# COSTS AND QUALITY OF LIFE IN MULTIPLE SCLEROSIS

## A Cross-Sectional Observational Study in Germany

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## ABSTRACT

We performed a cross-sectional, "bottom-up" observational study of resource consumption and quality of life of patients with multiple sclerosis (MS) in Germany. Six centers participated in the study. Patients were asked to complete a questionnaire, and a total of 737 patients returned the questionnaire (the answer rate being 66%). The questionnaire provided information on all resource consumption, medical and non-medical, work absence and informal care related to their MS. Simultaneously, medical charts were also abstracted for a sub sample of 202 patients. For this sub sample, disease scores (Expanded Disability Status Scale, EDSS) were available from the study centers. For the remainder, disease scores were assigned using a matrix of disease (mobility) descriptions and EDSS scores.

Mean total cost per patient and year was 65,400 DM, adjusted for usage of interferons, which was higher in this sample than the current average usage in Germany. When this cost is extrapolated to an estimated patient population of 120,000, total costs to society are estimated at 7.85 billion DM. Direct costs represented 57.5%, informal care accounted for 12.1% and indirect costs amounted to 42.5%. An estimated 24,800 DM per patient or 38% of total costs are paid for by public payers. Intangible costs were estimated 16,650 DM per patient and year.

The mean age of the cohort was 42 years (disease onset 33), the mean utility measured with EQ-5D was 0.552 (0.919 to –0.429), and the mean EDSS score 4.4 (1.0 to 9.5). All costs (direct, informal care, indirect) increased with increasing EDSS scores, while utilities decreased.

KEYWORDS: multiple sclerosis, cost-of-illness, quality of life, EDSS, utility

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# 0. SUMMARY

This report presents a cross-sectional, "bottom-up", prevalence-based observational study of the cost of multiple sclerosis (MS) in Germany and an analysis of how this cost relates to disease severity and quality of life. The study includes all costs caused by the disease, regardless of where and to whom they occur. Thus, direct and indirect costs are included, and intangible costs are estimated. Disease severity is measured with the Expanded Disability Status Scale (EDSS) and quality of life with the EuroQol (EQ-5D and VAS).

The mean total cost per patient and year in this sample is estimated at 72,150 DM of which indirect costs represent 38.6% or 27,800 DM. Direct medical costs (in- and outpatient care and drugs) are estimated at 22,600 (31% of total costs). Interferons represent approximately 19% of direct costs (8285 DM or 11.5% of total cost) in this sample. Around 43% of patients were treated with interferons, which is far higher than the average national proportion and is likely due to the fact that patients were enrolled at university hospitals. If the MS drug usage is adjusted to the national proportion, costs per patient for these drugs amount to 2866 DM, direct medical costs are estimated at 16,000 DM and total costs at 65,400 DM. Investments and house adaptations represent 7.2% of total costs, or 5220 DM, and with the exception of wheelchairs, almost all of these costs are borne by the patient. Services amount to 8540 DM or 11.8% of total costs, and the vast majority of these costs are borne by the patient. Informal care provided by the family represents 11% of total cost or 7,900 DM. Thus, total direct costs are estimated at 44,300 DM per patient and year in this sample, of which an estimated 23,800 DM (or 54% of direct costs) are paid for by public payers. After adjustment for interferon usage, total direct costs are 37,600, of which 17,100 or 45% are borne by public payers. Total costs to public payers, including transfer payments (invalidity

pensions) is estimated to 31,500 DM per patient and year for this sample and to 24'800 DM after adjustment for interferon usage (43% and 38% of total costs respectively).

Intangible costs are estimated at 16,650 using a value of 50,000 DM (US $ 25'000) for a QALY lost.

All costs (direct, informal, indirect) increase and quality of life (QoL) decreases as the disease progresses. When patients are grouped into different levels of disability, mild, moderate and severe MS, total costs per patient and year (unadjusted) are 35,650 DM for patients with mild disease (EDSS <=3.0), 76,100 DM for patients with moderate disease (EDSS 3.5 – 6.0) and 124,300 DM for patients with severe disease (EDSS >=6.5). Adjusted for interferon usage at each level, these costs are estimated at 27,800 DM, 71,250 DM and 119,700 DM respectively.

Costs to the public payers are 22'100 DM, 33'750 DM and 47'750 DM respectively (unadjusted) and 14'300 DM, 28'900 DM and 43'150 DM (adjusted at each level).

Disability classifications were almost exclusively limited to patients with severe disease (83%), and 30% were at level I, 49% at level II and 21% at level III. No patient with mild or moderate disease was at levels III, and only 6 patients with moderate disease were at level II.

Mean utility scores (QoL) are 0.76 for mild disease, 0.55 for moderate disease and 0.23 for severe disease.

This study attempts to estimate ALL relevant costs due to MS that occur to society, using the same methodology as a recent study in Sweden and in the UK [1] [2]. Comparing the cost per patient, total costs in Sweden are almost twice as high as in the UK, and about 25% higher than in Germany. The distribution of costs on the different types of resources is rather similar in Germany and

Sweden, although more informal care is required for German patients. Direct costs represent 54% and 63% in Germany and Sweden respectively, informal care costs 11% and 4%, and indirect costs 38.5%% and 33%. In the UK, the distribution is very different, with 28% being direct costs, 26% informal care costs and 46% indirect costs.

The total cost of MS in Germany, assuming a patient population of 120'000, is 7.85 billion DM according to our estimates (after adjustment for MS drug usage). Of these, approximately 1.45 billion DM are for patients with mild disease (EDSS <=3.0), 2.3 billion DM for patients with moderate disease (EDSS 3.5 – 6.0), and 4.1 billion DM for patients with severe disease (EDSS >=6.5). Of the direct costs, around 2 billion DM fall on public payers. This is substantially more than what had been estimated in the earlier top-down cost of illness study (1 billion DM) [3], but similar differences between top-down and bottom-up study results have been noted in Sweden [1] and is likely due to the fact that a certain number of costs are not available from statistical sources.

In conclusion, this study appears to be the most complete study performed in Germany so far, using standard and up-to-date cost-of-illness methodology, and the results indicate that the cost burden of MS to society is substantial, and the cost to public payers higher than previously indicated.

# 1. INTRODUCTION

## 1.1. Background

It is estimated that multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system, affects over 1 million people worldwide [4]. In industrialized countries, prevalence rates vary considerably between 15 and 145 per 100'000 [5]. Disease onset is typically between 20 and 40 years of age, with a higher incidence in females, and MS is the most common cause of disability in young adults [6].

The course of the disease is unpredictable, although a high frequency of severe exacerbations in the first two years after onset has been related to a poor prognosis [7]. A majority of patients (~80%) will have relapsing-remitting disease (RRMS) at onset, and a high proportion of these patients will convert to secondary progressive disease (SPMS), with a gradual progression of functional impairment punctuated by exacerbations (recurrent relapses) particularly in the earlier years of SPMS. A small proportion of patients (15-20%) will have progressive disease at onset (PPMS).

At present, the etiology of the disease is poorly understood and no cure exists. Current treatments focus on reducing and managing exacerbations, and research has focused on treatment that can affect the progression of the disease. Several new treatments have recently been introduced that have shown a clear effect on the frequency of exacerbations in RRMS [8-10]. Of three clinical trials with interferons in SPMS, one has shown a significant effect on disease progression [11], and all three have shown an effect on relapse rates.

These new agents are more expensive than previously used treatments, and there has been a concern about rising costs [12]. The cost-effectiveness of the new interventions has been questioned, and as a consequence, there is need for better knowledge of the actual cost of care and total cost caused by MS, as a basis for cost-effectiveness assessments and decisions about resource allocation.

Several cost of illness studies have been performed in different countries [1 13-19 3], but most of them have some limitations for use in cost-effectiveness analyses, due to either the size of the samples, or the type of costs included or excluded [20]. (For a comparison of the studies, see [1]). Other studies have assessed the impact of different disease variables such as disability levels or the presence of an exacerbation on costs and quality of life (QoL) [21-23]. In summary, these studies have shown that the burden of MS to society is substantial, and that

- indirect costs account for a high proportion
- informal care constitutes a substantial part of costs
- costs increase with increasing severity of the disease
- costs are higher during a relapse
- quality of life and employment status are significantly affected

## 1.2. Multiple sclerosis in Germany

It is estimated that in Germany a total of 120'000 patients are affected [3]. There is limited data available on resource consumption of these patients, and only one cost of illness study is in the public domain [3]. This study was based on available statistics (top-down approach) and presented thus a conservative estimate of direct costs due to MS in Germany of 1.03 billion DM, of which the majority was due to inpatient and nursing care (55%). There are some limitations to top-down studies, in so far as they by necessity ignore costs that do not occur to the health care or social systems and even within these systems, are limited to whatever databases are available. Costs to society estimated in such studies are thus likely to be underestimated, as has been illustrated by the comparison of two Swedish studies, using top-down and bottom-up (i.e. data collection directly from patients) approaches, where costs with the latter approach were more complete and therefore substantially higher [1].

## 1.3. The objective of this study

The cost of illness studies for MS published in various countries provide a scattered picture of costs, as they include different sets of resources and use different data collection techniques. In addition, patients were generally defined as mild, moderate and severe and grouped accordingly. This may make it difficult to relate these studies to currently published clinical trials where small incremental changes in disease severity are investigated. Only recently have studies attempted to include both a large representative sample and all costs regardless of to whom they occur, notably for Sweden and the United Kingdom [1 2].

There is an ongoing debate concerning the costs that should be considered when estimating the cost-effectiveness of interventions, for instance at the level of a national health service, and the official guidelines for economic evaluation introduced in several countries differ in their requirements. However, to give an accurate description of costs caused by and related to a disease, all costs (direct medical and non medical as well as indirect costs) must be included.

In MS, a large part of the costs is borne by the patients or their relatives, and top-down cost of illness studies using registries or patient charts will not allow such data to be collected. Also, as available studies have shown, the disease has a large effect on patients' ability to participate in the workforce, and such data are rarely available from databases. Lastly, any effect of the disease and the different levels of disease severity on QoL will be missing. Data in such detail can only be collected from patients directly, in a bottom-up observational study.

The objective of this study was hence to collect detailed cost data related to MS, in a representative sample of patients in Germany, and to investigate how costs and QoL relate to different levels of disease severity, measured by the Expanded Disability Status Scale (EDSS) [24]. A further objective was to compare data to the recently performed large observational studies in Sweden and the United Kingdom [1 2].

# 2. MATERIALS AND METHODS

## 2.1. Theories and methods used

This study follows closely the methodology used in the two observational studies in Sweden and the UK [1] [2]. It is hence a descriptive cost of illness study, based on the human-capital theory [25] [26] and relates all cost to the disease (MS). As MS is a chronic disease with an average duration of around 40 years, a prevalence- rather than incidence-based approach was used, estimating the cost per patient and year. This allows calculating the cost for all patients with the disease in a given year in a geographically defined area and relating the estimates to measures of annual health care expenditure in the area.

Data collection strategies for cost of illness studies can be "top-down" (i.e. using aggregate figures on resource consumption related to diagnoses from registries or published sources), or "bottom-up" (i.e. estimating costs in a sample of patients and extrapolating to the national level). Both approaches have advantages and drawbacks, the major drawbacks being data availability in the top-down approach and difficulties relating to the selection of a representative sample in the bottom-up approach. As the purpose of this study was to include <u>all</u> costs, regardless of where they occur, the bottom-up approach was used.

The objective of the study was to estimate costs related to MS, not costs for patients with the disease, and only MS-specific resource consumption was therefore included. It is possible that patients with a severe disease consume more resources also for other diseases and thus have overall higher costs. In these cases it is generally difficult to separate what part of total costs relates to the disease that is being investigated and what part to co-morbidities. For patients with MS, this is less of a problem, as the consequences of the disease are rather well defined, and in addition patients are in an age group where co-morbidities are generally limited. It was thus felt possible to collect only MS specific costs.

Data on resource utilization, QoL and disease severity was collected directly from patients, in a cross-sectional study, during the winter 1999/2000. In addition, in order to verify the indications from patients, hospital charts for a sub sample of patients distributed evenly over all participating centers were abstracted and hospitalization, outpatient visits, tests and medication collected.

## 2.2. Study centers and subjects

Six centers with neurological departments specializing in MS care were approached for this study and all agreed to participate:

- *Marianne-Strauss Klinik, Berg (Nikolaus König, Manuela Hüttinger)*
- *Knappschaftskrankenhaus, Bochum (Walter Gehlen, Michael Haupts)*
- *Klinikum, Erfurt (Hans-Wolfgant Kölmel, Philline Fasbender)*
- *Neurologische Klinik, Georg August Universität, Göttingen (Sigrid Poser, Andreas Bitsch, Markus Patscheke)*
- *Universitätsklinik für Psychiatrie und Neurologie, Rostock (Uwe Zettl)*
- *Neurologische Universitätsklinik, Bayrische Julius-Maximilians Universität Würzburg (Peter Rieckmann, Peter Flachenecker)*

A synopsis of the study protocol was submitted to the ethical committees and approval obtained in all centers prior to starting data collection.

Patients were selected from the hospital charts, and the last 200 patients in each center with a definite diagnosis of MS and who had been in contact with the hospital in the past two years and had not participated in a clinical trial during the previous year were included. A total of 1133 patients were thus identified. In 5 centers, patients were then mailed a questionnaire and an agreement to participating in the chart abstraction part of the study. In the sixth center, patients were first contacted regarding their willingness to participate in the study, and only those answering yes were mailed the questionnaire. The vast majority of patients contacted in this center agreed to participate (87%) and 80% of these did indeed return the

questionnaire. In total 1119 questionnaires were mailed and 737 questionnaires were returned, an overall return rate of 66%.

Hospital charts were abstracted consecutively for patients returning the questionnaire, and ensuring that all types of disease and levels of disability were represented. Patients consulting for second opinion, for a relapse or with a treatment period of less than one year were not included. A total of 202 charts were thus abstracted and resource consumption compared to the questionnaires.

By collecting data from patients who are in regular contact with a hospital department, it is likely that only a limited number of patients with very severe disease, particularly patients who are bed-bound or live in long-term care are included. Although one of the centers had a special long-term care facility and patients from this facility were included in the data collection, there is still a possibility of an underestimate. This is not a problem when costs and utilities are related to disease severity, but it has the potential to underestimate costs when the costs incurred by the study sample are extrapolated to the total patient population in Germany. In order to verify that the proportion of severely disabled patients in our sample was representative, we compared the findings in this study to the estimates in other studies or databases.

## 2.3. Data collection

### *2.3.1. Background variables and resource consumption*

Patients were asked in writing to answer questions regarding resource consumption, disease severity and QoL by completing a questionnaire. The questionnaire contained 3 sections with general and disease information and 5 sections with resource utilization:

- background variables (age, education level, living arrangements)
- hospitalization (overnight stays and day hospitalization) and medical visits to physicians, nurses, physiotherapists or home visits by these professionals
- visits to other professionals (psychologist, incontinence advisor, optician, social worker, other therapists)

- medication (interferons, other prescription drugs, OTC drugs)
- community and other services (home help, child care, meals on wheels, etc)
- investments (house adaptations, devices, etc)
- employment situation and changes in employment situation due to MS, as well as status regarding sick pensions
- disease related information (type of disease, ability to move around, etc.) and information on relapses

For health care resources and community services, patients were asked for their consumption during the past 3 months. An exception to this was hospitalization, where patients were asked for utilization during the past year. This was based on the assumption that it is possible to recall severe events such as hospitalization over a relatively long period of time, while it might be difficult to assign such events to a specific month. Similarly, large investments such as transformations to the house etc. were related to the past year. Patients were reminded at each question what the relevant time frame to consider was.

### *2.3.2. Quality of life (utilities)*

Quality of life data was collected with a generic preference-based instrument, the EQ-5D [27], from the descriptive part of which utility values on a scale between 0 (death) and 1 (full health) for different health states can be developed. In addition, a visual analogue scale (VAS) gives a score between 0 (worst imaginable state) and 100 (best imaginable state).

The EQ-5D is based on questions concerning 5 domains, with answers at 3 levels, yielding 243 possible combinations of answers. From these, health state descriptions were created and utilities assigned with the time trade-off method in the UK population [27]. A health state classification system was then developed from which utilities for the different combinations can be derived. For the development of utilities, interviewees had been specifically asked to ignore any effect on their

economic or working condition, in order to separate health-related QoL from cost implications.

### *2.3.3. Disease severity (EDSS)*

Disease severity was expressed as EDSS levels. However, in addition to grouping patients into mild, moderate, severe, we also used smaller groupings (essentially by 1 full EDSS point) that have been used in cost-utility models [28 29] . EDSS scores were available from the medical records for patients for whom these records were abstracted (i.e. for about 27% of patients). For the other patients, scores were derived from the specific disease section in the questionnaire. This section included specific questions regarding mobility, derived from the EDSS scoring system. We developed a matrix to assign an EDSS score (based on full EDSS points) and a grouping, and verified the accuracy of the matrix by comparing the actual scores from the charts and scores assigned from the questionnaire for a sub-sample of 100 patients for which both were available. The matrix predicted the groupings with over 90% accuracy, and considering the uncertainty and inter-rater variability involved in EDSS scoring, we considered it unnecessary to attempt to complete the missing values by telephone-interview or by calling the patients to the clinic for a visit.

## 2.4. Costing

In cost of illness studies or economic evaluations, data collection focuses on resource consumption, and each resource unit is then multiplied with its unit cost. Unit costs for a resource are the opportunity cost of that resource (or its value in its best alternative use). In normal well-functioning markets, market prices will reflect the opportunity cost, but in health care this is not always the case. In Germany, only tariffs are available and although for some resources tariffs may represent the actual opportunity costs, for many it will not. Tariffs may be set to include incentives for usage of a given resource (e.g. a high tariff may be used to encourage the use of a certain resource, while a very low tariff may be used to control over consumption). A

similar problem is encountered when using charges (billings), as some of the charges may be used to subsidize other activities and will hence not represent true opportunity costs.

For this study, costs were considered from two perspectives: the main analysis presents the societal perspective where all costs (direct medical, direct non-medical and indirect) are included, regardless of who pays for the resource. A second analysis presents costs from the perspective of the public payer, and includes costs to the statutory health insurance funds (Krankenkassen), to the nursing care insurance (Pflegeversicherung), to communities for social assistance and to invalidity pension plans.

We have used a number of sources for valuing health services and other public resources, while costs for investments and out-of-pocket expenses have been largely based on patients' estimates. Transportation costs have not been included, as it would be difficult to obtain detailed data, and direct non-medical costs will therefore be underestimated. Costs relate to the year 1999. Appendix A presents the unit costs and the sources.

### *2.4.1. Direct costs*

Direct costs relate to the cost of detection, treatment, rehabilitation and long-term care of an illness, and the purpose of this study was to include all costs related to MS from a societal point of view. Thus costs borne by the patient for services not paid for by, as well as informal care provided by family and relatives are also included. A separate estimate for costs to the public payer is provided as well.

Direct costs are grouped into inpatient care, ambulatory care, social services, drugs, investments and informal care. Unit costs for the resources were assigned as follows:

- Inpatient care and day hospitalization was valued using the PKV Database 2000 [30].

- For long term inpatient care, the cost per day was based on day hospitalization for the societal perspective, and on the monthly payments according to the level of disability by the nursing care insurance [31]
- Ambulatory care (visits to or by health professionals) was valued differently for the two perspectives of the study.
    - For the societal perspective, we calculated the average cost of a visit by dividing the average annual gross turnover of specialists' or general practitioners' practices, published in the "Kostenstrukturanalyse" [32], by 6000 visits (assuming 15 minute visits, for 200 work-days of 7-8 hours).
    - For the public payer perspective, costs were based on the points of the resource according to the EBM 2000[33] and a point value of 0.72 DM. As it was not possible to ask patients for detailed indications of tests and procedures performed during a given visit, we based the cost on the mean number of visits per quarter and the mean number of EBM points billed for MS patients by different specialists and general practitioners in the ADT Panel of the sick fund association in Nordrhein [34].
- Prescription drug prices were based on average recommended daily doses (DDD) and required package size prices in the Rote Liste [35] [36] for both perspectives. Pharmacy prices were adjusted for the 5% mandatory discount to the sick funds, and we assumed that MS patients are exempt from co-payment.
- OTC drug costs were taken mainly from patients' indications (available for over 90% of the items). When a patient had omitted to indicate a price, the cost was inferred by using indications for the same item from other patients or when not available, mean costs of similar items in the data base. OTC costs were included in the societal perspective, but excluded in the public payer perspective.
- Investment costs were used as indicated by the patients, and the full cost of an investment was assigned to the year. As this was a cross-sectional study, it would be impossible to obtain information regarding earlier investments in order to calculate annuities; however, in any given year, a proportion of patients would make such investments. When patients had not indicated any cost, we used the average cost indicated for the same investment by all other patients, excluding however large outliers. In the societal perspective, all investments were included, while in the public

payer perspective only investments for which patients had indicated that they were paid for by a public payer were included.

- The cost for home care, household help, child care and similar services was based on the tariffs of the nursing care insurance of Bayern [37]. In the societal perspective each service was included at the full tariff, while in the public payer perspective the total amount for each patient was "capitated" at the maximum monthly allowance (Sachleistungen) for each disability level (Pflegestufe). When patients did not indicate their disability level, we assumed level II.
- The cost of informal care was considered to be a direct cost, as in the absence of family or relatives, someone else would have to provide the service, likely on a paid basis. However, rather than using the full hourly wage rate as a shadow price, we used 35% as in other published studies. The national average hourly gross wage for adults was taken from official national salary statistics [38].

### *2.4.2. Indirect Costs*

Indirect costs are constituted by sickness absences, early retirement or premature mortality due to the disease. The questionnaires provided information concerning short-term sickness absence, early retirement due to MS, or changes in working hours due to MS. Information on premature mortality would have to be obtained from other sources, but this was excluded from the study, as the impact of MS on mortality is relatively small and very difficult to estimate. The loss of production due to sickness absence was calculated for each patient, based on her/his current working status, and an average cost per patient calculated.

- In the societal perspective, indirect costs due to early disease-related retirement was calculated as one full year at the average national salary, as again in any given year, a number of patients would have to take early retirement. The annual production loss was based on the average gross monthly salary by gender in 1999 [38] plus employers' contributions (22%). The mean cost per day of sick leave for employed patients was thus estimated at 188 DM (based on a 37 hour week and 52 weeks per year, adjusted for the higher prevalence of women in MS).
- In the public payer perspective, sick days exceeding the six weeks during which employers have to maintain the remuneration were included, at a rate of 80% of gross

earnings (excluding employers contributions), or 123 DM. Invalidity pensions as indicated by the patients were included (Berufsunfähigkeitsrente – 977 DM per month, Erwerbsunfähigkeitsrente – 1423 DM per month) [39].

### *2.5.3. Intangible costs*

Intangible costs, i.e. costs due to pain, grief, anxiety, social handicap, etc., are usually omitted in cost of illness study. However, Henriksson et al provided an interesting estimate of these costs in the recent population based study in Sweden [1]. We have used a similar approach, calculating the difference in utilities between our sample and an age and sex-matched sample of the normal population in the UK, and the number of quality-adjusted life-years (QALYs) lost by the MS sample in one year. By assigning a value to (or willingness to pay for) a QALY, intangible costs due to MS can calculated. We used a value of 50,000 DM (US $ 25,000) as a value for Germany, but also the same value that was used in the Swedish study, (US $ 60,000 [40 41]).

## 2.6. Analysis

Resources used by each individual patient were valued with the relevant costs and an average cost per patient in the sample, and an average cost per patient at different levels of disability computed (mild, moderate, severe). Costs for smaller groupings will be reported at a later stage, with the cost-effectiveness analysis.

The societal perspective includes all resource utilization, regardless of the payer, while the public payer perspective includes only direct costs, based on official tariffs as well as transfer costs such as sick pay and invalidity pensions.

We indicate mean cost per patient for the sample as a whole, but also mean costs for those patients using the different resources. We omit extrapolation of the different types of resources to the full estimated prevalence in Germany, as it might be more useful to perform these calculations for patients at the level of the Länder, rather than the national level.

# 3. RESULTS

## 3.1. Patient sample

A total of 737 patients were included in the study. The response rate in the centers varied between 51.5% and 73%, with an 80% answer rate in the center where patients were first asked about their willingness to participate. The overall response rate was 66%.

There was very little missing data, and it was mostly concentrated in the section on the employment situation, where 7.5% of patients did not answer the question about employment during the past month. The EuroQol was completed by all patients; 717 answers could be analyzed for the EQ-5D (patients with missing answers were excluded, as the EQ-5D does not provide a system to integrate missing answers) and 703 patients provided a score on the VAS.

## 3.2. Background variables

***Table 1 – Descriptive statistics, background variables (n=737)***

| Variable | Proportion (%) or Mean (SD) |
|---|---|
| Gender | |
| Male (%) | 27.0 |
| Female (%) | 73.0 |
| Age | |
| Mean, SD | 41.9 (11.4) |
| Marital status | |
| Single (%) | 25.1 |
| Married/With partner (%) | 69.5 |
| Widowed (%) | 4.1 |
| No answer (%) | 1.4 |
| Living conditions | |
| Alone (%) | 12.8 |
| With family (%) | 77.9 |
| Long term care (%) | 1.6 |
| Other (%) | 5.7 |
| No answer (%) | 2.0 |

As expected, the proportion of female patients was much higher with 73%. The mean age was 42 years with a disease onset around 33.4 years. The vast majority of patients was married or lived with a partner, and an even higher proportion (78%) lived with family.

Around one third of patients had high school or university education (Abitur, Hochschulabschluss), almost half of the patients had completed a professional education (Lehrabschluss) and around one fifth had an educational level at or slightly above the minimum required (Hauptschulabschluss, Mittlere Reife).

***Table 2a – Descriptive statistics, education (n=737)***

| Variable | Proportion (%) or Mean (SD) |
|---|---|
| Education level | |
| Abgeschlossene Lehre (%) | 46.0 |
| Abitur (%) | 6.1 |
| Fachhochschule oder Hochschulabschluss (%) | 24.6 |
| Hauptschulabschluss (%) | 12.6 |
| Mittlere Reife (%) | 8.8 |
| No answer (%) | 1.9 |

38% of patients were employed or self-employed, and of these, 54% indicated to work full-time and 31% part-time, while 7.5% provided no answer. 40% of patients indicated that they had to stop working because of, and another 14% indicated that they have had to modify their working situation since being diagnosed with MS.

A very high proportion of patients (44%) of patients received invalidity pensions (Berufs- or Erwerbsunfähigkeitsrenten), and almost 25% were entitled to nursing care at home (ambulante Pflege). Of these, the majority received care at levels I and II, although most of these patients had severe disease (EDSS 7.0 and above). Very few patients were in long-term care (stationäre Pflege) and no conclusions regarding a relationship between EDSS and long term care can be drawn.

## *Table 2b - Descriptive statistics, employment situation(n = 737)*

| Variable | Proportion (%) |
|---|---|
| Employed during last month | 37.8 |
| full time | 54.4 |
| self employed | 6.8 |
| reduced time | 31.1 |
| no answer | 7.5 |
| | |
| Employment situation | |
| working | 28.8 |
| house work | 8.7 |
| retired | 45.3 |
| unemployed | 5.4 |
| student | 2.8 |
| other | 4.7 |
| no answer | 4.2 |
| | |
| Change in work situation | |
| No change | 35.5 |
| changed work | 4.3 |
| changed working hours | 6.5 |
| changed work and working hours | 2.7 |
| stopped working | 39.8 |
| no answer | 11.1 |
| | |
| Insurances and pensions | |
| Unemployment benefit (Arbeitslosengeld) | 4.6 |
| Retirement pension (Altersrente) | 3.6 |
| Disability pension (Berufsunfähigkeitsrente) | 3.8 |
| Invalidity pension (Erwerbsunfähigkeitsrente) | 40.3 |
| Nursing care (Ambulante Pflege) | 24.6 |
| Level I | 9.4 |
| Level II | 10.8 |
| Level III | 4.4 |
| Long term care (Stationäre Pflege) | 0.4 |
| Level I | 0.1 |
| Level II | 0.0 |
| Level III | 0.3 |
| Other | 4.2 |
| Social assistance (Sozialhilfe) | 4.1 |
| Other social insurances (Sonstige Sozialversicherungsleistungen) | 5.6 |

The distribution of patients among the different courses of disease is as expected and confirms the representativity of the sample. Around 40% of patients had benign or relapsing-remitting disease, around 35% had secondary progressive disease and around 20% indicated to have primary progressive disease. About one fifth of patients indicated to have other diseases.

***Table 3 - Descriptive statistics, disease information (n = 737)***

| Variable | Proportion (%) or Mean (SD) |
|---|---|
| Age at first symptom of MS | |
| mean (SD) | 33.4 (14.1) |
| Disease situation | |
| - 1 – no limitations (%) | 9.6 |
| - 2 – very slight disturbances in vision or mobility, or muscle weakness (%) | 19.9 |
| - 3 – moderate limitations, but fully able to walk without help (%) | 13.8 |
| - 4 – some limitations, but able to walk without help for up to 500 meters, and only slight limitations in daily activities (%) | 9.9 |
| - 5 - moderate limitations, but able to walk without help or rest for up to 200 meters, and many limitations in daily activities (%) | 7.5 |
| - 6 – substantial limitations and requiring often walking aids (sticks, crutches) to walk 100 meters (%) | 9.9 |
| - 7 – substantial limitations and always requiring walking aids to walk 20 meters (%) | 10.4 |
| - 8 – severe limitations and requiring a wheel chair (%) | 15.9 |
| - 9 – very severe limitations, mostly bed-ridden, but able to use the arms (%) | 1.5 |
| - 10 – always bed-ridden (%) | 1.0 |
| - no answer (%) | 0.5 |
| Course of disease | |
| benign (%) | 17.8 |
| relapsing-remitting (%) | 23.2 |
| secondary progressive (%) | 23.7 |
| relapsing-progressive (%) | 11.5 |
| primary progressive (%) | 20.2 |
| no answer (%) | 3.4 |
| Patients with concomitant illness/es (%) | 19.5 |

## 3.3. Direct costs

### *3.3.1. Inpatient care*

Over half of the patients (425 patients or 57.7 %) reported hospital stays during the past year, with an average length of stay of 27.8 days, most often in the neurology ward (73%). For the entire cohort, this results in a mean of 16 hospitalization days (which compares to a mean of 5 days in the Swedish study and of 2 days in the UK study).

In order to verify the accuracy of patients' indication, we compared inpatient days obtained from questionnaires and from hospital charts. All patients with a hospitalization according to their charts were matched with the respective questionnaires and the number of hospitalization days compared. Of the 202 patients for which charts were abstracted, 105 were hospitalized during the preceding 12 months, with a mean length of stay of 27.15 days (range 108 days). The mean length of stay calculated from the questionnaires of the same 105 patients was 26.90 days (range 102 days). In view of this finding used the indications from all 737 questionnaires without any adjustments and analyzed the charts separately.

12 patients (1.6 %) lived in long-term care facilities. Of these patients only 3 indicated that they were receiving inpatient-nursing care, and we therefore only included these patients in the calculations of the costs to public payers.

***Table 4a – Mean costs of inpatient care (n = 737), societal perspective***

| **Inpatient care** | **Proportion using the resource** | **Average number of inpatient days per patient and year** | | **Mean cost per patient and year DM (1999)** | |
|---|---|---|---|---|---|
| | | Entire sample | Patients using | Entire sample | Patients using |
| Total inpatient days | 57.7 % | 16.2 | 27.8 | 6132 | 10634 |
| • *of which neurology* | *73.0 %* | 11.1 | 19.4 | 4142 | 7320 |
| Long-term care | 1.6 % | 5.9 | 365 | 547 | 33600 |
| **Total inpatient care** | **58.6 %** | **22.1** | - | 6679 | **11543** |

***Table 4b – Mean costs of inpatient care (n = 737), public payer perspective***

| **Inpatient care** | **Proportion using the resource** | **Average number of inpatient days per patient and year** | | **Mean cost per patient and year DM (1999)** | |
|---|---|---|---|---|---|
| | | Entire sample | Patients using | Entire sample | Patients using |
| Total inpatient days | 57.7 % | 16.2 | 27.8 | 6132 | 10634 |
| • *of which neurology* | *73.0 %* | 11.1 | 19.4 | 4142 | 7320 |
| Inpatient nursing care (stationäre Pflege, levels I-III) | 0.4% | - | - | 123 | 30400 |
| **Total inpatient care** | **58.6 %** | **22.1** | **-** | **6255** | **10784** |

## *3.3.2. Ambulatory care*

Patients had frequent contacts with physicians, most often with the neurologists, followed by the general practitioner. A large number of patients had physiotherapy, and one fifth had home visits by nurses. Patients also used practitioners that are not paid for by the health insurance system.

***Table 5a – Mean costs of ambulatory care (n = 737), societal perspective***

| **Practitioner** | **Used by (%)** | **Mean number of visits per patient and year** | | **Mean cost per patient and year in DM (1999)** | |
|---|---|---|---|---|---|
| | | Entire sample | Patients using | Entire Sample | Patient using |
| | | | | | |
| Day stays | 16.7 | 2.4 | 14.4 | 885 | 5308 |
| GP | 42.9 | 6.4 | 15.2 | 444 | 1036 |
| Neurologist | 66.1 | 7.2 | 10.4 | 557 | 843 |
| Other specialist | 25.0 | 2.8 | 10.4 | 198 | 794 |
| Home visit, physician | 17.9 | 3.2 | 18.4 | 225 | 1259 |
| Nurse or physiotherapist | 29.2 | 19.2 | 66.0 | 558 | 1914 |
| Home visits, nurse | 19.1 | 19.2 | 100.8 | 1438 | 7520 |
| Occupational therapist | 1.9 | 1.0 | 14.3 | 65 | 3682 |
| Chiropodist | 2.7 | 0.3 | 3.2 | 4.3 | 166 |
| Speech therapist | 1.6 | 0.5 | 8.7 | 9.5 | 637 |
| Continence advisor | 3.7 | 0.3 | 1.9 | 0.9 | 26 |
| Psychologist | 6.1 | 1.4 | 5.1 | 150 | 2164 |
| Social worker | 3.5 | 1.1 | 8.2 | 55 | 1607 |
| Optician | 12.6 | 0.7 | 1.4 | 21.7 | 175 |
| Other paramedical | 8.0 | 0.4 | 1.3 | 21 | 265 |
| **Total** | **91.5** | **66.1** | **-** | **4636** | **5069** |

***Table 5b – Mean costs of ambulatory care (n = 737), public payer perspective***

| Practitioner | Used by (%) | Mean number of visits per patient and year | | Mean cost per patient and year in DM (1999) | |
|---|---|---|---|---|---|
| | | Entire sample | Patients using | Entire Sample | Patient using |
| Day stays | 16.7 | 2.4 | 14.4 | 885 | 5308 |
| GP | 42.9 | 6.4 | 15.2 | 180 | 421 |
| Neurologist | 66.1 | 7.2 | 10.4 | 315 | 478 |
| Other specialist | 25.0 | 2.8 | 10.4 | 107 | 431 |
| Home visit, physician | 17.9 | 3.2 | 18.4 | 187 | 1026 |
| Nurse or physiotherapist | 29.2 | 19.2 | 66.0 | 558 | 1914 |
| Home visits, nurse* | - | - | | - | - |
| Occupational therapist | 1.9 | 1.0 | 14.3 | 65.0 | 3682 |
| Chiropodist | 2.7 | 0.3 | 3.2 | 4.3 | 166 |
| Continence advisor | 3.7 | 0.3 | 1.9 | 0.9 | 26 |
| Psychologist | 6.1 | 1.4 | 5.1 | 150.0 | 2164 |
| Social worker | 3.5 | 1.1 | 8.2 | 54.6 | 1607 |
| Other paramedical | 6.4 | 0.3 | 4.4 | 16.9 | 264 |
| **Total** | **88.6** | **26.4** | - | **2527** | **2813** |

* in the public payer perspective, home visits are included in nursing care (ambulante Pflege), Table 7b

### *3.3.3. Drugs*

Prescribed (and reimbursed) drugs accounted for 96% of all drug costs. The vast majority of drug costs in this cohort was for interferons that were used by 39% of the patients. This is not surprising, as patients were recruited at university centers where newer drugs are generally used in higher proportions. Similarly, Copolymer-1 that is not routinely available in Germany, was used by 4.2 % of patients in this sample. On a nationwide level, interferons are used by around 15%. (A similar finding was made in the Swedish study, where 42% of patients used interferons, while the nationwide use was around 10%.)

Thus, if our cost estimates are to be extrapolated to a national or regional level, drug usage has to be corrected by a factor of four. We therefore adjusted the usage to 12% for interferons and 1% of glatiramer acetate. No major difference in resource consumption between patients using interferons or not could be detected and no other adjustments were therefore made.

***Table 6 - Mean cost of prescription and OTC medication (n=737)***

| Drugs | Used by (%) | Cost per patient and year (DM) | |
|---|---|---|---|
| | | Whole sample | Only patients using the resource |
| Interferons | 38.9 | 8285 | 21275 |
| Azathioprine | 4.2 | 77 | 1832 |
| Glatiramer acetate | 4.2 | 1313 | 31218 |
| Other prescribed drugs | 53.4 | 1214 | 2318 |
| OTC drugs | 76.4 | 439 | 1063 |
| **All drugs (societal perspective)** | **84.0** | **11329** | **13489** |
| *adjusted for interferon use* | | *4596* | |
| **All drugs excluding OTC (public payer perspective)** | **76.4** | **10889** | **14254** |
| *adjusted for interferon use* | | *4157* | |

### *3.3.4. Community and other services*

Only a limited number of patients used home care in addition to nurse visits but as many as 118 patients required home help. Most of these services were paid for by patients themselves, except for nursing care and day care, which were paid for by the nursing insurance up to the relevant ceilings.

***Table 7a – Cost of using different services as a consequence of MS (n = 737), societal perspective***

| Services | Used by (%) | Cost per patient and year (DM) | |
|---|---|---|---|
| | | Entire sample | Only patients using the resource |
| Home care (Heimpflege)* | 5.3 | 5592 | 105668 |
| Home help (Haushaltshilfe) | 16.0 | 1270 | 7929 |
| Child care | 1.2 | 1267 | 103827 |
| Day care | 0.5 | 24 | 4469 |
| Meals | 2.2 | 47 | 2177 |
| Other | 9.1 | 341 | 3751 |
| **Total** | **25.2** | **8541** | **33845** |

* in addition to home visits by nurses, see table 5a

***Table 7b – Cost of using different services as a consequence of MS (n = 737), public payer perspective***

| Services | Used by (%) | Cost per patient and year (DM) | |
|---|---|---|---|
| | | Entire sample | Only patients using the resource |
| Nursing care (Ambulante Pflege)* | 14.4 | 1326 | 9220 |
| Day care | 0.5 | 24 | 4469 |
| Other | 5.3 | 101 | 1925 |
| **Total** | **18.6** | **1452** | **7806** |

**Including home visits by nurses*

### *3.3.5. Adaptations and investments*

Investment costs were dominated by adaptations to the house, modifications to the car and wheelchairs, both in terms of how many patients did require such adaptations and their cost.

Over 30% of patients made adaptations to the house, in particular to the bathroom and the kitchen, and the cost of these modifications ranged between 8000 and 13000 DM. 13 patients required a stair life, at a mean cost of over 22000 DM. 43 patients had their car modified, at a mean cost of almost 10000 DM. The mean cost of adaptations and special equipment per patient was 3934 DM and 64% of these costs were borne by the patients themselves.

Wheelchairs were required by 17% of patients and represent the highest cost per patient in the sample, 1288 DM, but this cost was paid for by public insurance for almost all patients (1278 DM per patient in the sample).

Overall, investment costs were 5322 DM, of which public insurance covered 2687 DM (50.5%).

***Table 8a – Investments, adaptations made and items purchased/received (n = 737) societal perspective***

| **Adaptations and items** | **Used/made by (%)** | **Cost per patient and year (DM)** Whole sample | Only patients using resource |
|---|---|---|---|
| Adaptation of kitchen | 4.1 | 521 | 12809 |
| Adaptation of bathroom | 11.4 | 917 | 8044 |
| Adaptation of other part of the house | 6.5 | 509 | 7816 |
| Bed elevator | 3.1 | 99 | 3176 |
| Stair lift | 1.8 | 395 | 22390 |
| Stair ramp | 1.9 | 70 | 3693 |
| Other ramps | 2.0 | 58 | 2877 |
| Alarm | 1.4 | 14 | 1053 |
| Adaptations at work | 0.5 | 0 | 0 |
| Adaptations of car | 5.8 | 571 | 9785 |
| Walking aids | 17.8 | 145 | 808 |
| Wheelchair | 17.0 | 1288 | 7587 |
| Spectacles | 17.4 | 150 | 463 |
| Special kitchen utensils | 1.9 | 11 | 629 |
| Special hygiene utensils | 5.7 | 49 | 730 |
| Special writing devices | 2.0 | 13 | 645 |
| Other | 11.0 | 508 | 4568 |
| **Total** | **48.2** | **5322** | **11049** |

***Table 8b – Investments, adaptations made and items purchased/received (n = 737) public payer perspective***

| **Adaptations and items** | **Used/made by (%)** | **Cost per patient and year (DM)** Whole sample | Only patients using resource |
|---|---|---|---|
| Adaptation of kitchen | 0.9 | 67 | 7444 |
| Adaptation of bathroom | 3.9 | 280 | 7179 |
| Adaptation of other part of the house | 1.9 | 128 | 6736 |
| Bed elevator | 2.7 | 91 | 3370 |
| Stair lift | 0.5 | 89 | 17800 |
| Stair ramp | 0.9 | 25 | 2777 |
| Other ramps | 1.2 | 33 | 2750 |
| Alarm | 0.8 | 7 | 875 |
| Adaptations at work | 0 | 0 | 0 |
| Adaptations of car | 1.5 | 124 | 8266 |
| Walking aids | 16.0 | 138 | 863 |
| Wheelchair | 16.6 | 1278 | 7699 |
| Spectacles | 3.8 | 15 | 395 |
| Special kitchen utensils | 0.4 | 2 | 500 |
| Special hygiene utensils | 2.6 | 32 | 1230 |
| Special writing devices | 0.3 | 1 | 333 |
| Other | 5.8 | 377 | 6500 |
| **Total** | **34.1** | **2687** | **7879** |

### *3.3.6. Informal care*

Patient in this cohorts lived predominantly at home, with their family, and thus informal care use was very frequent. 59.7% of all patients received care from family members, relatives or friends, for an average of 27 hours per week or 15 hours per week for the entire sample. Using a rate of 35% of the national average hourly gross wage for adults, the weekly cost per patient using informal care was 274.1 DM or 152.3 DM per patient in the entire cohort. The total mean cost of informal care per patient was 7917 DM.

## 3.4. Indirect costs

### *3.4.1. Short term sickness absence*

37.8 % of patients in the sample were employed. The average number of sickness-absence days for these working patients was 51.6 days per year. Correcting for reduced time employment, the average number of days lost per year was 34.7 which at a gross daily cost of 188 DM yields an average yearly cost of 6523 DM per employed patient, or 2466 DM per patient considering the entire sample.

An average of 9 days per patient (corrected for part time employment) exceeded the six weeks where remuneration is maintained by the employer, and thus the average yearly cost to the sick fund was 1107 DM per employed person, or 419 DM per patient considering the entire sample.

### *3.4.2. Long term sickness absence*

293 patients (39.8 %) stated that they have had to given up work due to MS. At an annual cost of 63,800 DM, the average cost per patient in the cohort was 25,364 DM in the societal perspective.

297 patients (40.3%) indicated that they received an invalidity pension (Erwerbsunfähigkeitsrente) and a further 28 patients (3.8%) indicated to receive a disability pension (Berufsunfähigkeitsrente). Thus, the total cost paid by public payers was 7326 DM per patient and year.

## 3.5. Total costs (direct and indirect)

Direct costs constitute 61.4% of total costs and amount to 44,324 DM per patient and year. Inpatient care constituted 15.1% of direct costs and 9.3% of total costs. Drugs represented 25.6% of direct and 15.7% of total costs, due to the higher than average use of interferons in this sample. If interferon treatment is adjusted to the national level, direct costs represent 57.5% of total costs (65,421 DM) and drugs make up for 12.2% of direct and 7% of total costs. Services such as home care, home help, adaptations and investments represent 31% of total direct and 19% of total costs and are largely paid for by the patients themselves. Informal care represents 17.9% of direct and 11% of total costs.

Indirect costs represent 38.6% of total costs in this sample (or 42.5% when direct costs are adjusted for interferon use). This proportion is lower than in most published cost of illness studies across the world, where indirect costs represented between 70-80% of all costs. However, it is very similar to what was found in the two similar bottom-up studies in Sweden and the United Kingdom, and confirms that most published studies did not include all costs related to MS.

***Table 9a – Mean total cost per patient and year, societal perspective DM, 1999)***

| Costs | Cost per person and year | Share of total cost %) |
|---|---|---|
| Hospital inpatient care | 6679 | 9.3 |
| Ambulatory care | 4636 | 6.4 |
| - day stays | 885 | 1.2 |
| - physicians | 1424 | 2.0 |
| - nurses/physiotherapists | 1996 | 2.8 |
| - paramedical | 331 | 0.5 |
| Drugs | 11329 | 15.7 |
| - interferons | 8285 | 11.5 |
| Services | 8541 | 11.8 |
| Adaptations | 5322 | 7.2 |
| Informal care | 7917 | 11.0 |
| **Total direct costs** | **44324** | **61.4** |
| **Total indirect costs** | **27830** | **38.6** |
| **Total cost** | **72154** | **-** |

Less than half of these total costs (43% before adjustment for interferon use, or 38 % after adjustment) are paid for by the public health care and insurance system.

***Table 9b – Mean total cost per patient and year, public payer perspective (DM, 1999)***

| Costs | Cost per person and year | Share of total cost %) |
|---|---|---|
| Hospital inpatient care | 6255 | 19.8 |
| Ambulatory care | 2527 | 8.0 |
| - day stays | 885 | 2.8 |
| - physicians | 789 | 2.5 |
| - nurses/physiotherapists | 558 | 1.8 |
| - paramedical | 292 | 0.9 |
| Drugs | 10889 | 34.5 |
| - interferons | 8285 | 26.3 |
| Services | 1452 | 4.6 |
| Adaptations | 2687 | 8.5 |
| Transfer costs | 7735 | 24.5 |
| **Total cost** | **31545** | - |

***Table 9c – Summary of mean total cost per patient and year, adjusted for national interferon usages (DM, 1999)***

| Costs | Cost per person and year | |
|---|---|---|
| | Societal perspective | Public payer perspective |
| Hospital inpatient care | 6697 | 6255 |
| Ambulatory care | 4636 | 2527 |
| Drugs | 4596 | 4156 |
| Services | 8541 | 1452 |
| Adaptations | 5322 | 2687 |
| Informal care | 7917 | - |
| Indirect costs | 27830 | - |
| Transfer costs | - | 7735 |
| **Total cost** | **65421** | **24812** |

## 3.6. Quality of life (utilities)

The EQ-5D was completed by 717 patients completed and the mean utility for the sample derived from the EuroQol health status matrix was 0.552. There was a slight difference between women and men, the values being 0.57 and 0.51 respectively, and patients with a relapse during the past month had slightly lower utilities. The values ranged from 0.919 to - 0.429. Negative values are possible with the EQ-5D, as some patients may judge a health states as being worse than death, and we used these negative values in our calculations.

703 patients had entered a value for the VAS. The mean value on the VAS was slightly higher than with the EQ-5D (56.85), which can be partly explained that there is no possibility of negative values on the thermometer.

***Table 10 – Mean utilities (EQ-5D and VAS)***

| | N | Mean values (SD) | Range |
|---|---|---|---|
| **EQ-5D** | | | |
| All patients | 717 | 0.552 (0.331 ) | -0.429, 0.919 |
| Relapses during the past month | | | |
| • patients with | 95 | 0.558 (0.285) | -0.331, 0.919 |
| • patients without | 622 | 0.551 (0.337) | -0.429, 0.919 |
| **Visual Analogue Scale** | | | |
| All patients | 703 | 56.85 (24.15) | 0 – 100 |

## 3.7. Functional status

EDSS values were available for those patients for which hospital charts were abstracted and these were used regardless of patients' answers on the mobility questionnaire. For the other patients, the matrix developed from the disease descriptions in the questionnaire was used to assign EDSS scores. The cohort covered the entire spectrum of the EDSS and the mean score was estimated at 4.4. There were relatively few bed-bound patients (disease description 9 and 10 or EDSS scores above 7.5) which could be due to the modalities of data collection. These patients represented thus only 2.4% which compares to 4-5% in the Swedish and UK studies. It

is thus possible that our study underestimates total costs slightly, as the mean cost for patients at this level is about 43% higher than costs for wheelchair bound patients.

***Table 11 – Functional status according to EDSS (n=733)***

| EDSS | Disease description | Number of patients | Proportion (%) |
|---|---|---|---|
| <= 3.0 | 1, 2, 3 | 320 | 43.6 |
| 3.5, 4.0 | 4 | 73 | 10.0 |
| 4.5, 5.0 | 5 | 55 | 7.5 |
| 5.5, 6.0 | 6 | 73 | 10.0 |
| 6.5 | 7 | 77 | 10.5 |
| 7.0 | 8 | 117 | 16.0 |
| >= 7.5 | 9, 10 | 18 | 2.4 |

## 3.8. The effect of functional status and QoL on costs

As in all previously published studies, costs increase as disability increases, and quality of life decreases as the disease progresses. In order to make these results comparable to published studies, results are presented for definitions of mild, moderate and severe patients.

***Table 11a - Annual cost per patient by disability level (unadjusted for interferon use)***

| | Utilities | Costs (DM, 1999) | | | | |
|---|---|---|---|---|---|---|
| Disability level | EQ-5D | Direct costs | Indirect costs | Informal care costs | Total costs | Public payer |
| Mild (43.6%) (EDSS <= 3.0) | 0.7569 | 19955 | 14168 | 1522 | **35646** | **22123** |
| Moderate (27.5%) (EDSS 3.5 – 6.0) | 0.5470 | 34891 | 34939 | 6249 | **76080** | **33756** |
| Severe (28.9%) (EDSS >= 6.5) | 0.2315 | 63521 | 41988 | 18824 | **124334** | **47750** |

***Table 11b - Annual cost per patient by disability level (adjusted for interferon use)***

| Disability level | Mean total cost per patient (DM) | |
|---|---|---|
| | Societal perspective | Public payer perspective |
| Mild (43.6) - (EDSS <= 3.0) | 27800 | 14300 |
| Moderate (27.5%) - (EDSS 3.5 – 6.0) | 71250 | 28900 |
| Severe (28.9%) - (EDSS >= 6.5) | 119750 | 43100 |

## 3.9. Intangible costs

Patients in our study lost a total of 230.5 QALYs due to their MS, or an average of 0.333 QALY per patient (0.317 for women, 0.375 for men). As population values for the EQ-5D by age and gender for Germany are not published, we used the original values from the UK to calculate this QALY loss for illustrative purposes.

Using 50,000 DM (25,000 US$) as a hypothetical value of a QALY as well as the hypothetical value of 120,000 DM (60'000 US$) used in the Swedish study, intangible costs per patient were 16,650 DM and 40'000 DM per patient and year, respectively.

***Table 12a– QALYs lost (women)***

| Age Group | Mean utility (UK population) | Mean utility (sample) | Difference | Number of patients | QALYs lost |
|---|---|---|---|---|---|
| 20-29 | 0.936 | 0.751 | 0.185 | 72 | 13.32 |
| 30-39 | 0.914 | 0.626 | 0.288 | 167 | 48.10 |
| 40-49 | 0.875 | 0.526 | 0.349 | 135 | 47.12 |
| 50-59 | 0.817 | 0.487 | 0.33 | 88 | 29.04 |
| 60-69 | 0.814 | 0.275 | 0.539 | 38 | 20.48 |
| 70-79 | 0.741 | 0.356 | 0.385 | 6 | 2.31 |
| **Total** | **n.a.** | **n.a.** | **n.a.** | **506** | **160.36** |

***Table 12b– QALYs lost (men)***

| Age Group | Mean utility (population) | Mean utility (sample) | Difference | Number of patients | QALYs lost |
|---|---|---|---|---|---|
| 20-29 | 0.941 | 0.782 | 0.159 | 16 | 2.54 |
| 30-39 | 0.915 | 0.543 | 0.372 | 64 | 23.81 |
| 40-49 | 0.890 | 0.531 | 0.359 | 68 | 24.41 |
| 50-59 | 0.804 | 0.343 | 0.461 | 26 | 11.99 |
| 60-69 | 0.782 | 0.231 | 0.551 | 10 | 5.51 |
| 70-79 | 0.773 | 0.157 | 0.616 | 3 | 1.85 |
| **Total** | **n.a.** | **n.a.** | **n.a.** | **187** | **70.11** |

# 4. DISCUSSION

## 4.1. General Discussion

This study used the same methodology as two recent observational studies in Sweden and the United Kingdom, with the objectives to estimate the total burden of multiple sclerosis in Germany, to relate disease severity to costs and to quality of life, and to compare the results to the Swedish and UK studies.

The study was performed at University Hospitals, which has the potential to bias the patient sample towards more severely ill patients. This is unlikely to be the case in MS, as MS patients are a well-defined group and are generally treated in specialized MS or neurology centers. On the contrary, if there was a bias, it is likely to be towards patients with mild and moderate disease, as patients with severe disease who are fully bed-bound will not be followed in these ambulatory centers. This is evidenced by the fact that only 2.4% of patients in the German sample were bed-bound, while the proportion was 5-6% in the Swedish and UK studies. As a consequence, patients with mild disease constituted a larger proportion in the German cohort. As mean costs for bed-bound patients were approximately 43% higher than those for wheelchair-bound patients, mean total costs per patient might be slightly underestimated. It is difficult to assess by how much costs might have been underestimated, but if we were to increase the proportion of bed-bound patients to 5%, mean total cost per patient in the cohort would increase by about 500 DM.

University hospitals also tend to use newer and more expensive treatments, and this can be clearly seen in the high proportion of patients treated with interferons (39%) and glatiramer acetate (4%). An almost identical result was found in the Swedish study where data collection was in the Stockholm area. In order to be able to estimate the total cost of MS treatment in Germany, we have adjusted interferon use to the national average (~12-15%).

Except for these two potential biases, the cohort appears representative of the German MS population: Patients are distributed across the entire spectrum of the

disease and around 16% of patients were fully wheelchair bound. Similarly, the sample appears representative for the course of the disease, with about 20% of patients with primary progressive, 35% with secondary progressive, 23% with relapsing-remitting and 18% with benign disease.

In economic studies, the societal perspective is generally preferred, as the relevant question is the cost of a disease to society as a whole, rather than what monetary flows actually take place. Thus, all costs should be included, regardless to whom they occur, and resources should be valued with their opportunity cost. However, opportunity costs are rarely available in Germany, where tariffs are generally used – and while for some resources tariffs may accurately reflect their costs, for many resources this is not the case. We have attempted to estimate opportunity costs for some of the resources such as ambulatory visits, but this has not been possible for inpatient care. We also used the full cost for nursing care regardless of the maximum amounts fixed by the nursing care insurance, as well as the full costs of other services as patients indicated them. Nevertheless, it is possible that total costs to society are still underestimated, as tariffs appear to include incentives for a reduction in usage and are hence lower than the full opportunity costs.

Unit costs used in this study represent tariffs from the Statutory Health Insurance (GKV) for all patients, although approximately 10% of patients in Germany are privately insured. However, it is impossible to establish the exact charge to private insurers for each of the resources collected in this bottom-up study. As they might be higher than the GKV tariffs, this may again lead to an underestimate of total costs.

A cost of illness study as the one presented here is however also interesting from a public payer perspective, and we therefore present costs paid for by the public insurance system (health care, nursing care, invalidity pensions). Not surprisingly, less than half of total costs are paid for by the public insurance system, and patients and their family bear a substantial amount of costs themselves. This was even more pronounced in the UK study, where the National Health Service covered an estimated 20% of costs, mostly due to the fact that informal care constituted the largest cost component. Contrary to this, the Swedish system covers between 80-90%.

## 4.2. Comparison of the Swedish, UK and German Studies

It is interesting to compare the results of the three studies, as for the first time in this field large studies using an identical methodology are available. And not surprisingly, the patient demographics are very similar, while resource consumption – or rather how patients are cared for – varies substantially.

The major similarities are:

- the proportion of female versus male patients - around 70% to 30%.
- the mean age - between 40 and 50
- family situation – around 70% married or cohabiting, with most patients living at home
- employment situation – around 40% working
- onset of disease – between 30 and 35
- change in working situation – around 40% retired early due to MS
- mean EDSS level – between 4.4 and 5.1 (lowest in Germany)

The major differences are found in inpatient care, ambulatory visits and nursing care services:

- more patients were admitted to hospital in Germany than in the other two countries – 58% in Germany versus 3% in Sweden and 20% in the UK
- patients in Germany also had far more inpatient days in a year (16 days) than their counterparts in Sweden (5 days) and the UK (2 days)
- outpatient visits were more frequent in Germany than in the other countries
  - patients were seen by neurologist on average 7.2 times in Germany versus 4.1 times in Sweden and 2.4 times in the UK
  - general practitioner visits were 6.4 in Germany versus 0.8 in Sweden and 4.2 in the UK
- physiotherapy was used intensively in Germany and Sweden – 19.2 and 26.4 visits respectively, but not in the UK (7.2 visits)
- although all three studies included patients in university centers, interferon use was very different – over 40% of patients received interferons in

Germany and in Sweden (national average in both countries around 12-15%), compared to only 2.6% of patients in the UK

- OTC drugs were used by 76.4% of patients in Germany, versus 43% in Sweden and 47% in the UK
- Services such as home help and child care were used by a similar proportion in all countries, but home care varied substantially; although comparisons are somewhat difficult because services are organized in a very different ways, it appears that Sweden is providing most and the UK least services, with Germany somewhere in the middle.
- The major difference is found in the provision of personal assistants to about 23% of patients in Sweden, a service that does not exist elsewhere. As a consequence, fewer patients can live alone at home in Germany (12.8%) and the UK (13.4%) than in Sweden (34%).

A direct comparison of total costs between the three countries is difficult, as German costs are essentially based on tariffs, while full societal opportunity costs are available in the other two countries. We have tried to adjust partly for this, but the comparison must still be considered with caution.

- Costs in Germany, 65,400 DM or 32,000 € (corrected for interferon use), are midway between Sweden at 409'000 SEK or 49,000 € (corrected for interferon use) and the UK (16'700 £ or 27,000 €). (Figure 1)
- Direct costs (excluding informal care) represent 57.5% in Germany, versus 63% in Sweden and 28% in the UK. (Figure 2)
- The largest difference is found in informal care costs that represent 11% of total costs in Germany, while they represent 4.7% in Sweden and 26% in the UK. (Figure 3)
- The difference in indirect costs is less pronounced, with 38.5% in Germany versus 33% in Sweden and 46% in the UK, and similar amounts of patients indicated that they had to stop working or change their employment because of their MS. (Figure 4)

***Figure 1 – Comparison Germany, Sweden, UK – Mean total costs***

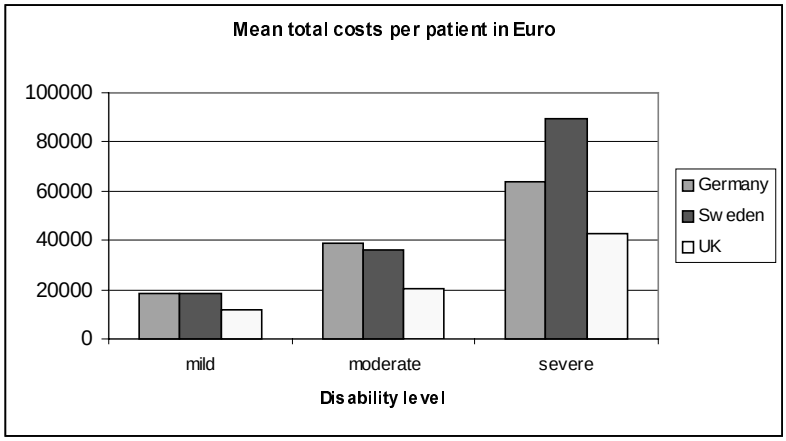



***Figure 2 – Comparison Germany, Sweden, UK – Mean direct costs***

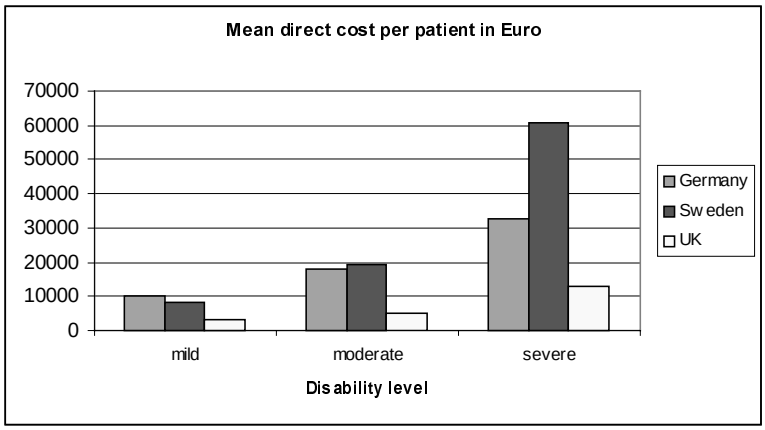



***Figure 3 – Comparison Germany, UK and Sweden – Mean informal care costs***

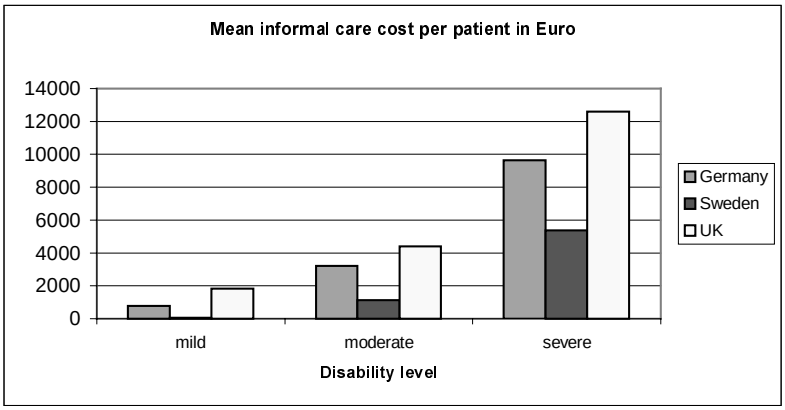
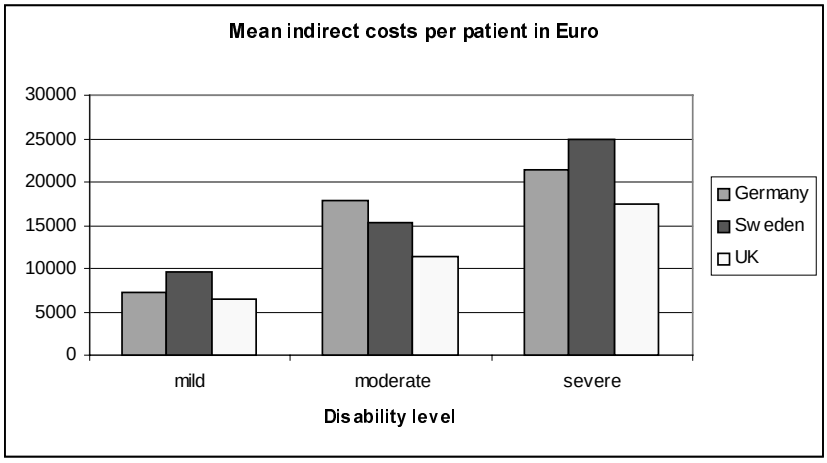
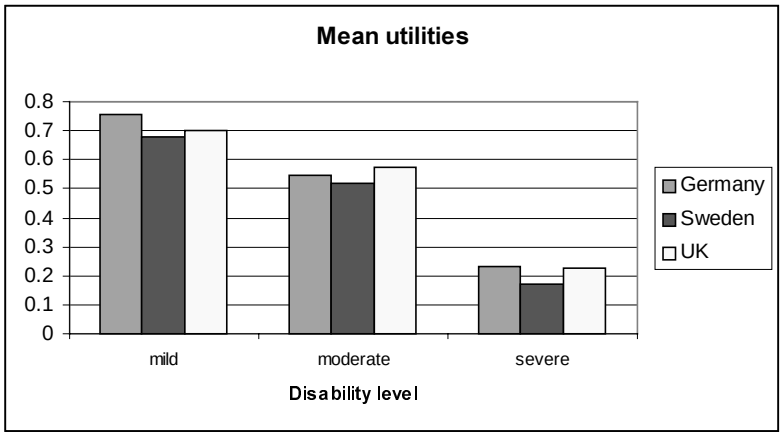


***Figure 4 – Comparison Germany, UK and Sweden – Mean indirect costs***




- Utility values with the EQ-5D were similar in the three countries, as were differences in quality of life between patients with mild, moderate and severe disease. (Figure 5)
- The average QALY loss due to MS was 0.33 in Germany, 0.49 in Sweden, and 0.39 in the UK. It is however difficult to draw any conclusions from this, as population values in Germany are not available and UK values have been used. If Swedish population values (which are overall higher than the UK values) are used, the average QALY loss in Germany is 0.38 – which would lead to an intangible cost of 19,000 DM.

***Figure 5 – Comparison UK and Sweden – Mean utilities by disease level***



## 4.3. Comparison of the German Top-Down and Bottom-Up Studies

A further very interesting comparison is between the results of the available top-down cost of illness study for Germany and our results (payer perspective). Direct costs in the bottom-up study are, as expected, substantially higher than in the top down study, 2.05 billion DM versus 1.03 billion DM. A similar relationship was found when comparing the top down and bottom up studies in Sweden. The reasons for this are different for different types of resources, but the majority of the difference is due to the fact that a considerable part of the costs cannot be found in official statistics. Resource use in databases is identified using codes, generally ICD codes, and only utilization under the selected code or codes is included. Thus, all costs that are coded slightly differently will be omitted. While this ensures that only MS-related costs are included, it will likely underestimate resource use. Conversely to this, patient indications may overestimate resource use, as it may sometimes be difficult to separate costs due exclusively to MS from other costs.

- The mean number of hospitalization days in our study was 28 days for those patients that were hospitalized (16 if the entire cohort is considered), while the earlier study found 19 days. It is conceivable that patients overestimate inpatient days, but the comparison of the charts to the questionnaires indicate that this was not the case, and the difference it more likely due to an underestimate in the top-down study, where only admissions coded for MS (ICD-340) were captured.
- Costs for ambulatory care, including rehabilitation programs and nursing care are similar. The comparison is somewhat difficult, as the grouping of costs was slightly different in our study, because of the difficulty to separate nursing care from home visits in the questionnaire.
- Drug costs in our study are higher for similar reasons as above: only those prescriptions coded for MS were included, and in addition, interferon use was more limited in 1998. On the other hand, our study may overestimate some of the drug costs, as most patients did not indicate the dose and duration of prescription drugs. Estimates based on defined daily doses, average duration and package sizes may not be entirely accurate, but this could lead both to over- and underestimates.

- Costs of devices and investments, even when paid for by an official organization, will be very difficult to capture in statistics and the far higher costs in our study are therefore not surprising.
- Costs for sick-leave are difficult to compare between the two studies, as the top-down study included both costs to the sick-funds and to employers, while our study only included sick-days exceeding 6 weeks. However, it appears that the findings are similar, with around 60 days per patient and year in the top-down study and 52 days in our study.
- The cost for invalidity pensions was higher in our study, and this difference appears to be due to methodological differences. In the top-down study, approximations had to be made regarding the proportion of MS patients in the total number of pensions, which is difficult. Contrary to this, the exact proportion of MS patients that do receive a pension could be established and costs hence more accurately estimated.

| **Type of cost** | **Total estimated costs for 120'000 patients** | |
|---|---|---|
| | ***Top Down Study 1997/8 DM*** | ***Bottom Up Study 1999 DM*** |
| Inpatient cost | 353 million | 750 million |
| Ambulatory cost (incl. nursing care and rehabilitation) | 437 million | 477 million |
| Drugs<br>of which Interferons, glatiramer acetate | 218 million<br>143 million | 498 million<br>344 million |
| Devices and investments | 23 million | 322 million |
| **Total health insurance** | **1031 million** | **2047 million** |
| Sick leave | 113 million | 50 million |
| Invalidity pensions | 288 million | 880 million |
| **Total public payer** | **1432 million** | **2977 million** |

Note: for both studies, these figures are estimates based on extrapolations

In conclusion, we believe that this study represents a more complete picture of costs due to MS, although we cannot exclude that some expenses (e.g. drugs) may have been overestimated.

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# Appendix A – Costing

| Main Resources | Societal Perspective | Tariffs | Payer Perspective | Source / Assumptions |
|---|---|---|---|---|
| | | | | |
| **Hospitalisation (days)** | | | | |
| - Neurology | 376.61 | 376.61 | 376.61 | PKV Database 2000 |
| - General Medicine | 279.18 | 279.18 | 279.18 | PKV Database 2000 |
| - Internal Medicine | 279.18 | 279.18 | 279.18 | PKV Database 2000 |
| - DAY STAYS | 369.30 | 369.30 | 369.30 | PKV Database 2000 |
| - Long term care | 120.80 | | Nursing care | |
| | | | | |
| **Ambulatory visits** | | | | |
| Visits to physicians: | | | | |
| - GP | 68.00 * | 26.64 / 3.60 | 27.65 ** | EBM 2000 Ziff 1,2 *** |
| - Neurologist | 82.00 * | 9.72 / 3.60 | 46.45 ** | EBM 2000 Ziff 1,2 |
| - Urologist | 75.00 * | . / 3.60 | 40.75 ** | |
| Home visits: | | | | |
| - GP | 28.84 + visit | 28.84 + visit | 28.84 + visit | EBM 200 Ziff 25 |
| - Nurse | 29.00 | -- | 29.00 | -- |
| Other professionals: | | | | |
| - Occupational Therapy | 64.00 | | 64.00 | 4 Munich practices |
| -Chiropractor | 12.98 | 12.98 | 12.98 | EBM Ziff 3211 |
| - Speech Therapy | 18.25 | 18.25 | 18.25 | EBM Ziff 1634 |
| - Psychologist | 104.55 | 104.55 | 104.55 | EBM Ziff 860 |
| - Social Assistant | 49.00 | | | |
| - Optician | 30.00 | | | Patient indications |
| | | | | |
| **Services** | | | | |
| - Homecare | 74.49 | 74.49 | Capitated at nursing care levels | LK 1, 2a, 3, 4 plus 2x transportation **** |
| - Household help | 18.38 | 18.38 | As above | LK 10 **** |
| - Child care | 68.79 | 68.79 | As above | LK 1,2a, 3, 4 plus 1x transport costs **** |
| - Day clinic | 120.80 | 120.80 | As above | EBM 2000 Ziff 63-66 mean value |
| **Nursing Care** | | | | |
| Ambulatory care<br>Homecare,household help,etc<br>- level I<br>- level II<br>- level II<br>- | All services | (cash/in kind)<br><br>400 / 750<br>800 / 1800<br>1300 / 2800 | (capitated)<br><br>750/month<br>1800/month<br>2800/month | Pflegeversicherung |
| Inpatient care<br>Long/medium term care<br>- level I<br>- level II<br>- level II<br>- | 120.80/day | <br><br>2000/month<br>2500/month<br>2800/month | <br><br>2000/month<br>2500/month<br>2800/month | EBM 2000 Ziff 63-66 mean and Pflegeversicherung |
| Informal care | 10.15 / h | | - | 35% of hourly wage |

| Main Resources | Societal Perspective | Tariffs | Payer Perspective | Source / Assumptions |
|---|---|---|---|---|
| | | | | |
| **Work related costs** | | | | |
| - Early retirement (year) | 68,700.00 | 56,300.00 | - | Mean annual salary 1999, adjusted for gender, including 22% employers contributions |
| - Sickness absence (day) | 188.00 | 154.00 | 123.00 | Mean annual salary 1999, adjusted for gender + 22% (80% of mean salary for payer perspective) |
| - Incapacity pension (month) | | 977.00 | | VDR: Rentenversicherung in Zeitreihen, 1999, pg. 18 ff, 86 ff |
| - Invalidity pension (month) | | 1423.00 | | VDR: Rentenversicherung in Zeitreihen, 1999, pg. 18 ff, 86 ff |

* Kostenstrukturanalyse: Practice turnover divided by 6000 visits (assuming 15 minute visits, 200 working days of 7-8 hours)

** ADT panel of sick fund associations of Nordrhein, mean billing, point value 0.72 DM

*** EBM = Mundenbruch R.: Einheitlicher Bewertungsmasstab Januar 2000, Zauner Druck- und Verlagsanstalt Dachau, 30th Ed, 1999

*** Vertrag gem § 89 SGB XI über die Vergütung der ambulanten Pflegeleistungen und der hauswirtschaftlichen Versorgung, für Bayern – Anhang 4