Costs, Quality of Life and Disease Severity in Multiple Sclerosis – A Population-Based Cross-Sectional Study in Sweden

***Freddie Henriksson*[*], *Sten Fredrikson*[**], *Bengt Jönsson*[*]**

Stockholm School of Economics
SSE/EFI Working Paper Series in Economics and Finance, No 361
March 2000

Abstract

This study has used a cross-sectional, 'bottom-up' design to determine the cost to society of multiple sclerosis (MS) in Sweden in 1998. The total cost of MS was estimated at 4 868 MSEK, meaning an annual cost of 442 500 SEK per patient. Direct costs accounted for about 67% of total cost, and direct costs were dominated by the cost of personal assistants and drugs. Indirect costs accounted for about 33% of total costs and were totally dominated by the cost of long-term sickness absence from work and early retirement. Intangible costs were estimated at 2 700 MSEK. A former Swedish study on MS for 1994, using main diagnosis to calculate costs, showed the total cost to be 1 736 MSEK. Increased disability as measured by EDSS was found to have a major impact on the cost of the disease and on quality of life. Both direct, indirect and informal care costs rose significantly with increased EDSS and were higher during a relapse. Quality of life declined substantially with increased EDSS and was lower during a relapse. In summary, this study showed that a severe, chronic, disabling disease like MS that strikes early in life has major implications for both the society as a whole and for the affected patients.

KEYWORDS: multiple sclerosis, cost-of-illness, quality of life, EDSS, utility
JEL Codes: I10, I12, I19

[*] Stockholm School of Economics, Centre for Health Economics, Box 6501, S - 113 83 Stockholm, Sweden. Phone +46 8 736 9376, fax +46 8 30 21 15, e-mail HEFH@HHS.SE
[**] Division of Neurology, Karolinska Institutet, Huddinge Hospital
[*] Stockholm School of Economics, Centre for Health Economics

TABLE OF CONTENTS

Summary……..3

1. Introduction……...4

1.1 Multiple Sclerosis – a disease with new treatment possibilities…….4

1.2 Former cost-of-illness studies in MS…….…..5

1.3 The objectives of this study…….....6

2. Materials and Methods…….…8

2.1 Theories and methods used……..…8

2.2 Design……..…9

2.3 Setting and subjects…….…....9

2.4 Data collection…….…..…..9

2.5 Costing……..….…10

2.6 Analysis……..….…...11

3. Results…….….….…12

3.1 Background variables…….….…...12

3.2 Direct costs……...….…13

3.3 Indirect costs……...….…..18

3.4 Total cost of MS in Sweden in 1998……..…..…..19

3.5 Quality of life and functional status…….…….…21

4. Discussion…….….…...24

5. Conclusions…….…..…...29

References…….…...…..30

Appendix 1……...…….…...….35

Appendix 2…….……52

Appendix 3…….……53

Appendix 4…….……55

Appendix 5…….……58

SUMMARY

This study has used a cross-sectional, 'bottom-up' design to determine the cost to society of multiple sclerosis (MS) in Sweden in 1998. All relevant costs both within and outside the health care system have been included. The total cost of MS was estimated at 4 868 MSEK, meaning an annual cost of 442 500 SEK per patient. Direct costs (including informal care) accounted for about 67% of total cost, and direct costs were dominated by the cost of personal assistants and drugs. Indirect costs accounted for about 33% of total costs and were totally dominated by the cost of long-term sickness absence from work and early retirement. To these economic costs, intangible costs due to reduced quality of life should be added as well. These costs were estimated at 2 700 MSEK in the study. A former Swedish study on MS for 1994, using main diagnosis to calculate costs, which means that less cost items are included, showed the total cost to be 1 736 MSEK.

An assessment of the impact on costs and quality of life of disease severity and relapse was also made. Increased disability as measured by EDSS was found to have a major impact on the cost of the disease and on quality of life. Both direct, indirect and informal care costs rose significantly with increased EDSS and were higher during a relapse. The total annual cost for an individual with severe disability (EDSS $\geq$ 6,5) was almost 5 times higher than for an individual with mild disability (EDSS $\leq$ 3,0) Quality of life declined substantially with increased EDSS and was lower during a relapse.

This study has presented an in-depth investigation of the economic aspects of MS in Sweden. MS was found to be associated with much higher costs to society than have been found in former Swedish studies. Furthermore, MS reduces quality of life substantially, and quality of life is much lower for MS patients compared to the general population. In summary, this shows that a severe, chronic, disabling disease like MS that strikes early in life has major implications for both the society as a whole and for the affected patients.

1. INTRODUCTION

1.1 Multiple Sclerosis – a disease with new treatment possibilities

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the Central Nervous System (CNS). It is the second most common cause of neurological disability in young and middle-aged adults [1]. The onset of the disease normally takes place between 20-40 years of age and women are affected about twice as often as men. At onset, about 80% of the patients develop the relapsing-remitting (RRMS) form of MS [2]. A majority of these patients will later on develop secondary progressive MS (SPMS). A minor fraction of the patients (about 15-20 %) develop primary progressive MS (PPMS). The mean time to need an aid for ambulation is 15 years [3] and survival after onset in high risk areas is in the order of 35 to 40 years [4]. The most common symptoms include spasticity, motor- and sensory impairment, ataxia, tremor, vision changes, fatigue and bowel, bladder and sexual dysfunction. The course of the disease for a specific patient cannot be predicted.

The distribution of MS worldwide shows a very skewed pattern with maxima in the two areas with temperate climate. No single factor that can explain this skewed distribution has been found, but both climate and hereditary factors correlate roughly with the MS prevalence. The prevalence in Sweden is about 1/800, meaning that the number of cases is approximately 11 000, and prevalence seems stable over time.

No cure for the disease exists and treatment has traditionally focused on treatment of exacerbations and improved recovery after exacerbations, prevention of exacerbation and management of symptoms and disability. However, recently new disease-modifying treatments for MS were introduced (interferon-beta), which can change the natural course of MS. Several studies have shown effect on relapsing-remitting MS [5,6,7] and recently also one study on secondary progressive MS [8]. These new agents are more expensive than drugs used only to treat relapses and the introduction of them has focused attention of the economic burden of MS and the cost-effectiveness of different interventions. There has been a concern about rising costs [9] and there has been a need for further studies, serving as a base for decisions about the use of scarce resources in health care.

1.2 Former cost-of-illness studies in MS

Cost-of-illness studies are descriptive studies that give information about the cost of a disease to society. Ultimately, they should show all relevant costs to society for prevention, detection, treatment, rehabilitation and long-term care due to a disease, both within and outside the health care system. Table 1 presents and compares three cost-of-illness studies from the UK and two from Norway and Sweden. The studies by O'Brien [10] and Blumhardt and Wood [11] are for England and Wales, while the one by Holmes, Madgwick and Bates [12] is based on a sample of 672 MS patients aggregated to represent the entire UK.

Table 1. Costs of MS in the UK, Norway and Sweden (million £, million NOK, million SEK).

	UK 1986/87 [10]	**UK 1993/94 [11]**	**UK 1994 [12]**	**Norway 1991 [14]**	**Sweden 1994 [13]**
Direct costs	18.2	48.1	73.9	5.8	370
Hospital	14.2	35.5*	67.3*	5.6	354
Ambulatory care	1.7	10.5	4.6	0.2	13
Drugs	2.4	2.1	2.0	-**	3
Indirect costs	100.0	250.1	395.0	28.6	1 506
Sickness absence				1.8	183
Early retirement				23.6	1 183
Mortality				3.2	140
Total costs	**118.2**	**298.2**	**468.9**	**34.4**	**1 876**

**) Includes inpatient care and hospital outpatient visits*
***) Data on drugs were not available in the study*

All three studies from the UK show that indirect costs, i.e. costs due to loss of production, are the dominating economic burden in MS. However, the absolute level of costs vary considerably between the different studies. The main explanation for this is differences in the definition of costs and the data used for the estimations. The Swedish study [13] is for the Swedish population and based on register data, whereas the Norwegian study [14] was undertaken for the counties Möre and Romsdal in Norway. Both studies show that indirect costs are higher than direct costs and that direct costs are dominated by hospital inpatient care.

Another cost-of-illness study was undertaken in the USA for 1994 [15]. The annual cost of MS was estimated at over 34 000 USD per person, translating into a conservative estimate of national annual cost of 6.8 billion USD. The major components of cost were indirect costs (loss of production) and cost of informal care. Informal care includes care by spouses, children, grandchildren, relatives, friends, other volunteers etc, i.e. care that are normally not

paid for and has no market price. High informal care costs were also found in another study [16], which indicates the importance of including indirect costs and caregiver costs in a cost-of-illness study on MS.

Other studies have not only calculated the cost due to MS, but also assessed the impact of different variables on costs. Parkin et al [17] found that there was a significant increase in costs when patients have a relapse and that costs increase with the severity of the disease, measured with the Kurtzke EDSS scale [18]. The cost, quality of life and employment status for different levels of severity was investigated in a Canadian study [19,20]. Table 2 shows the relationship between cost, quality of life and employment status.

Table 2. Cost of MS in Canada.

	Cost	**Quality of Life (SF-36)**			**Employment status**	
EDSS	Cost per patient (C$)	Physical function	Social Function	General health	Change in employment	Active full year/time
Mild ≤ 2.5	14 500	63.9	64.3	55.7	37%	37%
Moderate = 3.0-6.0	18 400	35.2	58.1	54.3	62%	28%
Severe ≥ 6.5	34 000	8.7	7.6	52.0	82%	4%

In summary, these former cost-of-illness studies have shown that the burden of MS to society is substantial and that indirect costs are higher than direct costs. It has also been shown that the cost of informal care is important to include. Further, costs increase with the severity of the disease and are higher during a relapse. Both quality of life and employment status are significantly affected by the severity of the disease.

1.3 The objectives of this study

The former Swedish cost-of-illness study [13] used public registers to find data for cost calculation. This means that costs for resources not available in registers have not been possible to include in this former estimate, which means that the figure is very conservative. Important cost items such as costs of informal care, rehabilitation, personal assistants, adaptations etc have not been included. The first objective of this study was to make a more comprehensive assessment of the total cost of MS, aiming at including the entire range of

costs. A second objective was to investigate how costs and quality of life are effected by the presence of a relapse and by disease severity, measured with the Kurtzke EDSS scale.

In Jönsson et al [21], a generic Markov model was presented, which described the natural course of secondary progressive MS. The aim with the study was to estimate the cost-effectiveness of treatments that have an effect on disease progression, and the first version was based on international clinical data and published cost and utility data from the UK. However, costs and utilities were based on a small number of observations and extrapolated from large groupings of disease severity to smaller steps in progression. The authors conclude that further research is required on the costs and utilities related to different states, i.e. EDSS levels. The third purpose of this study was to supply the model with relevant Swedish data on costs and utilities for different EDSS levels, based on a much larger sample of patients.

2. MATERIALS AND METHODS

2.1 Theories and methods used

This study used the cost-of-illness approach [22,23], based on the human-capital theory, to calculate the cost to society for the disease Multiple Sclerosis. A cost-of-illness analysis is a descriptive type of study, relating all costs to a specific disease or event. Cost-of-illness studies use either a prevalence-based or an incidence-based approach. Cost-of-illness in relation to the prevalence of a disease takes account of all cases existing during a given year and has the advantage of relating to measures of total annual health care expenditure, which is particularly relevant for a chronic disease like MS. Therefore a prevalence approach was chosen in this study.

When estimating the cost-of-illness, either a 'top-down' or a 'bottom-up' approach or a combination of the two can be chosen [24]. The 'top-down' strategy uses aggregate figures on resource consumption related to diagnoses and relies on available published data. The 'bottom-up' approach usually starts from a selected sub-population with the actual disease and all costs related to the disease are estimated and then extrapolated to the national level. The 'top-down' approach is dependent on the availability and quality of available data, and has the advantage that it relates directly to total health care costs without extrapolating and avoids the risk of double-counting costs. The 'bottom-up' approach makes it possible to undertake an in-depth investigation of the patient sample and to include data that are not available in public registers. The drawbacks are that a representative sample has to be selected and an accurate prevalence figure is needed to be able to make a proper extrapolation and that there is a risk of double-counting costs, i.e. when the cost of all diseases are added up, they amount to more than the total cost-of-illness. Since the purpose of this study was to include all relevant costs and also to relate cost per patient and utility to disease severity, a 'bottom-up' approach was needed. In addition, this study enables a comparison between two different cost-of-illness approaches applied on the same disease; 'top-down' [13] and 'bottom-up' (this study).

This study calculated the MS specific cost, and we therefore excluded resources used or lost due to reasons other than MS. If the aim would be to investigate the cost for patients with MS, all resources would have to be included, independent of the underlying diagnosis. Often it is

difficult to make the separation between the cost of a disease and the cost of patients with a specific disease. For MS this problem is not so great since the majority of the patients are in age groups where costs for other diseases are rather small.

2.2 Design

This study used a cross-sectional approach, in which resource utilization data and quality of life data (utilities) were collected at a single time point. Resource utilization data covered a 1-month period preceding data collection for all resources except for adaptations (house, work-place and car) and items purchases, which covered the preceding year. These data were used to calculate the cost of MS in Sweden for a defined year (1998).

2.3 Setting and subjects

The study was carried out at the Division of Neurology at Huddinge Hospital in southern Stockholm, Sweden, and was approved by the local ethics committee (Karolinska Institute, Huddinge Hospital). All patients with a confirmed diagnosis included in the medical records at the Division of Neurology were included in the search (N=615). However, 56 patients participated in another survey study and were therefore excluded. Another 25 patients had to be excluded for other reasons, e.g. that no address was found or that the person was dead. The number of selected MS patient were finally 543 and 413 of those responded, a response rate of 76%.

2.4 Data collection

Each patient received a letter containing a covering letter with patient information about the study, a questionnaire and a stamped envelope for returning the answered questionnaire. Data collection was performed with this patient questionnaire with MS related questions (see Appendix 1). The questionnaire was structured into 8 different parts: background information, medical visits (inpatient stays, visits to physicians, visits to nurses and visits to rehabilitation centers), other visits (to paramedical practitioners), drug use, services used, adaptations made and items purchased, employment status and quality of life. Quality of life data was gathered with the standardized EQ-5D questionnaire [25], which both give a utility value between 0

(death) and 1 (full health) based on a five dimensional health state classification and a score from 0 to 100 through a visual analogue scale[1], VAS (similar to a thermometer). Apart from the questionnaire, data on disease severity (EDSS scores), was gathered from the medical records. The Expanded Disability Status Scale is used to show functional status and can take values from 0 to 10, where 0 is equal to no disability at all and 10 is equal to death due to MS.

2.5 Costing

A basic costing principle is to collect information on resource consumption and then to multiply each resource (quantity) with a unit cost (price). The correct valuation of a specific resource is the opportunity cost of that resource, i.e. the value of that specific resource in its best alternative use [26] and in the case of well functioning markets, market prices mirror opportunity costs.

Costs are normally classified into three categories: direct, indirect and intangible costs [27], where direct costs are defined as the cost of detection, treatment, rehabilitation and long-term care arising from an illness. In theory, all relevant health care and non-health care cost should be included in direct costs. In this study, the ambition was to include all relevant direct costs due to MS. Informal care costs are costs due to un-paid inputs, such as help from relatives and friends, and when these costs are included, they should be included in direct costs. However, they are often left out, since they are difficult to quantify and value.

Indirect costs are defined as costs due to loss of production due to an illness, and normally short-term absence from work, early retirement and premature mortality is included. In this study, short-term absence from work, long-term absence from work and early retirement have been included in indirect costs. Costs due to premature mortality have been excluded, since the impact of MS on mortality is relatively small and difficult to assess. To quantify loss of production due to early retirement and long-term sickness absence, the average working hours for men and women in different age groups have been used [28], see Appendix 2. The average cost of labor in Sweden was used to value loss of production.

[1] On this scale, 0 represents worst imaginable health state and 100 best imaginable health state.

Intangible costs are related to pain, grief, anxiety and social handicap. Due to estimation problems, they are usually omitted in cost-of-illness studies. The standardized quality of life instrument used in this study gives a description of the current health status (utility value) for each patient, and the score can be used for calculating the intangible costs due to MS. By comparing the difference in utility between the MS sample and the general population for different age groups, the number of QALYs (quality adjusted life years) [29] lost due to MS can be calculated. By imputing a monetary value on each QALY lost, an estimate of the intangible costs due to MS can be obtained. The monetary value per QALY lost is calculated from bench-mark values used in economic evaluations where the number of QALY gained is used as an outcome measure.

Unit costs were obtained from published sources, such as the Federation of County Councils [30], hospital price lists [31,32,33], the pharmaceutical lexicon FASS [34] and through personal communication. Most sources contain true and complete costs, i.e. not charges and overhead costs included. On the other hand, many costs stem from accounting figures, and are therefore affected by accounting principles, which means that some costs do not reflect the true opportunity cost [35]. Appendix 3 shows a summary of resource items and unit costs included in the study.

2.6 Analysis

Data on resources used, sickness absence (short-term and long-term) and early retirement was collected from the questionnaires. Each resource was multiplied with a unit cost obtained from external sources in order to calculate direct and indirect costs for each patient. Since most data was collected for a 1-month period, cost per patient was multiplied with a factor of twelve to obtain annual cost per patient[2]. In order to extrapolate the sample cost estimate to a population level estimate, the overall Swedish prevalence of diagnosed MS was used (11 000 individuals). For the estimates of the relationship between disease severity, measured with EDSS, and quality of life (utilities) and costs, disease severity was divided into three groups: mild disability (EDSS $\leq$ 3,0), moderate disability (EDSS 3,5 – 6,0) and severe disability (EDSS $\geq$ 6,5). Average values for utilities and costs in each group were calculated.

[2] This method ignores any possible seasonal variation which may exist.

3. RESULTS

3.1 Background variables

Table 3 shows descriptive statistics for the patients in the sample.

Table 3. Descriptive statistics (n=413).

Background variable	**Values**
Gender	
male (%)	29
female (%)	71
Age	
mean, std	49.0, 12.3
Age at first symptom of MS	
mean, std	31.9, 10.6
Marital status	
married (%)	53
cohabiting (%)	13
live alone (%)	34
Education level	
high school and lower (%)	28
secondary school (%)	32
university and higher (%)	39
Living	
own living (%)	96
special living (e.g. nursing homes, veteran homes) (%)	2
Other ()	2
MS related questions (self-assessment)	
relapsing-remitting MS (%)	34
primary progressive MS (%)	26
secondary progressive MS (%)	37
had a relapse last month (%)	9
had a substantial deterioration last year (%)	42
had a stable disease last year (%)	35
Patients with concomitant illness/es (%)	26
Self-assessed mobility (measured on a scale from 1-4)[3]	
mean, std	2.7, 1.1
min, max	1, 4
Employment status	
had a job last month (%)	40
- of which full-time (%)	40
Have changed employment statues due to MS	
no (%)	30
have changed working hours (%)	12
have changed assignment (%)	4
have changed both assignment and working hours (%)	11
have been forced to quit my employment (%)	43

[3] 1 = move without problems, 2 = have some problems in walking about, 3 = need walking aid, 4 = need wheelchair or is devoted to bed

The majority of the patients were women, which is to be expected. The average age was 49 years and the average age at first symptoms was 32, which means a disease duration of 17 years. The individuals in the sample had a rather high educational level and almost no one lived at institutions. About 34% of the patients had the relapsing-remitting form of MS, 26% had the primary progressive form and about 37% had secondary progressive MS (self-assessed conditions). As much as 42% had a substantial deterioration during last year and 9% had a relapse last month, whereas for 35% the disease has been stable during the last year. Regarding employment, 40% had a job last month and 40% of those worked full-time. However, as much as 43% have been forced to quit their employment because of their MS and a number of patients have been forced to change working hours and/or working assignment. Considering both the long disease duration, the large fraction of patient that had a recent substantial deterioration of the disease and the rather large number of patient that have been forced to quit employment, it is clear that many patients in our sample have reached a disabling state of the disease.

3.2 Direct costs

3.2.1 Hospital inpatient care and rehabilitation

Inpatient hospital care was used by 3,1% of the patients in the sample. The total number of bed-days for the sample during a 1-month period was 147 at neurological wards and 25 at other wards (infectious diseases ward and ICU) meaning a total number of bed-days during a year amounting to 2064. Applying ward specific unit costs to these quantities, the average cost per patient and year is 21 097 SEK or 232 MSEK for the entire MS population. These figures were compared with inpatient data for 1996 and 1997 obtained from the inpatient register at National Board of Health and Welfare (Epidemiological Center) and the comparison shows a slight difference between data from the questionnaires and data from the register. Appendix 4 shows a summary of the data from the inpatient register.

Rehabilitation Centers were used by 9,2% of the patients and the average number of rehabilitation days per patient and year was 19,8, meaning an annual cost per patient of 37 950 SEK or 417 MSEK for the MS population.

3.2.2 Ambulatory care

Table 4 shows an overview of visits to different ambulatory care practitioners and related costs.

Table 4. Visits to ambulatory care practitioners and related costs.

Practitioner	Average number of visits per patient and year	Cost per patient and year (SEK)	Cost for the MS population (MSEK)
Neurologist	4,1	4 629	50,9
General Practitioner	0,8	687	7,6
Other specialist	0,9	1 149	12,6
Physician home visit	0,09	143	1,6
Nurse	9,2	4 132	45,5
Nurse home visit	6,5	5 248	57,7
Physiotherapist	26,4	8 337	91,7
Occupational therapist	6,9	3 429	37,7
Chiropodist	1,5	436	4,8
Speech therapist	0,8	895	9,8
Continence advisor	0,7	314	3,5
Psychologist	1,1	1 104	12,1
Almoner	2,0	2 005	22,1
Optician	0,7	120	1,3
Other paramedical practitioners	1,7	491	5,4
Total	**63,4**	**33 119**	**364,3**

The total number of visits to ambulatory care practitioners per patient and year was about 63, resulting in a total annual cost of 33 119 SEK per patient or 364 MSEK for the MS population. Regarding visits to physicians, the majority of visits were to neurologists and very few visits took place in the patient's own home. An average patient visited nurses about 9 times a year and it was much more common to have home visits by nurses than by physicians. By far, the most frequently visited ambulatory care practitioner were physiotherapists. An average patient has more than 26 visits per year, resulting in a cost of 8 337 SEK per patient. Another paramedical practitioner that was rather common to visit were occupational therapists, which had about 7 visits per year on average. For other paramedical practitioners, an average patient had about 1 visit per year to each of these. Time costs and traveling expenses were not included in the cost estimate.

3.2.3 Drugs

The use of drugs for MS has been divided into interferon drugs (Betaferon, Avonex, Rebif), other prescribed drugs and non-prescribed or OTC drugs (Table 5).

Table 5. The use of drugs for MS, cost per patient and the annual cost for the MS population.

Drugs	**Used by (%)**	**Cost per patient and year (SEK)**	**Cost for the MS population (MSEK)**
Interferon drugs	42%	46 992	516,9
Other prescribed drugs	38%	1 097	12,1
OTC drugs	43%	356	3,9
Total	**na**	**48 445**	**532,9**

From the questionnaires, data on the use of drugs for treating MS and MS related symptoms was gathered. Data from the questionnaires has been verified by checking against a sample of patient journals. About 42% of the patients in the sample used interferon drugs and this is a very high figure. The national average for Sweden is about 15%, but it has been shown that the prescription of interferon drugs varies to a large extent in different regions in Sweden [36]. Huddinge hospital is a University hospital, meaning that the hospital is involved in different research projects, and in this respect the patients at the Division of Neurology at Huddinge hospital are not representative for the Swedish MS population as a whole. The extensive use of interferon drugs affects cost substantially; 97% of the drug costs in the sample were due to interferon drugs. The annual cost per patient and year for the sample of patients at Huddinge hospital is almost 47 000 SEK, and if this figure is extrapolated to national level it would result in a drug cost for interferon drugs amounting to 517 MSEK per year. The total sales of interferon-beta drugs amounted to 194 MSEK in 1999 [37], which shows that extrapolating interferon drug costs from the sample in this study leads to an overestimation.

Other prescribed drugs were used by 38% of the patients, and the number of drugs were limited to a few commonly used, such as Baklofen (for spasms), Detrusitol (for incontinence), Tegretol (antiepilepticum), Ditropan (antikolinergicum) and Cipramil (for depression). The average cost per patient and year was 1 097 SEK or 12 MSEK, if extrapolated to the whole population.

Non-prescribed or OTC drugs were used by 43% of the patients and many patients use several different OTC drugs. The most commonly used are vitamines, analgesics and different health food. Despite being frequently used the effect on costs is small because of relatively low prices. The cost of OTC drugs for an average MS patient in the sample was only 356 SEK per year, meaning a total cost for the population amounting to 3,9 MSEK. Summing the cost of interferon drugs, other prescribed drugs and OTC drugs result in an annual per patient cost of 48 445 SEK or 533 MSEK for the MS population, which is a high figure because of the high share of interferon users in the sample.

3.2.4 Services

It is well-known that many patients with MS have a high need of different services supplied by others that the health care sector, for example the municipalities, but it has not been possible to collect information about these resources with the approach used in former Swedish cost-of-illness studies on MS. In Table 6 the use of different services is shown.

Table 6. The use of different services due to MS, annual cost per patient and annual cost for the MS population for these services.

Services	**Used by (%)**	**Cost per patient and year (SEK)**	**Cost for the MS population (MSEK)**
Personal assistant	23	89 562	985,2
Home help/home care	12	5 813	63,9
Child care	2,4	2 331	25,6
Other services	9,4	1 100	12,1
Total	**na**	**98 806**	**1086,8**

The need of personal assistance varies a lot between different patients. In the sample, 23% of the patients had a personal assistant. For those who needed a personal assistant, the average number of days using a personal assistant during one month were 21 days and the average number of hours used per day were 11 hours. However, there were a number of patients that needed personal assistance full time, i.e. 24 hours per day, every day. The high need of personal assistance affects costs substantially, and the average cost per patient and year was 89 562 SEK, i.e. a cost of 985 MSEK for the MS population. Home help and home care was used by 12% and the average annual cost amounted to 5 813 SEK. Child care was only used by 2,4% resulting in an annual per patient cost of 2 331 SEK. Including also other services

(such as transportation) the total cost per patient of different services was 98 806 SEK per year or 1087 MSEK for the MS population.

3.2.5 Adaptations made and items purchased

In the questionnaires, information about adaptations made and items purchased or received during the last year due to MS was gathered. We used an incidence approach regarding adaptations, which means that we gathered information about adaptations made and items purchased during a year, and distributed the entire investment cost to this year. An alternative would be to gather information about adaptations made during a longer period, e.g. during the last ten years, and distribute a part of the cost (an annuity) to each year. Table 7 shows the results from this part of the questionnaire.

Table 7. Adaptations made and items purchased or received during last year due to MS, and the related annual costs.

Adaptations and items	Used/made by (%)	Cost per patient and year (SEK)	Cost for the MS population (MSEK)
Adaptation of kitchen	6	1 889	20,8
Adaptation of bathroom	17	5 012	55,1
Adaptations of other parts of the house	8	3 874	42,6
Roof lift	8	1 998	22,0
Lift	4	291	3,2
Stair elevator	4	2 906	32,0
Ramps	10	1 017	11,2
Safety alarm	12	617	6,8
Adaptations at the job	0,7	218	2,4
Adaptation of the car	8	2 542	28,0
Wheelchair	23	1 351	14,9
Electric wheelchair	9	9 855	108,4
Electric moped	10	2 906	32,0
Walking stick	17	7	0,08
Walking aid (rollator)	11	113	1,2
Special kitchen utencils	11	218	2,4
Special hygiene items	34	688	7,6
Special writing devices	6	121	1,3
Other	13	1 191	13,1
Total	**na**	**36 813**	**404,9**

The total cost per patient and year for adaptations and devices amounted to 36 813 SEK or 405 MSEK for the MS population. Nine per cent of the patients were supplied with an electric wheelchair during last year, and due to a relatively high unit cost (110 000 SEK) it had a rather large impact on the average cost. Adaptations of the bathroom were more common than adaptations of the kitchen or of other parts of the house. Adaptations at the job were very uncommon, and made by less than 1% during last year. More than a third of the patients needed special hygiene items, but due to low unit costs for these items the impact on cost was small. Forty per cent of the patients required a wheelchair, an electric wheelchair or an electric moped the last year, which indicates that many patients in the sample have reached a moderate to high level of disability during the previous year.

3.2.6 Informal care

As was mentioned earlier, informal care constitutes care that is normally not paid for, but still has an opportunity cost. Other studies [15,16], that have included informal care, have shown that it is an important resource to include and value in a cost-of-illness study on MS. In our study, informal care was used by 26% in the sample. For those using informal care, the average number of hours per week using informal care were 30, i.e. about 4 hours a day, but some patients needed informal care full time. We have used the opportunity cost of leisure time to value informal care (50 SEK per hour), which is a rather conservative value. The average cost per patient and year for informal care was 20 668 SEK or 227 MSEK for the MS population.

3.3 Indirect costs

3.3.1 Short-term sickness absence

In the questionnaires, employment related questions were used to gather information about short-term sickness absence, long-term sickness absence and early retirement. Forty per cent of the patients in the sample were employed and 40% of those were employed full-time. Of those working, the average number of sickness-absence days per individual and year was 23 days. Correcting for part-time work, the average number of productive days lost per individual and year was 14. Using the average cost of labour per hour in Sweden for valuing loss of production per hour, the total loss of production due to short-term sickness absence

amounted to about 7 885 SEK per person and year in the sample. Extrapolating this figure to the MS population, resulted in an indirect cost due to short-term sickness absence of 87 MSEK.

3.3.2 Long-term sickness absence and early retirement

Of the 60% currently not working in the sample, 58% had an early retirement pension and 11% had long-term sickness absence from work. The vast majority, or 97% of all early retirement pensions, were full-time pensions. To calculate loss of production due to long-term sickness absence and early retirement, the average cost of labour per hour was used as a base. We assumed that if the individuals would not be early retired they would be working and earning a salary according to the average for the general population (see Appendix 2 regarding hours worked). The loss of production due to long-term sickness absence and early retirement per MS patient and year amounted to 137 692 SEK. Extrapolating this figure to the MS population level resulted in a cost of 1 515 MSEK. For a disabling disease like MS, it is obvious that long-term sickness absence and early retirement are rather common and that it has a substantial impact on the cost of the disease.

3.4 Total cost of MS in Sweden in 1998

Table 8 shows a summary of all direct and indirect costs per year due to MS.

Table 8. Cost of MS in Sweden in 1998 (per person, for the MS population and as a share of total cost).

Costs	**Per person and year (SEK)**	**For the MS population (MSEK)**	**Share of total cost (%)**
Hospital inpatient care	21 097	232	4,8
Rehabilitation	37 950	417	8,6
Ambulatory care	33 119	364	7,5
physicians	6 609	73	1,5
nurses	9 380	103	2,1
paramedical practitioners	17 130	188	3,9
Drugs	48 446	533	10,9
Services	98 806	1 087	22,3
Adaptations and devices	36 813	405	8,3
Informal care	20 668	227	4,7
Total direct costs	**296 899**	**3 266**	**67,1**
Short-term sickness absence	7 885	87	1,8
Long-term sickness absence and early retirement	137 692	1 515	31,1
Total indirect costs	**145 577**	**1 602**	**32,9**
Total cost	***442 476***	***4 868***	***100***

The total cost of MS in Sweden in 1998 amounted to 4 868 MSEK, which resulted in a cost of 442 476 SEK per patient. Direct costs amounted to 3 266 MSEK and constituted the largest share of total cost; 67%. Services were the largest cost item in direct costs, and almost the entire cost of services was due to the frequent use of personal assistants. Other large components of direct costs were drugs and rehabilitation, followed by adaptations and devices. Informal care amounted to 227 MSEK or 5 % or total cost, and was not a dominating cost item in this study, contrary to findings in former studies [15,16]. Indirect costs amounted to 1 602 MSEK and constituted 33% of total cost. Indirect costs were totally dominated by the cost of long-term sickness absence and early retirement, which was the single most costly item overall. To these economic costs, intangible costs (costs due to reduced quality of life) should be added as well. These costs are estimated and discussed in the next section.

3.5 Quality of life and functional status

3.5.1 Quality of life scores and functional status values

Table 9 shows a summary of the results from the quality of life part in the questionnaire and from the functional status values (EDSS) from the medical records.

Table 9. Summary statistics of the quality of life scores and the functional status values (EDSS).

EuroQol	
N	384
average	0,42
standard deviation	0,39
min	-0,594
max	0,919
Visual Analogue Scale (VAS)	
N	396
average	56,3
standard deviation	24,3
min	0
max	100
EDSS	
N	408
average	4,93
standard deviation	2,52
min	0
max	9,5

The average score obtained by combining the descriptive part of the questionnaire with population based values for different states [38] was 0.42 on a scale from 0 to 1. The scores ranged from –0,594 to 0,919. Sometimes respondents give negative values for severe health states, and this should be interpreted as a health state considered worse than dead. The visual analogue scale (the thermometer) showed an average value of 56,3 on a scale from 0 to 100. The absolute value received with VAS is, hence, a bit higher than the value received with the five dimensional health state questions (utilities). However, the VAS is answered by the patients themselves, whereas the utility values are tariff values derived from health states rankings by the UK general population. It has been found [39] than severe health states are rated higher by the patients themselves compared with the general population, and this may be a reason for the discrepancy, since a number of patients in this study are in severe health states.

The utility values obtained from the MS patients in our study can be compared to utility values obtained in general population [40]. By comparing the difference in utility between the MS sample and the general population for different age groups, the number of QALYs lost due to MS can be calculated. By imputing a monetary value on each QALY lost, an estimate of the intangible costs due to MS is obtained (see Appendix 5). The intangible cost due to MS was estimated at 2 702 MSEK in Sweden. Hence, the intangible cost was higher than indirect costs and almost as high as direct costs due to MS, which clearly shows the substantial impact on quality of life of the disease.

The Expanded Disability Status Scale (EDSS) is used to show functional status. The average value for the patients in the sample was 4,93 (ranges from 1 to 9,5), which show patients that in general have a moderate disability level. There was also an almost perfect correlation between EDSS values obtained from the medical records and the self-assessed mobility obtained from the questionnaires (r = 0,86).

3.5.2 The effect of disease severity on quality of life and costs

Table 10 shows how quality of life is affected by increased disability expressed in the three levels: mild disability, moderate disability and severe disability.

Table 10. Utility values (averages in each group) by disability levels.

Disability level	**Utility**
Mild (EDSS ≤ 3,0) (n=126)	0,68
Moderate (EDSS 3,5 – 6,0) (n=121)	0,52
Severe (EDSS ≥ 6,5) (n=162)	0,17

Quality of life (utility) is substantially reduced with increased disability. The average utility score for the patients in the mild group was 0,68, which can be compared to 0,52 in the moderate group and 0,17 in the severe group. The dramatic decline in utility can be observed when the patients enter the severe state of the disease. In addition, patients were asked whether they experienced a relapse during last month. The utility value for those individuals experiencing a relapse was on average 0,0635 units lower than for those who were in

remission. As could be expected, also the presence of relapses affects quality of life in a negative way.

Costs have been divided into direct, indirect and informal care costs when studying how costs are affected by increased disability (see Table 11).

Table 11. Annual costs per patient (SEK) by disability levels.

Disability level	**Direct costs (SEK)**	**Indirect costs (SEK)**	**Informal care costs (SEK)**	**Total costs (SEK)**
Mild (EDSS ≤ 3,0) (n=126)	75 179	80 438	503	156 120
Moderate (EDSS 3,5 – 6,0) (n=121)	165 185	128 346	9 540	303 072
Severe (EDSS ≥ 6,5) (n=162)	511 836	207 822	44 746	764 403

Both direct, indirect and informal care costs increased significantly with disability as measured by EDSS. The average annual total cost for a patient with mild disability was 156 100 SEK. The total cost increased to 303 100 SEK for a patient with moderate disability and to 764 400 SEK for a patient with severe disability. Hence, a patient with severe disability had an annual total cost that was about 5 times higher than a patient with mild disability. The largest difference in costs between the mild and severe group was found for informal care costs. Patients with mild disability had almost no need of informal care at all resulting in very low costs, whereas patients in the severe group had an annual cost amounting to about 45 000 SEK, which is about 89 times higher than the mild group. For indirect cost, the difference between the three disability levels was more moderate, which can be explained by the fact that even in the mild state, early retirement and long-term sickness absence was rather common.

Costs were also calculated separately for those who experienced a relapse and for those who were in remission. Three months were regarded as an appropriate time period for capturing the extra costs due to a relapse. The extra total cost for a three month period for those who experienced a relapse was 25 700 SEK, of which 16 800 SEK were direct costs. This result is in accordance with former studies, which also have shown the impact on costs of a relapse.

4. DISCUSSION

This study has shown that the disease multiple sclerosis represents a high economic burden to society. By using a 'bottom-up' approach and gathering data by means of patient questionnaires, it has been possible to capture all relevant cost both within and outside the health care system. When comparing this 'bottom-up' study with a former Swedish 'top-down' study, relying on register data, it is evident that the cost due to MS is substantially higher than the former figures indicated. The total annual cost per patient was estimated at 442 500 SEK for 1998, which results in a total cost for the MS population of 4 868 MSEK. This can be compared with a total cost of 1 736 MSEK (mortality costs excluded) found in the former 'top-down' study for Sweden for 1994 (see Table 12).

Table 12. The cost of MS in Sweden obtained with two different approaches (SEK).

Costs	**Top-down study for 1994 [13]**	**Bottom-up study for 1998 (this study)**
Total direct costs	370	3 266
institutional care	354*	649**
ambulatory care	13	364
drugs	3§	533
other direct costs	-	1 720
Total indirect costs	1 366	1 602
short-term sickness absence	183	87
early retirement	1 183	1 515⊥
Total costs	**1 736**	**4 868**

* inpatient care and nursing home care
** inpatient care and rehabilitation
§ no interferon drugs
⊥ early retirement and long-term sickness absence

The former study showed that indirect costs (loss of production) were the dominant burden, and accounted for 79% of total cost. The cost due to early retirement was about the same in the former study and this study, whereas the cost due to short-term sickness absence was higher in the former study. The absolute cost figures for indirect costs were about the same in the former study (1 366 MSEK) based on main diagnosis and register data and this study (1 602 MSEK). Even if costs due to long-term sickness absence and early retirement were the single most dominant cost item, indirect costs constituted only about 33% of total cost in this study. Including resource data not found in registers, such as rehabilitation, visits to paramedical practitioners, services and adaptations, direct costs increased significantly in this

study. Contrary to the former Swedish cost-of-illness study, direct costs are the major burden in this study and constituted 67% of total costs. The extensive use of interferon-beta drugs and the high need of personal assistance, are important factors for explaining the high direct costs in this study. Costs due to personal assistance and interferon drugs were not included at all in the former Swedish study. In that study, direct costs accounted for 21% of total cost and direct costs were totally dominated by the cost due to institutional care, i.e. inpatient hospital care and care at nursing home. The cost of institutional care (inpatient care and rehabilitation) was 649 MSEK in this study. Costs due to ambulatory care and drugs were 13 MSEK and 3 MSEK respectively in the former study when only cases where MS was the main diagnosis in Medical Index Sweden were taken into account. In this study, the cost of ambulatory care was 364 MSEK of which 71 MSEK were related to visits to physicians, exclusive home visits. Drug costs were in total 533 MSEK of which 12 MSEK were for prescribed drugs other than interferon drugs.

According to need, patients can get a personal assistant from the municipality. The personal assistants help patients with their daily activities, and the goal is that patients should be able to stay in their own homes as long as possible. Hence, the alternative to personal assistants is an increased need of institutionalization, for example at nursing homes. In our sample only 2% of the patients lived at institutions. The high direct costs for personal assistants in this study must be seen in this context.

To the economic costs, intangible costs due to reduced quality of life should be added as well. Based on the utility values obtained from the patients in our sample and another study showing utility values in the general population, the intangible costs were estimated at 2 700 MSEK for the MS population in Sweden in 1998. No such estimation has been done for MS before. Since the value of a QALY is debatable, we made a sensitivity analysis with the values 300 000 SEK and 700 000 SEK per QALY. The lower valuation of a QALY results in intangible costs of 1 621 MSEK and the higher valuation results in 3 783 MSEK.

Informal care costs amounted to 20 668 SEK per patient and year or 227 MSEK for the MS population, meaning a share of 5% of total cost. The dominance of informal care found in other studies was not found in this study. However, a critical issue is how informal care is valuated. We used the opportunity cost of leisure time (50 SEK per hour), which is a rather conservative approach for valuating informal care. Another possibility would be to use the

opportunity cost of labour time and use the average cost of labour as the appropriate unit cost (180 SEK per hour). Still another valuation principle, is to use a replacement cost, for example the cost of labour of a nurse (140 SEK per hour). Both these valuation principles would result in higher unit costs and hence an increase in the costs due to informal care. If the latter valuation principle would have been applied, the cost of informal care would rise to 57 900 per patient and year or 637 MSEK for the MS population, which is about 13% of total cost.

In the Skåne region in southern Sweden, health care utilization for the general population is followed on a regularly basis [41]. The average annual cost for inpatient care, outpatient care and drugs for the general population in Skåne was about 10 500 SEK in 1997. One study [42] has calculated the direct cost for patients with type 2 diabetes in Sweden, also including inpatient care, ambulatory care and drugs, and the annual direct cost for a type 2 patient was estimated at 25 000 SEK. The MS specific cost for inpatient care, outpatient care and drugs in our study was about 100 000 SEK, i.e. almost 10 times higher than the cost for the general population. The cost for patients with MS is even higher, since not only resources used or lost specifically due to MS is included, but all resources independent of the underlying reason. This shows that MS is very costly, both compared with the general population and compared with a chronic disease like type 2 diabetes.

This study also assessed the impact on costs and quality of life of disease severity and relapse. Increased disability as measured by EDSS was found to have a major impact on the cost of the disease. Both direct, indirect and informal care costs rose significantly with increased EDSS. The total annual cost for an individual with severe disability (EDSS ≥ 6,5) was almost 5 times higher than for an individual with mild disability (EDSS ≤ 3,0). Also the presence of a relapse increased costs. The excess total cost during three months for a patient experiencing a relapse was 25 700 SEK compared with a patient in remission.

Quality of life is also affected by disease severity and relapse. The average utility score for a patient with mild disability was 0,68, for a patient with moderate disability 0,52 and for a patient with severe disability 0,17. A patient experiencing a relapse had in general a utility score that was 0,0635 units lower that a patient in remission. A Swedish study performed in the general population (n=4649) found the mean utility value for the age group 40-49 years to be 0,93, hence significantly higher even compared to patients with mild disability. The

Canadian studies [19,20] used the SF-36 questionnaire to assess the impact of disease severity on quality of life. Also this studies showed that disease severity affects quality of life in a negative way. In the study by Parkin et al [17], SF-36 scores for an MS sample were compared to the UK general population with long-standing illness and without long-standing illness. The figures showed that MS patients have significantly lower quality of life scores both compared with the general population and to individuals with other chronic diseases. All these studies support the fact that MS is a severe disease that lowers quality of life substantially.

This study used a cross-sectional design, in which retrospective data for a 1-month or a 1-year period (adaptations and devices) was collected by means of patient questionnaires. The study design relies on the memory of the patients, and recall bias may affect the reliability of the results. To mitigate this problem, a rather short retrospective period (1 month) was chosen. In addition, crucial information from the patient questionnaires was validated against other data sources, such as the inpatient register and the medical records. One advantage with a retrospective design compared with a prospective design, is that the collection of data is not affected by patient or physician behaviour. Furthermore, there are no protocol-driven costs. When we compared inpatient care data given by the patients themselves and data from the inpatient register we did not find that recall bias was a problem. On the contrary, the number of bed-days was less in the registers compared with the numbers given by the patients. If we instead would have used the quantitative data from the registers for calculating costs due to inpatient hospital care, the annual cost for the MS population would be about 130 MSEK. Using data from the questionnaires gave an annual cost for the MS population of 232 MSEK. Disregarding that we compared different years, it seems like patients had a tendency to overstate their inpatient care consumption. This tendency could, however, not be found when we compared the use of interferon drugs stated in the questionnaires and data from medial records.

One important issue when undertaking a ‘bottom-up’ study is that the selected patient sample is representative for the underlying population. When looking at the descriptive statistics of the background variables, our sample seems representative. The gender distribution was normal as well as age at first symptoms of MS. Also the MS specific questions and the questions about employment status showed results that were to be expected and have been shown in other studies. In this sense, our patient sample seems to be representative. However,

the patients in our study were selected at Huddinge Hospital, which is a university hospital, meaning that the hospital is involved in medical research to a higher extent. This might affect the way the patients are treated and followed up. For example, the use of interferon-beta drugs was much higher in our sample than for Sweden as a whole. In this sense, our sample might not be representative for the Swedish MS population.

Another source of potential bias may the response rate. Even if the response rate was good (76%), one could speculate if those patients not answering the questionnaire differ in any way, for example that they are more ill than those who have answered and this is a reason for not answering. If this is the case, the sample will not include the most severely ill MS patients, and the cost per patient in our study will be lower than the true figure.

This study has presented an in-depth assessment of the cost to society of MS, and showed how costs are affected by disease severity and by the presence of relapses. However, cost-of-illness studies are descriptive by nature and cannot be used to evaluate the cost-effectiveness of different interventions. To answer such questions we must introduce explicit alternatives, and include the consequences of the disease in terms of survival and quality of life in the analysis. This study provides important new data on the relationship between costs and severity of the disease that can be used in simulation models and studies based on clinical trials for assessing the cost-effectiveness of new interventions aimed at reducing the burden of MS on the patient and society. This is a highly demanded area for future research in MS.

5. CONCLUSIONS

The disease multiple sclerosis is associated with substantial costs to society due to its early onset and the chronic and disabling nature of the disease. A variety of costs accrue outside the health care system, which makes it important to have a societal perspective when studying the cost-of-illness of MS and to use a 'bottom-up' design in order to find resource data that are not present in public registers. Furthermore, costs vary to a large extent with the severity of the disease. Individuals with severe disease have substantially higher total costs than individuals with mild disease. Quality of life is lower for individuals with MS compared with both age-matched individuals in the general population and with individuals with other chronic diseases. Quality of life is also much affected by the severity of the disease. Since both costs and quality of life is highly correlated with the severity of the disease, a key issue in treating the disease is to slow down the progression. A recent clinical study has shown effect on disease progression of treatment with interferon-beta. Since interferon-beta drugs are relatively expensive, there has been a concern about rising costs and a need to include health economic evaluations in treatment guidelines for MS. Individual data on costs and utilities presented in this study, are crucial inputs in models used to perform such evaluations. Furthermore, a study like this increases the knowledge about the health economic aspects of MS, and can assist decisions about the distribution of scarce resources, so that these resources are used in an efficient way to treat the disease.

REFERENCES

1. Hauser SL. Multiple Sclerosis and other demyelinating diseases. In: Isselbacher KJ, Braunwald E, Wilson JD et al., editors. Harrison's principles of internal medicine. 13th ed. New York: McGraw-Hill, Inc., 1994;**22**:81-94.

2. Medical Products Agency (Läkemedelsverket). Behandlingsriktlinjer (in press).

3. Weinshenker BG, Bass B, Rice GPA *et al*. The natural history of multiple sclerosis: a geographically based study. *Brain* 1989;**112**:133-46.

4. Brönnum-Hansen H, Koch-Henriksen N, Hyllested K. Survival of patients with multiple sclerosis in Denmark: a nationwide, long-term epidemiologic survey. *Neurology* 1994;**44**:1901-7.

5. IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;**43**:655-61.

6. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR. Intramuscular Interferon Beta-1a for Disease Progression in Relapsing Multiple Sclerosis. *Ann Neurol* 1996;**39**:285-94.

7. PRISMS (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998;**352**:1498-1504.

8. The European Study Group of Interferon Beta in Secondary Progressive MS., Interferon Beta-1B delays progression of disability in secondary progressive multiple sclerosis: Results of a European multicenter randomised study. *Lancet* 1998;**352**:1491-97.

9. Tolley K, Whynes D. Interferon-b in multiple sclerosis. Can we control its costs? *Pharmacoeconomics* 1997;**11**:210-15.

10. O'Brien B. Multiple Sclerosis, 1987. Office of Health Economics: London, UK.

11. Blumhardt LD, Wood C. The economics of multiple sclerosis: a cost of illness study. *British Journal of Medical Economics* 1996;**10**:99-118.

12. Holmes J, Madgwick T, Bates D. The cost of multiple sclerosis. *British Journal of Medical Economics* 1995;**8**:181-93.

13. Henriksson F, Jönsson B. The economic cost of multiple sclerosis in Sweden in 1994. *Pharmacoeconomics* 1998;**13**:597-606.

14. Midgard R, Riise T, Nyland H. Impairment, disability and handicap in multiple sclerosis. A Cross sectional study in Möre and Romsdal County, Norway. *J Neurol* 1996;**243**:337-44.

15. Whetten-Goldstein K, Sloan F, Goldstein LB, Kulas ED. A comprehensive assessment of the cost of multiple sclerosis in the United States. *Multiple Sclerosis* 1998;**4**:419-25.

16. Murphy N, Confavreux C, Haas J, König N, Roullet E et al. Economic evaluation of multiple sclerosis in the UK, Germany and France. *Pharmacoeconomics* 1998;**13**:607-22.

17. Parkin D, McNamee P, Jacoby A, Miller P, Thomas S et al. A cost-utility analysis of interferon beta for multiple sclerosis. Report to the National Health Service Health Technology Assessment programme. December 1997. University of Newcastle: Newcastle.

18. Kurtzke J. Rating neurological impairment in multiple sclerosis and expanded disability status scale (EDSS). *Neurology* 1983;**33**:1444-52.

19. The Canadian Burden of Illness Study Group. Burden of Illness of Multiple Sclerosis. Part I: Cost of Illness. *Can J Neurol Sci* 1998;**25**:23-30.

20. The Canadian Burden of Illness Study Group. Burden of Illness of Multiple Sclerosis. Part II: Quality of Life. *Can J Neurol Sci* 1998;**25**:31-8.

21. Jönsson B, Jönsson L, Kobelt G. Modelling Disease Progression and the Effect of Treatment in Secondary Progressive MS. EFI Research Report ISBN no. 91-7258-520-X, Stockholm School of Economics, August 1999.

22. Hodgson TA, Meiners MR. Cost-of-illness methodology: A guide to assessment practices and procedures. *Milbank Memorial Fund Quaterly/Health and Society* 1982;**60**:429-91.

23. Rice DP. Estimating the cost of illness. In: Health Economic Series, vol.6. Washington, DC: US Government Printing Office, Public Health Service, 1966.

24. Tolpin HG, Bentkover JD. Economic costs of illness: decision making applications and practical considerations. In: Scheffler R, Rossiter L, editors. Advances in health economic and health service resourses. Greenwich (CT): JAI Press, 1983.

25. The EuroQol Group. EuroQol: a new facility for the measurement of health related quality of life. *Health Policy* 1990;**16**:199-208.

26. Katz ML, Rosen HR. Microeconomics. Second Ed, Richard D Irwine Inc, ISBN 0-256-11171-5, international edition, 1994.

27. Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford Medical Publications, 1987.

28. Statistics Sweden. Arbetskraftsundersökningen (AKU), Statistics Sweden, Stockholm, 1999.

29. Weinstein MC; Stason WB. Hypertension: a policy perspective. Cambridge, MA: Harvard University Press, 1976.

30. Federation of County Councils. Kostnader per intagen patient, vårddag, läkarbesök mm 1996. Stockholm: Federation of County Councils, 1999.

31. Affärsavtal 1999 för Södra Sjukvårdsregionen. Regionala priser 1999. Malmö: Södra Samverkansnämnden, 1999.

32. Riks- och regionvård 1998. Linköping: Landstinget i Östergötland, 1998.

33. Prislista 1998. Sluten och öppen vård. Uppsala: Akademiska sjukhuset, 1998.

34. FASS. Läkemedel i Sverige (Pharmaceutical lexicon). Läkemedelsinformation AB. ISBN 91-85314-71-4, Stockholm, 1999.

35. Hjortsberg C, Svarvar P. Kostnadsjämförelse mellan sluten sjukhusvård och medicinskt omfattande hemsjukvård – Cancer i livets slutskede. IHE Working Paper 1999:2, The Institute for Health Economics, Lund, 1999.

36. Andersson A, Persson PM, Fredrikson S. Bostadsort avgör om MS-sjuk får interferon beta-behandling. *Läkartidningen* 1999;**96**:5492-5.

37. Corporation of Swedish Pharmacies. Sales statistics from computer archives. Margareta Marcusson, personal communication.

38. Dolan P, Gudex C, Kind P et al. The time trade-off method: results from a general population study. *Health Economics* 1996;**5**:141-54.

39. Zethraeus N, Johannesson M. The comparison of patient and social tariff values derived from the time trade-off method. *Health Economics* 1999;**8**:541-5.

40. Lundberg L, Johannesson M, Isacson DGL, Borgquist L. Health-state utilities in a general population in relation to age, gender and socioeconomic factors. *European Journal of Public Health* 1999;**9**:211-17.

41. Malmöhus läns landsting. Data from the patient administrative system PAS.

42. Henriksson F, Agardh C-D, Berne C, Bolinder J, Jönsson B et al. Direct costs for patients with type 2 diabetes in Sweden (submitted).

43. Fuchs V. Economists, values, and health care reform. *American Economic Review* 1996;**86**:1-24.

44. Newhouse JP. US and UK Health Economics: Two disciplines separated by a common language? *Health Economics* 1998;**7**:S79-S92.

APPENDIX 1.

The multiple sclerosis questionnaire used in the study (in Swedish).

APPENDIX 2.

Per annum working hours for men and women in different age groups.

Age group (years)	Men	Women
16-19	1362	1056
20-24	1924	1628
25-34	2085	1737
35-44	2132	1747
45-54	2142	1804
55-59	2085	1721
60-64	1893	1591

Source: AKU (Arbetskraftsundersökningen), Statistics Sweden, Stockholm, 1999.

APPENDIX 3.

Resource items and unit costs for different resources in the study.

Resource item	Unit cost (SEK)	Note
Direct Costs		
Inpatient care and rehabilitation		
Bed-day at neurological ward	4 200	
Bed-day at ophthalmological ward	5 989	
Bed-day at infectious diseases ward	4 156	
Bed-day at ICU	4 505	
Bed-day at rehabilitation Ccenter	1 988	An average for 4 rehabilitation centers (St. Sköndal, Ersta, Frösunda, Humlegården)
Ambulatory care		
GP visit	910	
GP visit at home	1 638	A home visit is costed 1,8 times higher than a normal visit [35]
GP phone contact	60	Based on the cost of labor and the average time for a phone contact
Neurologist	1 138	
Other specialists	1 236	An average for a large number of different specialists
Nurse visit	450	
Nurse visit at home	810	A home visit is costed 1,8 times higher than a normal visit [35]
Physiotherapist	316	
Occupational therapist	500	
Chiropodist	300	
Speech therapist	1 100	
Incontinence advisor	450	A specialized nurse
Psychologist	1 000	
Almoner	1 000	With location at a hospital
Optician	180	The price for a visual test
Acupuncturist	300	
Chiropractor	300	
Dentist	510	
Gym instructor	90	
Drugs		
Interferon drugs	110 900	The average annual cost based on prices and recommended doses for Betaferon, Avonex and Rebif and weighted for their usage (shares).
Other prescribed drugs	2 850	The average annual cost based on prescribed drugs from a sample of patient journals.
OTC drugs (only a few examples given)		The average monthly cost based on prices and normal usage.
Alvedon	25	
C-vitamine	12	
Enomdan (vitamines)	14	
Garlic tablets	20	
Ginseng	50	
Panodil	25	

Q-10	80	
Selenium	15	
St. John's wort	75	
Zinc	20	
Services		
Personal assistant	130	The cost of labor per hour, based on the monthly salary + payroll taxes and an assumption of 21 working days per month.
Home help/home care	130	
Child care	130	
Transportation (färdtjänst)	65	Based on an average distance of 10 km and a cost per km of 6,50 SEK (which is the normal taxi fee in Sweden).
Adaptations and items purchased		
Adaptation of kitchen	30 000	We have used an incidence approach, meaning that the entire cost of each investment is distributed to the year it was made.
Adaptation of bathroom	30 000	
Adaptations of other parts of the house	50 000	
Roof lift	25 000	
Lift	8 000	
Stair elevator	75 000	
Ramps	10 000	
Safety alarm	5 000	
Adaptations at the job	30 000	
Car adaptation	30 000	
Wheelchair	6 000	
Electric wheelchair	110 000	
Electric moped	30 000	
Walking stick	40	
Walking aid (rollator)	1 000	
Special kitchen utencils	2 000	
Special writing devices	2 000	
Door opener	10 000	
Wider doors	1 000	Per door
Remove doorsteps	3 000	Per doorstep
Movable bed with remote control	25 000	
Shower chair	700	
Foot bar	3 000	
Informal care	50	The opportunity cost of time (leisure time) per hour, valuated as 35% of the gross wage rate.
Indirect Costs		
Loss of production per hour	180	The average cost of labor per hour in Sweden in 1998.

APPENDIX 4.

Hospital inpatient costs based on register data

The costs calculated below are based on data from the inpatient register from the National Board of Health and Welfare. The number of patients is 553 (615 = target population – 56 = from other study – 6 = missing identity).

Bed-days and costs in 1996 (number and SEK)

Ward	**Bed-days (total)**	**Bed-days (MS main diagnosis)**	**Costs (total)**	**Costs (MS main diagnosis)**
Internal medicine	168	88	536 760	281 160
Respiratory medicine	52	0	195 988	0
Infectious diseases	77	0	320 012	0
Rheumatology	18	0	63 810	0
Endocrinology	3	0	9 531	0
Child and adolescent	5	0	27 405	0
Neurology	1 078	879	4 527 600	3 767 400
Geriatric	158	109	390 260	269 230
Surgery	74	4	344 914	18 644
Gastroenterology	49	2	128 037	5 226
Orthopedic	28	0	135 296	0
Urology	105	0	391 860	0
Gynecology	40	0	202 720	0
ENT	8	0	48 392	0
Psychology	10	0	28 290	0
Total	**1 873**	**1 100**	**7 350 875**	**4 341 660**

The 553 patients in the sample had in total 1 873 bed-days in 1996. In 1 100 of these, MS was registered as the main diagnosis at discharge. The most frequently visited ward was neurological with 1 078 bed-days, which is 60 % of the total number of bed-days. Other frequently visited wards were internal medicine, geriatric and urology. Inpatient costs per individual and year in the sample amounted to 13 293 SEK (7 350 875/553), or 7 851 SEK (4 341 660/553) if we only include cases where MS was the main diagnosis. The number of bed-days and annual cost per individual based on the answers from the questionnaires was 2 064 and 21 097 SEK respectively. Disregarding that we are comparing different years (1999 in the questionnaire and 1996 here), the number of bed-days and cost per patient is lower when relying on register data compared to data from the questionnaires. If we extrapolate the cost per patient based on register data to the population level it results in a cost due to inpatient hospital care of 133 MSEK or 78 MSEK (MS as main diagnosis). The latter figure is rather

close to the estimate of 66,5 MSEK in the former Swedish cost-of-illness study on MS in Sweden for 1994 [13].

Bed-days and costs in 1997 (number and SEK)

Ward	**Bed-days (total)**	**Bed-days (MS main diagnosis)**	**Costs (total)**	**Costs (MS main diagnosis)**
Internal medicine	173	43	552 735	137 385
Respiratory medicine	32	4	120 608	15 076
Infectious diseases	109	5	453 004	20 780
Rheumatology	1	1	3 545	3 545
Cardiovascular	1	0	3 207	0
Child and adolescent	5	5	27 405	27 405
Neurology	1 005	888	4 221 000	3 729 600
Cardiology	7	0	29 792	0
Geriatric	111	23	274 170	56 810
Surgery	102	0	559 320	0
Gastroenterology	6	0	15 678	0
Orthopedic	44	0	212 608	0
Urology	37	16	138 084	59 712
Gynecology	55	0	278 740	0
Ophthalmology	5	0	30 015	0
ENT	1	0	6 049	0
Oncology	19	0	84 892	0
Psychology	21	0	594 409	0
Total	**1 734**	**985**	**7 070 261**	**4 050 313**

The patients in the sample had in total 1 734 bed-days in 1997. In 985 of these, MS was registered as the main diagnosis at discharge. Hence, the number of bed-days was somewhat lower in 1997 compared to 1996. The most frequently visited ward was neurological with 1 005 bed-days. Other frequently visited wards were internal medicine, geriatric, infectious diseases and surgery. Inpatient cost per individual and year in the sample amounted to 12 785 SEK, or 7 324 SEK if we only include cases where MS was the main diagnosis. Also for this year the costs calculated from register data were lower than the cost based on data from the questionnaires.

Our pre-study hypothesis was that, due to recall bias, some patients have forgotten a number of their inpatient days. However, hospitalization is a rare event and evidently something you normally recall. The fraction of patients that were hospitalized during a certain time period was about the same in the registers and in the study. However, the length of stay was longer according to the patients themselves compared with register data. This may be due to several factors. One could be reporting bias, in the sense, that patients want to stress the severity of

their disease by recalling (consciously or unconsciously) more bed-days. Another source of bias could be that patients misinterpret the time period and include bed-days for a longer period than a month. Still another could be that negative experiences, such as hospital inpatient stays, are ex post experienced longer than they in fact were.

APPENDIX 5.

An estimate of the intangible costs due to MS

In the table below, utility values obtained from the EQ-5D instrument in our questionnaire are compared with utility values obtained from another study [40]. This study used a self-administered postal questionnaire distributed randomly to 8 000 individuals aged 20-84 in Uppsala county in Sweden (68% response rate). Health state utilities were obtained through a visual analogue scale and through a time-trade off question (TTO). Even if the TTO technique used in this study is a bit different from the one underlying the utility scores obtained from EQ-5D, a comparison gives an idea of the quality of life difference between the general population and individuals with MS. By multiplying the utility difference in each age group with the number of individual in that group the number of QALYs lost during a one year period is obtained (assuming no difference in mortality).

An estimation of the number of QALYs lost in the sample

Age (years)	**Mean utility value - general population (n=4649)**	**Mean utility value – individuals with MS (n=413)**	**Difference in utility**	**Number of individuals with MS in each age group**	**QALYs lost**
< 29	0,94	0,57	0,37	21	7,77
30-39	0,94	0,48	0,46	73	33,58
40-49	0,93	0,47	0,46	110	50,60
50-59	0,92	0,39	0,53	127	67,31
60-69	0,87	0,34	0,53	64	33,92
70-79	0,73	0,19	0,54	18	9,72
Total	**na**	**na**	**na**	**413**	**202,9**

The number of QALYs lost for the 413 MS patients in the sample due to reduced quality of life is 202,9. Extrapolation to the MS population level results in 5 404 QALYs lost (11 000/413 * 202,9). Two recent studies conducted among both UK and US health economists [43,44] showed a high degree of consensus regarding how to value a year of human life. The mean value was found to be about 60 000 USD, which means about 500 000 SEK. This value of a human life is in accordance with the value used in Sweden by the Swedish Road Safety Office, when performing cost-benefit analyses of road investments. Multiplying this figure by the 5 404 QALYs lost, results in intangible costs due to MS in Sweden of **2 702 MSEK**.