseases may have to pay higher premiums for this additional (re-)insurance. In general, the healthcare providers are paid directly by the health insurance companies and patients have no direct payments. Healthcare providers working in academic hospitals are usually paid through salaries. General practitioners and non-academic physicians are paid on a capitation basis for the public insured patients and on fee per service basis for private insured patients. Physiotherapists working in the ambulatory sector are paid per service. All other healthcare providers are salaried. Historically, in The Netherlands there is a strong primary care organisation acting as gatekeeper towards access to secondary and tertiary care.

In France, healthcare costs as well as sickness and work disability benefits are paid by the Sécurité Sociale (SS), which is financed through social contributions by employers and employees. The social

contribution equals 19.6% of the employee's gross wage (12.8% paid by the employer and 6.8% by the employee) but these include contributions to pay for sick leave and work disability. Patient contributions for healthcare are substantial and can be as high as 40% of the total costs. Therefore, 80% of French patients have an additional private health insurance at one of the many competing insurance companies. Premiums, risks covered and level of coverage of the risks differ greatly among kinds of insurance chosen and among the health insurance companies. Patients with a chronic disease may have to pay higher premiums for the additional private health insurance. On the other hand, some patients with a chronic disease (among which severe AS) can be exempted from out-of-pocket contributions imposed by the SS and disease related healthcare costs will be fully reimbursed. Physicians and other healthcare providers working in academic hospitals are salaried. General practitioners, non-academic physicians and physiotherapists are paid on a fee per service basis. Patients pay their own contribution directly (ticket modérateur) to the healthcare provider. In contrast to the situation in The Netherlands, access to specialist care is not limited by the gatekeeper role of primary care.

In Belgium, healthcare provisions are mainly paid by a limited number of health insurance companies which are financed partly by social contributions (7.35% of the gross wage; 3.55% by the employer and 3.80% by the employee) and a (small) premium by the members. In addition, there are important patient contributions which are maximised. For elderly, severely handicapped, widows without income and orphans the level of patient's contribution is lower. Possibilities for reinsurance for patient contribution are limited to the costs of hospitalisation. Physicians and other healthcare providers working in academic hospitals are salaried. General practitioners, non-academic physicians and physiotherapists are paid on a fee for service basis. Depending on the service consumed, patients pay only the personal contribution (technical procedures and drugs) or pay the whole amount and are reimbursed afterwards (physician visits). Access to specialist care is not limited by the gatekeeper role of the general practitioner.

Table 1 Financing of healthcare at macro-economic level

	The Netherlands	France	Belgium
Social contributions from taxes	4.80%	5.90%	34.80%
Public health insurance premiums	73.80%	66.40%	40.60%
Private health insurance premiums	14.10%	9.10%	5.80%
Patient contribution	7.30%	17.00%	17.90%
Other sources	0.00%	0.80%	1.00%

Appendix 2: Sources of the unit costs for resources used, separate for the societal and the financial perspective.

Societal perspective All countries		Financial perspective		
		Netherlands*	France	Belgium
Direct healthcare costs				
Physicians visits	DGPES	National tariff (private or public insured)	Country specific national tariff (exclusive patient contribution)	
Other care providers	DGPES	National tariff (private or public insured)	Country-specific national tariff (exclusive patient contribution)	
Alternative medicine	Dutch study on mean costs	National tariff specialist (private or public insured)	National tariff (specialist)	National tariff (GP)
Drugs	Dutch market price + delivery fee	Market price & delivery fee	Country price (exclusive patient contribution)	
Technical procedures	True cost estimation by University Hospital Maastricht	National tariff	Country-specific national tariff (exclusive patient contribution)	
In-patient care	DGPES	National tariff (exclusive pt contribution of € 3.6/day)	Country-specific national tariff (exclusive patient contribution)	
Family help	DGPES	Country-specific reimbursement by home-help organisation		
Aids and appliances	Dutch market price	Mean tariff different insurers	National tariff	
Adaptations at house	Dutch market price	Country-specific reimbursement by country-specific authorised organisation.		
Spa treatment	Market price	Mean tariff insurers	Mean tariff insurers	No external payer
Direct non-healthcare costs				
Private household help	DGPES	Personal budget (if applicable)	No external payer	No external payer
Informal help	DGPES	No external payer	No external payer	No external payer
Transport	DGPES	Reimbursement by insurer	Reimbursement by insurer	No external payer
Contributions care organisations	Market price	No external payer	No external payer	No external payer
Swim- & exercise-group	Market price	No external payer	No external payer	No external payer
Adaptations work-place	Market price	Employer	employer	No external payer

DGPES: Dutch guideline pharmacoeconomic studies

Appendix 3: Differences in costs among several subgroups of patients.

Table 1: Societal costs stratified by gender.

	Female patients (=62)	Male patients (n=147)
	€/pt/yr: Mean [median]	€/pt/yr: Mean [median]
General practitioner	28 [9]	33 [9]
Specialist	172 [95]	193 [115]
Physiotherapy	434 [421]	317 [77]
Other care providers	33 [0]	16 [0]
Medication	352 [226]	325 [192]
In-patient care	395 [0]	835 [0]
Technical examinations	166 [60]	216 [52]
Aids and adaptations	287 [0]	70 [0]
Formal home care	464 [0]	166 [[0]
Direct healthcare costs	2,329 [1,172]	2,121 [978]
Contributions	45 [0]	40 [12]
Informal care	994 [0]	82 [0]
Transport costs	71 [23]	76 [38]
Direct non-healthcare costs	1,110 [134]	197 [81]
Total direct costs	3,439 [1,522]	2,318 [1,125]

Appendix III

Table 2: Societal costs stratified by educational level.

	≤ 12 years education	12 years education
	(n=149)	(n=59)
	€/pt/yr: Mean [median]	€/pt/yr: Mean [median]
General practitioner	35 [9]	26 [9]
Specialist	202 [115]	150 [84]
Physiotherapy	384 [134]	252 [43]
Other care providers	26 [0]	12 [0]
Medication	353 [180]	290 [180]
In-patient care	730 [0]	676 [0]
Technical examinations	216 [63]	168 [48]
Aids and adaptations	153 [0]	38 [0]
Formal home care	261 [0]	62 [0]
Direct healthcare costs	2,359 [1,152]	1,672 [792]
Contributions	47 [21]	25 [15]
Informal care	347 [0]	385 [0]
Transport costs	77 [39]	62 [25]
Direct non-healthcare costs	471 [122]	472 [50]
Total direct costs	2,830 [1,435]	2,146 [924]

Appendix III

Table 3: Societal costs stratified by disease activity (BASDAI).

	BASDAI<4 (n=131)	BASDAI≥4 (n=78)
	€/pt/yr: Mean [median]	€/pt/yr: Mean [median]
General practitioner	23 [9]	47 [10]
Specialist	161 [76]	232 [126]
Physiotherapy	290 [77]	455 [153]
Other care providers	13 [0]	36 [0]
Medication	289 [168]	415 [296]
In-patient care	177 [0]	1,631 [0]
Technical examinations	137 [40]	316 [95]
Aids and adaptations	42 [0]	278 [0]
Formal home care	103 [0]	425 [0]
Direct healthcare costs	1,235 [928]	3,835 [1,745]
Contributions	35 [9]	52 [55]
Informal care	63 [0]	522 [0]
Transport costs	56 [27]	107 [58]
Direct non-healthcare costs	233 [74]	888 [147]
Total direct costs	1,468 [1,053]	4,723 [2,513]

Appendix III

Table 4: Societal costs stratified by presence of extra-spinal manifestations.

	No extra-spinal manifestations (n=143) €/pt/yr: Mean [median]	Extraspinal manifestations (n=66) €/pt/yr: Mean [median]
General practitioner	27 [9]	43 [18]
Specialist	149 [76]	268 [160]
Physiotherapy	314 [85]	432 [317]
Other care providers	24 [0]	15 [0]
Medication	258 [154]	495 [348]
In-patient care	363 [0]	1,444 [0]
Technical examinations	142 [44]	330 [105]
Aids and adaptations	127 [0]	149 [0]
Formal home care	100 [0]	476 [0]
Direct healthcare costs	1,504 [872]	3,653 [1,690]
Contributions	35 [9]	55 [55c]
Informal care	93 [0]	526 [0]
Transport costs	62 [30]	101 [54]
Direct non-healthcare costs	294 [79]	846 [150]
Total direct costs	1,798 [1,063]	4,499 [1,971]