# The economic burden of juvenile idiopathic arthritis – results from the German paediatric rheumatologic database

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## Abstract

### Objective

*To estimate the cost of juvenile idiopathic arthritis (JIA) and to evaluate the influence of specific disease characteristics on the various costs domains.*

### Methods

*Data on JIA outpatients (n=369) who were enrolled in the national paediatric rheumatologic database and completed a cost questionnaire were analysed. Direct JIA-related costs, families' out-of-pocket expenses and parents' income loss were calculated per patient and year, using physicians' reports, parents' 3-month recall, and average prices as the basis.*

### Results

*The mean total cost of JIA was estimated to be 4,663 euros per patient per year. The highest costs were calculated for patients with seropositive polyarthritis and systemic arthritis (7,876 euros), and the lowest costs were seen for patients with persistent oligoarthritis (2,904 euros). Health-care costs accounted for 89% of total costs, and medication contributed to almost half of this value. A considerable amount of the cost was borne by the families, with a mean out-of-pocket cost of 223 euros and a mean indirect cost due to time loss from work of 270 euros per year per family. Cost increased with disease activity and pain, disease duration, and time period from symptom onset to first paediatric rheumatologist visit; it also increased with the presence of uveitis. However, function, as measured by the Childhood Health Assessment Questionnaire, was the only factor significantly contributing to the variation in patient total costs.*

### Conclusion

*JIA imposes a significant economic burden. Medication (i.e. biologic drugs) contributes substantially to the total costs. However, these must be considered in the light of the patients' long-term outcomes.*

### Key words

Cost of illness, juvenile idiopathic arthritis, direct cost, out-of-pocket cost, cost driver.

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## Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease and one of the most important causes of acquired impairment and disability in children and adolescents (1, 2). While the consequences of disease on patients' body functions and structures, functioning and participation have been comprehensively explored, its economic consequences have been less well evaluated (3-7). This is unsatisfactory in view of both the tremendous burden of JIA and the potential influence of cost evaluations in determining the extent of funding for particular paediatric interventions. Only five studies published thus far have examined costs associated with JIA and the factors driving these costs. Just three of them estimated the costs incurred by children with JIA and their families in the era of biologic therapies (5-7).

Therefore, the aims of this study were to determine i) the total cost of care incurred by a group representative of JIA in the community and ii) which socio-demographic and clinical variables are associated with high costs. The established national paediatric rheumatologic database (NPRD), which provided a cost module in the year 2003, was used for this purpose.

## Materials and methods

### *Study design*

This was a cross-sectional study that estimated 12-month costs associated with JIA from a societal perspective.

### *Study population and assessments*

Data from the NPRD, details of which have been described elsewhere (8), were used for this analysis. In brief, within the database, paediatric rheumatologists from almost all German paediatric rheumatology units are supposed to register each outpatient (newly referred or prevalent case) with an inflammatory rheumatic disease once a year. The physicians' questionnaire collects information regarding demographic data of the patient, diagnosis, disease onset, current disease activity (physicians' global rating on a numeric rating scale from 0 to 10 [NRS]), drug treatment, selected laboratory results, as well as the number of joints with active arthritis and/or limited range of motion.

In addition to physicians, patients (over 12 years of age) or their parents contemporaneously complete a comprehensive questionnaire. They report on onset time of symptoms, first visit to a paediatric rheumatologist, number of days they missed from school during the last 4 weeks or stayed in hospital during the last 12 months, and usage of complementary treatment measures such as physiotherapy, occupational therapy, splints, and/or patient/parent education. In addition, patients (or their parents) record their current pain and overall well-being on NRSs and functional status by means of the German version of the Childhood Health Assessment Questionnaire (CHAQ) (9).

In 2003, a cost questionnaire was additionally employed in order to inquire about the use of JIA-related medications and health services, family's out-of-pocket expenses, and parents' time loss from work due to their children's rheumatic illness within the 3 months prior to the visit. Out of 33 units that had participated in the NPRD in 2003, 14 applied the cost module. At these units, the cost questionnaire was given to the parents of all consecutive outpatients with JIA (according to the modified International League of Associations for Rheumatology [ILAR] criteria for JIA (10)) who were seen on a regular basis within the first quarter of the year 2003.

### *Cost calculations*

Direct costs were estimated for each patient for the 12 months prior to documentation. Table I summarises the estimates of the unit prices for individual services used in this article and the resource utilisation.

Non-health care costs expended by the patients' families covered three months and included disease-related expenditures due to *e.g.* transportation, home alterations, and special equipment for patient assistance. In addition to the families' expenditures, costs for special school services (*e.g.* transportation to school, extra set of books) provided by the communities were considered.

The indirect costs of JIA were evaluated by considering parents' time away from paid work due to their children's rheumatic illness (productivity loss). An estimate of the loss of productivity was obtained by multiplying the cumulative number of work days lost over the preceding 12 months by the gross annual income from dependent work, divided by the total number of people employed in dependent jobs (16) and by 365 days. Thus, the cost of lost productivity amounted to approximately 95 euros per person and day.

### Statistical analysis

Statistical analyses were performed using SPSS version 14.0 and SAS version 9.1. The distribution of costs was skewed, that means a low proportion of patients with high costs had a high influence on the mean costs. Therefore, not only means and standard deviations (SD) but also median costs are provided. Bootstrap methods were used to calculate the 95% confidence intervals (CI) of the mean costs. This calculation was done by means of GAUSS Mathematical and Statistical System software (17). Nonparametric tests (Kruskal-Wallis test, Mann-Whitney test, non-parametric analysis of variance as proposed by Brunner and Puri (18)) were applied to compare costs and patient characteristics between groups. Proportions were compared by $\chi^2$ test.

Determinants of costs were explored by logistic regression analyses, with total cost dichotomized into low and high cost (low = lowest quartile, high = three highest quartiles) as dependent variable. As independent variables, sociodemographic and disease parameters were chosen: age, gender, disease activity (NRS value <2; 2-4, >4) and disease duration, JIA subgroup, presence of uveitis, pain intensity, and CHAQ score (0; >0 to <0.625; ≥0.625). A $p$-value <0.05 was considered statistically significant.

#### *Sensitivity analysis*

Due to the large range of reimbursement rates for outpatient visits and inpatient stays across Germany, applied generic unit cost for outpatient visits and inpatient stays were uncertain parameters. In 2003, rates for outpatient visits varied by 30% depending on federal state, health insurance, and specialist (19), whereas cost for inpatient care varied by 25% among the different federal states (14). In order to investigate the sensitivity of the cost estimated, the applied prices for the respective parameters were thus varied by the above-mentioned percentages.

Biologic drugs are regarded as a cost driver in rheumatology. Cost data were obtained in the year 2003, when only 5% of all JIA patients recorded received biologic drugs. Since in 2006 (for which last data of the NPRD are available), 10% of all JIA patients recorded in the NPRD were under biologics, we assumed a prescription rate of biologic drugs of 12.5% in 2008. This rate was considered to calculate the mean total 12-month cost per patient in 2008.

### Results

#### *Patients*

Data from 263 girls and 106 boys with JIA aged 2–18 years was considered for the cost analyses. Table II presents detailed characteristics for all patients (n=1,583) recorded at those 14 units that had applied the cost module. Characteristics are separately given for patients with versus without completed cost questionnaires. Patients for whom the cost module was available had a mean age of 12 years and a mean disease duration of 5 years. Despite some differences in the

**Table I.** Sources of unit costs and resource use (cumulative number of used resources per year, proportion of patients having used that resource).

| Expenditure costs assessed | Resource use | | Applied unit prices in euros (superscripts are references) |
|---|---|---|---|
| | Annual number | Number of patients (%) | |
| Direct costs | | | |
| Health care costs | | | |
| Outpatient costs: | | | |
| Paediatric rheumatology service use | 476 | 369 (100) | Average tariff per visit, by specialty (the first visit in quarter was valued differently than subsequent) [11] |
| Ophthalmologist service use | 319 | 155 (44) | |
| Other JIA-related physician service use | 763 | 356 (96) | |
| Non-physician service use | 3,934 | 284 (77) | Average tariff per session[12] |
| Surgery | 0 | 0 (0) | Average charge[14] |
| Medication | n/a | 322 (87) | Average price per day (or year) calculated from pack sizes and dosage[13] |
| Devices and aids | n/a | 245 (66) | Average price per item, using an incidence approach |
| Inpatient costs: | | | |
| Acute hospital facilities | 1,603 days | 139 (38) | Average adjusted cost of 305 per day[14] |
| Surgery | 13 | 13 (4) | Case-based lump sum[14] |
| Non-acute hospital facilities (rehabilitation) | 47 | 47 (13) | Average cost of 2,232 per stay[15] |
| Non-health care costs: | | | |
| Patient expenditures (3 months) | n/a | 224 (61) | |
| Indirect costs: | | | |
| Loss of productivity | 228 days | 84 (23) | 95 per day[16] |

n/a - not applicable

**Table II.** Characteristics of JIA patients recorded within the database: patients with *vs.* without completed cost questionnaires.

| | JIA study cohort with cost data | JIA patients without cost data | *p*-value |
|---|---|---|---|
| Number of patients | 369 (23%) | 1,214 (77%) | |
| Female [n, (%)] | 263 (71) | 778 (64) | 0.011 |
| JIA subgroups [n, (%)] | | | 0.013 |
| Systemic arthritis | 21 (6) | 92 (7) | |
| Oligoarthritis, persistent | 136 (37) | 517 (43) | |
| Oligoarthritis, extended | 42 (11) | 83 (7) | |
| Seronegative polyarthritis | 54 (15) | 137 (11) | |
| Seropositive polyarthritis | 6 (2) | 33 (3) | |
| Psoriatic arthritis | 25 (7) | 58 (5) | |
| Enthesitis-related arthritis | 58 (16) | 210 (17) | |
| Other arthritis | 27 (7) | 84 (7) | |
| Mean age [years, (SD)] | 11.9 (4.3) | 11.3 (4.3) | 0.012 |
| Mean time period from symptom onset to first paediatric rheumatologist visit [months, (SD)] | 8.7 (15.3) | 10.9 (19.7) | 0.104 |
| Mean disease duration [years, (SD)] | 5.3 (3.4) | 4.4 (3.5) | <0.001 |
| Mean CHAQ-score (SD), (score-range: 0-3) | 0.24 (0.4) | 0.25 (0.4) | 0.760 |
| Mean disease activity (SD), (NRS-range: 0-10) | 1.4 (1.8) | 1.7 (1.9) | 0.010 |
| Mean pain intensity (SD), (NRS-range: 0-10) | 1.6 (2.2) | 1.6 (2.3) | 0.757 |
| DMARD use [n, (%)] | 242 (68) | 620 (54) | <0.001 |
| Biological drug use [n, (%)] | 20 (6) | 54 (5) | 0.305 |

**Table III.** Components of out-of-pocket costs in euro per year per JIA-patient family.

| Cost categories | Mean (SD) |
|---|---|
| Co-payment to treatments prescribed | 13 (91) |
| Cost for comprehensive alternative (non-prescription) medicine | 41 (140) |
| Transportation cost | 132 (306) |
| Extra telephone cost | 9 (35) |
| Costs for home alterations | 9 (116) |
| Costs for domestic help and care for patients and/or their siblings | 2 (24) |
| Remaining costs | 19 (73) |
| Total | 223 (468) |

patient characteristics, patients with cost data did not present with a more severe disease at the time of documentation when compared to those without cost information.

At the time of documentation, 34% of the patients had an active disease (NRS >1) and 34% reported on pain (NRS >1). More than two-thirds of patients were receiving disease modifying antirheumatic drugs (DMARDs), with methotrexate being the most frequently prescribed drug (54%) and followed by sulfasalazin (8%) and etanercept (6%).

*Cost components*

For this JIA patient cohort, the mean total cost was estimated to be 4,663 euros (95% CI: 3,987 to 5,415 euros) per patient and year. Mean direct costs were 4,403 euros (95% CI: 3,743 to 5,130 euros). Almost 90% of the total cost and 95% of the direct cost was incurred by the health care service. Approximately 60% of the health care cost was spent for outpatient and about 40% for inpatient care, *i.e.* acute-care hospitalisation (33%) and inpatient rehabilitation (6%). Medications were the largest contributor to health care costs (47%). Ninety-six percent of the drug costs were due to DMARDs, and 77% of the drug costs were due solely to biologic drugs. All other drug treatments, including NSAIDs, glucocorticoids, osteoporosis treatment/prophylaxis, gastroprotective agents, and eye drops/ointments, were responsible for only 4% of medication costs. Visits to physicians (general practitioner/paediatrician, paediatric rheumatologist, and ophthalmologist in descending order) accounted for 7% of the health care cost, whereas visits to nonphysicians (physical or occupational therapists) contributed to 3% to these costs.

Non-health-care costs contributed to 5% of the total and direct cost. The entire out-of-pocket family expenditure is shown in Table III. The total out-of-pocket cost amounted to18 euros per month and accounted for less than 1% of the average disposable monthly family income in Germany (2,771 euros) in 2003 (16).

Considering the parents' time loss from work, mean indirect costs averaged to 270 euros (95% CI: 178 to 383 euros) for the 12-month period and accounted for 6% of the total cost. Twenty-three percent of mothers and/or fathers had missed some work because of their children's illnesses (average 3.6 days over 3 months, or about 14.5 days annually). Time lost from independent and household work as well as other activities was not calculated. Its consideration would have increased time loss from 228 days (see Table I) to 329 days per year. In addition to parental loss of time, 12% of the patients had missed on average 6 days of school over the preceding 4 weeks or 78 days annually due to their illness. The resulting disease-related school absence rate for the whole JIA cohort corresponded to a mean of 0.7 absent days per month or 8.4 days per year.

*Cost determinants*

The mean total cost diverged significantly among the various JIA subgroups ($p<0.001$). The subgroup-related total and health care costs are summarised in Table IV. Highest total costs were calculated for patients with seropositive polyarthritis. They were due to high medication cost, caused by biologic drug use in half of these patients. Due to the small number of patients, this result has, however, to be interpreted with caution.

Costs increased with disease activity ($p=0.028$), pain ($p<0.001$) and functional limitation ($p<0.001$). In addition, there was a tendency towards higher cost incurred by patients with

**Table IV.** Estimated 12-month total cost and health care cost per JIA subgroup.

| JIA subgroup | Mean total cost ± SD (Median; IQR) | Mean health care cost ± SD (Median; IQR) |
|---|---|---|
| Systemic arthritis | 7,876 ± 10,271<br>(3,847; 1,186 – 10,049) | 6,934 ± 9,666<br>(3,522; 976 – 9,416) |
| Oligoarthritis, persistent | 2,904 ± 4,318<br>(1,330; 572 – 3,374) | 2,468 ± 4,120<br>(964; 446 – 2,686) |
| Oligoarthritis, extended | 5,412 ± 7,269<br>(2,433; 912 – 5,812) | 4,992 ± 7,102<br>(2,207; 562 – 5,217) |
| Seropositive polyarthritis | 16,172 ± 11,646<br>(21,496; 2.233 – 25,409) | 13,883 ± 12,569<br>(15,606; 767 – 25,409) |
| Seronegative polyarthritis | 5,238 ± 7,575<br>(2,011; 763 – 5,514) | 4,763 ± 7,117<br>(1,604; 653 – 5,229) |
| Psoriatic arthritis | 4,005 ± 7,180<br>(2,800; 899 – 3,969) | 3,637 ± 6,965<br>(1,838; 720 – 3,774) |
| Enthesitis-related arthritis | 5,476 ± 7,976<br>(2,693; 951 – 6,539) | 5,013 ± 7,767<br>(2,182; 656 – 5,906) |
| Other arthritis | 5,012 ± 5,417<br>(4,570; 754 – 7,411) | 4,676 ± 5,257<br>(4,570; 674 – 6,556) |
| All patients | 4,663 ± 6,928<br>(2,023; 773 – 5,367) | 4,172 ± 6,644<br>(1,381; 569 – 1,381) |

SD: Standard deviation; IQR: Interquartile range.

longer disease duration, uveitis, and a longer time period from symptom onset to first paediatric rheumatology visit (Table V).

Of all the variables included in the multiple regression analysis, only functional status ($p$=0.016) was a statistically significant contributor to higher total costs in JIA, *i.e.* cost of more than 792 euros (corresponding to the 1st quartile). However, functional status explained only 10% of the variance of costs.

### Sensitivity analysis

The variation of the uncertain variables like reimbursement rates for outpatient visits and inpatient stays by ±30% and ±25% resulted in a maximal change in health-care cost of 9% and a maximal change in total cost of 8%. In fact, the lower extreme for the mean health-care cost (*i.e.* after reducing outpatient cost by 30% and inpatient cost by 25%) was 3,779 euros (median 1,268 euros), and the upper extreme (*i.e.* after increasing outpatient cost by 30% and inpatient cost by 25%) was 4,565 euros (median 1,509 euros). When estimating the lower and upper extremes for the mean total 12-month cost, they amounted to 4,270 and 5,056 euros (median 1,806 and 2,215 euros), respectively.

Patients undergoing treatment with biologic drugs incurred a mean cost of 27,771 euros per year, whereas those not provided with biologic drugs incurred a total cost of 3,155 euros. Considering this and assuming a prescription rate of biologic drugs of 12.5% and a discount rate of 3%, the mean total cost per JIA patient would be 5,300 euros in the year 2008.

**Table V.** Mean annual total cost in euro by selected disease parameter.

|  | n | Mean (SD) | Median (IQR) | $p$-value |
|---|---|---|---|---|
| Disease activity* |  |  |  | 0.028 |
| 0–1 | 228 | 3,860 (5,801) | 1,651 (633 – 4,476) |  |
| 2–4 | 97 | 5,490 (7,749) | 2,292 (1,055 – 7,149) |  |
| 5–10 | 18 | 7,826 (9,554) | 4,398 (440 – 15,450) |  |
| Pain intensity* |  |  |  | <0.001 |
| 0–1 | 227 | 3,956 (6,451) | 1,582 (617 – 3,996) |  |
| 2–4 | 76 | 4,907 (6,119) | 2,780 (899 – 7,176) |  |
| 5–10 | 40 | 7,064 (8,454) | 3,828 (1,684 – 9,169) |  |
| Functional status, CHAQ score |  |  |  | <0.001 |
| 0 | 185 | 3,422 (5.899) | 1,372 (575 – 3,714) |  |
| >0 – <0.625 | 126 | 4,608 (6.012) | 2,366 (820 – 5,908) |  |
| ≥0.625 | 50 | 9,169 (10.029) | 5,505 (2,225 – 11,171) |  |
| Disease duration |  |  |  | 0.105 |
| ≤2 years | 90 | 3,502 (4.487) | 1,606 (570 – 5,357) |  |
| 3–5 years | 120 | 3,896 (5.953) | 1,959 (771 – 4,442) |  |
| >5 years | 159 | 5,900 (8.427) | 2,516 (896 – 6,737) |  |
| Eye involvement |  |  |  | 0.330 |
| no | 300 | 4,530 (6.954) | 1,794 (755 – 4,916) |  |
| yes | 54 | 5,146 (6.969) | 2,407 (865 – 6,254) |  |
| First visit to paediatric rheumatologist |  |  |  | 0.135 |
| ≤8 weeks after symptom onset | 88 | 3,797 (5.518) | 1,555 (631 – 5,266) |  |
| >6 months after symptom onset | 81 | 5,442 (8.248) | 1,848 (954 – 5,490) |  |

*numeric rating scale 0-10; IQR, interquartile range.

## Discussion

The study findings substantiate previous work on economic consequences of rheumatic diseases beginning in childhood. Costs of JIA were estimated to be approximately Euros 4,500 per patient per year. Health care costs were responsible for the major share of cost, amounting to more than 4,000 Euros per patient a year. Despite almost universal insurance coverage in Germany, there was also a financial impact on the families of children with JIA. Their mean out-of-pocket costs amounted to more than 200 euros per family per year, to which added the costs of almost the same magnitude due to time loss from work. Of course, the costs of the disease were not uniformly distributed among the JIA population. This skewing, evidenced by the finding that mean costs mostly exceeded median costs, is reflected by the fact the 10% of patients with the most severe JIA were responsible for 50% of all costs.

The JIA-related health care costs estimated in this study were higher than those determined recently by Thornton *et al.* (7) and Bernatsky *et al.* (6). This is due to differences in the health care systems, patient cohorts assessed, and methods applied. In the British study, health care costs were estimated only for patients with a disease duration of one year, who incurred relatively low drug costs. The lower medication costs at least partially explain the lower mean health care costs of 2,391 euros in the British study in comparison to our data. In the Canadian study, the mean health care costs of JIA were Can$ 3,002. The Canadian patient cohort does not seem to differ substantially at first sight from the patient cohort assessed by us with respect to subgroup distribution or prescription rate of biologic drugs. However, the patients in our study had been treated more intensively than those in the Canadian study: almost 70% had received DMARDs, and more than half (54% *vs.* 32%) had received MTX. This, and especially the higher acquisition costs of etanercept in Germany, contributed to the relatively high medication cost and consequently health care costs in the present study. In addition, there were significantly higher costs due to inpatient care in our study, reflecting a specific feature of health care in Germany.

In comparison to previous cost assessments in juvenile arthritides (3, 4), components of health care costs have changed during the past 15 years. When Allaire *et al.* (3) estimated the economic impact of juvenile arthritis for the first time in 1989, medication contributed to only 7% of the health-care cost. In contrast to this, drugs are currently the main cost-driver in both early JIA and adult-onset chronic arthritides (20, 21, 22). This is mostly due to the introduction of biologic drugs into the treatment of rheumatic diseases. Haapasari *et al.* (5), Brunner *et al.* (23), and Bernatsky *et al.* (6), who all assessed costs in very different JIA cohorts, consistently found medication (if biologics were used) to be responsible for almost half of the health care cost. This is in line with our study results, where DMARDs or biologic drugs in particular relevantly contributed to the health care costs (45 and 36%, respectively). However, these data should not lead to the conclusion that biologic drugs simply increase the cost of illness. Haapasari *et al.* showed in their small study that adding etanercept to the previous therapy reduced the indirect costs of refractory JIA by 50% during a 12-month follow-up and therefore increased the total cost of JIA only slightly. Of course, the costs incurred in childhood have to be seen in view of lifetime pain, disability, and patient impairment (24, 25, 26). Biologic drugs now promise an improvement of the prognosis of JIA refractory to conventional treatments and therefore offer enormous cost savings over the long-term. However, this needs to be proven in adequate long-term outcome studies.

Cost driving factors were found to include disease subtype, disease activity, pain intensity, and level of disability. This is in accordance with previous studies that described higher costs incurred by patients with more severe disease subtypes (3, 4) and higher disease activity (6). In addition, we found a tendency towards higher costs incurred by patients seen later by paediatric rheumatologists. One might expect that early specialised care saves costs; however, this has not been demonstrated so far. Of the disease parameters, poor function (CHAQ-score) was the major cost driver in this study. This is in agreement with other economic analyses, which have described functional disability as the most important determinant of arthritis-related health expenditures (20).

As with any study, our results have to be viewed in light of the study's limitations. First, even though we assessed a relatively large cohort of JIA outpatients with a subgroup distribution similar to that of population-based cohorts, we cannot assume that the sample is representative of all individuals with JIA. With regard to the differences between the two JIA groups from the NRPD (*i.e.* that with and without cost information), those considered for the analyses may have been somewhat more severely affected. Therefore, an overestimation of cost due to patient selection cannot be excluded. Second, this study estimated costs incurred within the preceding three months and relied on proxy-reported data. Recall bias cannot be ruled out. Third, "standard" assigned costs per day, per visit, or per prescription based upon publicly available figures were used in this analysis. The actual cost may vary from those considered. Fourth, this study was done in Germany, where therapeutic approaches to JIA, such as the practice of hospitalising patients to facilitate proper multidisciplinary care, may be different to other parts of the world. Therefore, the results may not be generalisable to other healthcare systems.

It can be concluded that JIA imposes a tremendous economic burden. Further research should involve patients with recent JIA onset and prospectively collect detailed cost data that can be used to assess efficacy and cost-effectiveness of different treatment strategies for JIA.

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