

Global Economic Impact of Multiple Sclerosis



multiple sclerosis
international federation

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Literature Review

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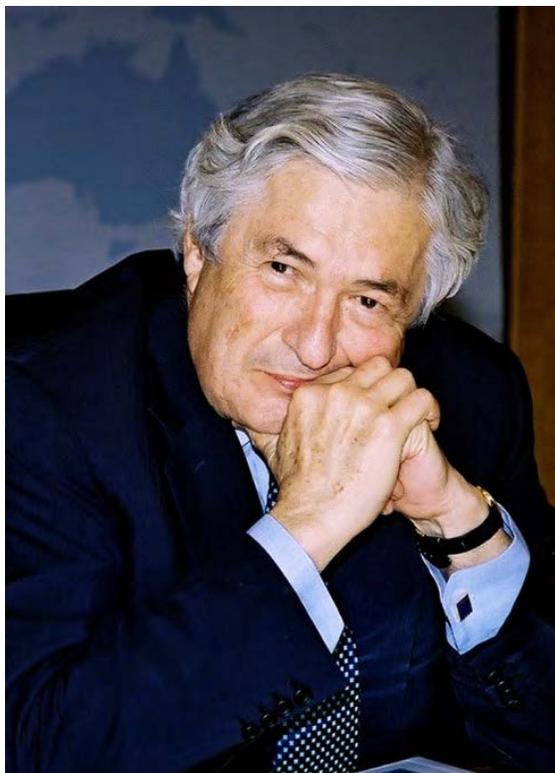
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As I'm sure is the case with many who are involved in the fight against multiple sclerosis, I first came to care passionately about this cause through a personal connection. Jacqueline du Pré, the acclaimed cellist and a close friend of mine, was diagnosed with MS in 1973. I watched her struggle bravely and with dignity as the disease robbed her of her ability to perform, and ultimately cut short her inspiring life.

Unwilling to sit helplessly on the sidelines, I jumped at the opportunity to get involved with the work of the MS International Federation, which I had the privilege to lead as President for six years. During this time we expanded MSIF's work into new

countries, and deepened our understanding of the disease and what can be done to respond to it, work that has continued and strengthened in the years since.

But despite the great work of the Federation, there is much, much more that remains to be done, a vital component of which is the need for further high quality research. That is why efforts such as this groundbreaking endeavor to understand the global costs of MS are so important.

This literature review reveals the significant economic burdens MS imposes on those suffering with the disease, on their families, and on society as a whole. It also identifies the six main costs associated with MS, which together represent over 75 percent of the cost burden of the disease: informal care, disease modifying drugs, professional home care, hospitalizations, cost of other prescriptions, and early retirement and loss of employment. Of these, early retirement and employment is the most significant factor – an area where we can make real progress with the cooperation of governments, employers, and people affected by MS.

I commend the authors for this significant publication, and hope that its findings are widely disseminated and help inform policymakers across the world.

James D. Wolfensohn
Chairman and CEO
Wolfensohn & Co.
Former President of the World Bank (1995-2005)

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EXECUTIVE SUMMARY

INTRODUCTION

Multiple sclerosis (MS) is a chronic, disabling disease that affects 2 million people worldwide and is typically diagnosed between ages 20 and 40. Common symptoms that include upper and lower extremity disabilities, visual disturbances, balance and coordination problems, spasticity, altered sensation, abnormal speech, swallowing disorders, fatigue, bladder and bowel problems, sexual dysfunction, and cognitive and emotional disturbances. MS can substantially and adversely affect an individual's quality of life (QOL) and is associated with high costs for MS patients, their families, and society as a whole.

A key issue for policy makers and advocacy organizations is the cost to society of MS. Cost of illness studies quantify the economic burden of specific diseases and can be used by policy makers to allocate research and service funding. Several cost of illness estimates for MS in many different countries have been published over the past 10 years, with all finding a high cost on a per person basis.

To help raise awareness of the high global costs of MS, this literature review provides international data that are useful for estimating the costs and QOL impacts of MS at the national level. A companion report includes a cost calculator that can be used to estimate the economic impact of MS at the country level.

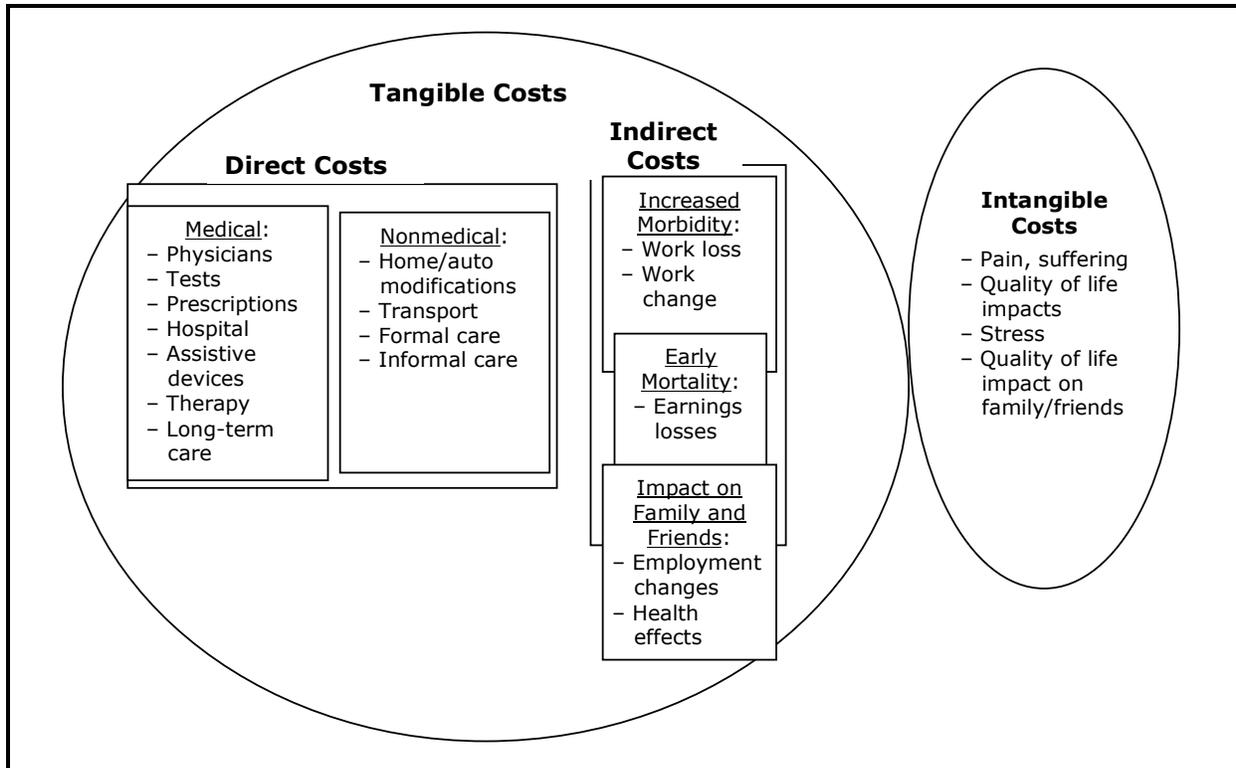
Figure 1 presents the conceptual model of the tangible and intangible costs of MS that was used to guide this literature review and the development of the cost calculator. This model categorizes the elements of costs that ideally should be included in a cost of illness study. The conceptual model divides the impact of MS into two broad categories: tangible costs and intangible costs. Tangible costs include direct medical and nonmedical costs. Direct medical costs include costs such as prescription drugs, physician services, hospital stays, and nursing home stays. Direct nonmedical costs include home and automobile modifications, informal care provided by family and friends, and most home and community-based services. Indirect costs address the labor productivity losses and wages associated with withdrawal from the workforce by people with MS and employment and health impacts on their family and friends. Finally, intangible costs refer to the impact of MS on QOL for patients and their primary caregivers.

LITERATURE REVIEW METHODOLOGY

This literature review on the cost of MS included two steps. The first step involved conducting a detailed literature search, including electronic databases of peer-reviewed journal articles. To identify potential articles for the literature review, we searched 11 electronic publication databases, including PubMed, PsycINFO, CINAHL, Cochrane Database of Scientific Reviews, and others, for articles relevant to the cost of MS, published after 1997. The second step involved reviewing citations found in the literature search, selecting relevant journal articles for more detailed review, and abstracting data on the economic burden of MS from the selected articles using a standardized abstraction form. A total of 1,608 possible

articles were identified for review, of which 215 were abstracted. Relevant articles about 19 countries were identified.¹

Conceptual Model of MS Cost Categories for Economic Burden Analysis



PREVALENCE OF MS BY COUNTRY

The first step in determining the economic impact of MS in a particular country is to identify the total number of MS patients residing in that country. Data on the prevalence of MS per 100,000 people were recently estimated for 122 countries by the World Health Organization (WHO) and the Multiple Sclerosis International Federation (MSIF) (WHO and MSIF, 2008). Globally, the median estimated prevalence of MS is 30 people per 100,000. Countries with the highest estimated prevalence included Hungary (176), Slovenia (150), Germany (149), United States (135), Canada (133), Czech Republic (130), Norway (125), Denmark (122), Poland (120), and Cyprus (110).

A study by Pugliatti et al. (2006) on European MS epidemiology found broadly similar results as those reported in the MS Atlas, although the estimates differ for some countries. They conducted a literature review of studies published over the past three decades on the epidemiology of MS in Europe. They found an overall estimated prevalence rate of MS in Europe of 83 per 100,000, with higher rates in

¹ The 19 countries are Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Mexico, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, the United Kingdom, and the United States.

northern countries. They reviewed studies from 33 countries, with a wide range in prevalence rates from lows of 36 to 39 per 100,000 in Spain to highs of 116, 135, 165, 153, and 186 in Denmark, Ireland, Norway, Sweden, and the United Kingdom, respectively. Mean MS prevalence rates tended to be higher in countries where the degree of disease investigation is higher, where better survey methodologies are used, and where assessments have been repeatedly conducted over time, often based on nationwide surveys or registry systems. A number of studies have found lower rates in countries located closer to the equator and higher rates in northern and southern latitudes. Lower prevalence rates have been found in non-white populations.

TOTAL COSTS

Total costs of MS varied substantially across countries for which studies have been conducted but are substantial in all countries. As shown in Table 1, for the 15 countries for which we have complete estimates, total average cost per person with MS in 2007 varied from a low of 16,400 U.S. international dollars in France to a high of 54,500 U.S. international dollars in Norway and Sweden, for an overall prevalence-weighted average of 41,000 U.S. international dollars (2007). Estimated costs varied because of the availability and costs of medical care, the use of paid and unpaid home and community-based services, and the extent to which people withdraw from the labor force and the resultant loss of income. Estimates also reflect differences in study methodologies and the specific categories of costs included across countries.

DIRECT COSTS

Direct costs of a disease represent the value of all resources consumed to diagnose, treat, or accommodate people with the condition. A wide variety of MS-related direct costs are reported in the literature. Examples include the costs of neurologist visits, the costs of installing wheelchair ramps at home, and the value of caregiving provided by family or friends. Our review considered two broad categories of direct costs—direct medical costs and direct nonmedical costs—a categorization typically used in cost-of-illness and cost-effectiveness studies. Most MS cost analyses estimated direct costs for the prevalent population with MS for a specified time period, such as 1 year. These analyses are known as prevalence-based cost studies. We reviewed 28 recent studies that report original analyses of the direct medical or nonmedical costs of MS. For the 15 countries for which we have complete cost data, total direct costs ranged from a low of 5,600 U.S. international dollars in Canada to a high of 37,000 U.S. international dollars in Sweden, for an overall prevalence-weighted average of 24,600 U.S. international dollars. For these studies, direct costs accounted for 26% to 87% of total costs.

Direct Medical Costs

Direct medical costs include all costs related to patient encounters with the health care system, including inpatient hospital care, nursing homes, rehabilitation hospitals, outpatient hospital services, physician services, prescription drugs, diagnostic testing, ancillary services, and medical supplies.

Most of the studies used a bottom-up approach to estimate direct costs, meaning they collected data on resource utilization from a sample of patients and estimated medical costs for those patients. Two studies used a top-down approach to allocate national estimates of health care spending to MS. Many of the earlier studies took place before the widespread use of disease-modifying drugs or specifically excluded disease-modifying drug costs from direct medical cost calculations.

All of the studies found that MS is associated with large direct medical costs, which vary greatly across countries. For the 15 countries for which we have data, direct medical costs varied from a low of 3,200 U.S. international dollars in Canada to a high of 24,000 U.S. international dollars in the United States, for an overall prevalence-weighted average of 13,200 U.S. international dollars. For these studies, direct medical costs accounted for 15% to 69% of total costs. Differences in use of disease-modifying drugs account for much of this variation.

In addition to the studies that involved primary data collection, Sobocki et al. (2007) estimated per-person direct costs in each country by adjusting for differences in health care spending, gross domestic product, and wages between the estimation country and the nine original European countries studied by Kolbelt et al. Using this ratio approach, they estimated 2005 per-person direct costs (medical and nonmedical) of MS ranging from less than €10,000 (2005) in Estonia to over €30,000 in Sweden.

Many of the studies disaggregated direct costs of MS by Expanded Disability Status Scale (EDSS) category, which is a measure of impairment for people with MS, finding that costs increased with EDSS level. Patwardhan et al. (2005) found that direct costs for patients at the highest EDSS levels are generally 2.5 to 7 times the direct costs of patients at the lowest EDSS levels.

Direct Nonmedical Costs

Direct nonmedical costs include all nonmedical resources that are consumed to care for MS patients, including paid nonmedical home care (e.g., personal care or help with activities of daily living), informal care provided by family and friends, MS adult day care, home or automobile modifications, mobility devices (e.g., wheelchairs, scooters), transportation services, job retraining, and other resources (e.g., child care, housekeeping).

We reviewed 24 recent studies that describe original analyses of the direct nonmedical costs of MS. For the 15 countries for which we have complete cost data, direct nonmedical costs varied from a low of 2,400 U.S. international dollars in Canada to a high of 21,600 U.S. international dollars in Sweden, for an overall prevalence-weighted average of 11,400 U.S. international dollars. For these studies, direct nonmedical costs accounted for 11% to 42% of total costs. The largest share of nonmedical costs of MS is for informal care. For example, informal care costs in the United States are 63% of total nonmedical costs. Differences in informal care costs across countries are sensitive to differences in the amount of paid home and community-based services provided by government and other sources. Informal care costs are also higher in countries with lower female labor force participation rates, such as in Spain and Italy.

Most studies used a replacement cost method to value informal care, meaning they applied the hourly wage rate for those who provide home care or personal assistance to the time spent by family members providing care for the person with MS. The nine European studies used a disposable income approach, where the value assigned to home care was net income after social contributions and income tax.

The cost of investments in home and auto modifications and mobility aids averaged about €1,000 (2005) per person per year across the nine Kobelt et al. studies. Additionally, other than in Sweden, per-person costs for home help and personal assistance were close to €2000 (2005) per year.

INDIRECT COSTS

Work Loss

People with MS often have difficulty continuing to work, due to the disabilities, fatigue, cognitive impairments, transportation difficulties, speech impairments, and other aspects of the disease. A substantial body of research documents the significant adverse impact of MS on labor force participation. These costs include short-term and long-term absence from work, reduced hours of work, changing the type of work to a less physically challenging and stressful nature (usually at lower pay), and early retirement. We identified 22 original studies, one synthesis article, and one systematic review that contained quantitative data on labor force participation by MS patients. For the 15 countries for which we have complete cost data, indirect costs, mostly work loss, varied from a low of 5,600 U.S. international dollars in France to a high of 31,000 U.S. international dollars in Norway, for an overall prevalence-weighted average of 16,800 U.S. international dollars. For these studies, indirect costs accounted for 13% to 74% of total MS costs.

Although these costs vary by disability level, MS resulted in reduced productivity and substantial income loss for MS patients. Indeed, this indirect cost constitutes at least one-third of the total costs of MS in most of the studies of the cost of the illness.

Not surprisingly, given the duties of being an informal caregiver, all of the studies that examined the effect of caring for a person with MS on labor force participation found that this role had a negative impact or that there was work-related strain because of work adjustments. Compared to studies of caregiver strain, this research is more limited.

Early Mortality

Premature death from MS or its complications causes an economic burden due to the underlying economic value of the lost years of healthy life. MS is usually viewed as a disease that results primarily in morbidity, disability, and loss of QOL, but without dramatic impacts on life expectancy. However, recent studies across multiple countries show a consistent, significant negative impact on life expectancy due to MS. Estimates of reduced life expectancy due to MS in these studies range from 5 to 15 years. In addition, these studies find that average survival time of MS patients is long, ranging from 20 to nearly 45 years from the onset of disease symptoms and that MS is not generally lethal by itself, but death is usually the result of high levels of disability, increasing age, or concurrent diseases. Treatments adopted

to improve MS symptoms and to prevent and cure complications in more disabled persons may result in improved survival for MS patients.

Total Costs of MS by Reference Country

In the table below, although MS cost estimates from each study have been updated to a common currency and year, because of differences across studies in the time period for analysis and the methodologies used, cross-country comparisons of MS costs are not recommended. Differences in MS costs across countries are driven by differences in the categories of costs included in each study, differences in the typical care provided to MS patients during the time period of analysis, and differences in cost analysis approaches, in addition to underlying differences in the costs of MS treatment and management. For example, because the most recent published studies for Canada and France used patient data from 1995, treatment costs from those studies do not reflect patterns of treatment that have been adopted and in wide use after the late 1990s.

Country	Total Direct Medical Cost (2007 Int'l Dollars)	Total Direct Non-Medical Cost (2007 Int'l Dollars)	Total Indirect Costs (2007 Int'l Dollars)	Total Cost (2007 Int'l Dollars)
Australia	\$18,809	\$16,167	\$6,890	\$41,866
Austria	\$20,738	\$10,010	\$17,569	\$48,317
Belgium	\$13,746	\$10,108	\$13,267	\$37,121
Canada	\$3,162	\$2,421	\$15,932	\$21,514
France	\$6,078	\$4,718	\$5,582	\$16,378
Germany	\$20,246	\$6,986	\$19,946	\$47,178
Italy	\$13,001	\$19,225	\$13,237	\$45,462
Netherlands	\$9,845	\$8,910	\$15,849	\$34,605
Norway	\$10,995	\$12,472	\$31,023	\$54,489
Poland	\$3,495	\$2,713	\$11,423	\$17,631
Spain	\$15,973	\$16,498	\$11,544	\$44,015
Sweden	\$15,431	\$21,607	\$17,427	\$54,465
Switzerland	\$10,211	\$13,365	\$14,473	\$38,048
United Kingdom	\$10,969	\$19,858	\$17,995	\$48,822
United States	\$23,975	\$7,844	\$18,888	\$50,707
Weighted average ^a	\$13,198	\$11,383	\$16,755	\$41,335

^a Weighted by prevalence of MS in each country.

INTANGIBLE COSTS

QOL has become a widely used health care outcome measure. For chronic diseases, it is important because diseases such as MS can dramatically affect the QOL of patients for many years without causing death. As a result, a significant but unquantifiable component of the economic burden of MS is its impact

on QOL. QOL can be measured for general domains common across multiple diseases and for disease-specific domains that are more closely related to the morbidity or disability impacts of MS.

Quality of Life: Generic Domains

Studies of the generic QOL impact of MS consistently show substantial negative effects from the disease. Overall, 13 studies were identified that analyze the impacts of MS on generic QOL across multiple domains. Several patterns across different QOL domains can be identified from these studies. First, the impacts on physical functioning were larger than those on social functioning or mental functioning. In addition, the physical health QOL impacts increase as the disease progresses over time and physical impairments become more severe. Significant impacts on social and mental functioning were also found.

Overall, these studies indicate a 30% decline in physical functioning for mild MS, increasing to 40% for moderate MS and 50% for severe MS. A 20% decline in social functioning can be identified for mild and moderate MS, increasing to 30% for severe MS. Mental functioning declined by about 10% across the range of severity levels.

Quality of Life: MS-Specific Domains

MS has a broad range of impacts on QOL, and many of them are not captured in the generic measures of utility and QOL. As a result, a comprehensive assessment of the burden of MS includes an assessment of the impacts of MS not captured by the generic QOL measures. Studies find that MS has a negative impact on QOL through cognitive impairment, bladder dysfunction, bowel dysfunction, sleep problems, and sexual dysfunction.

Utility Measures

Utility measures are similar to QOL measures, although they are based on economic theory rather than the psychological theories that underlie QOL concepts. The loss in utility due to MS was consistent across the European and American studies at between 0.20 and 0.31 out of a range of 0.0 to 1.0. Thus, an overall estimate of the burden of MS in terms of utility is an average loss of 0.25. Using the U.K. population norm for the overall population of 0.86 as a baseline, this 0.25 decline in utility can be interpreted as a loss of 29% of utility by people with MS compared to an overall population norm.

Impacts on Family and Friends

People with MS often require help performing daily tasks because of health care problems and functional and cognitive impairments. This care is mostly provided by informal caregivers, principally spouses and other relatives. In addition to the direct cost related to the hours of care that informal caregivers provide, the disabling aspects of the disease, its impact on mortality, the financial burdens, and MS's uncertain course often create additional psychological stress and anxiety for the informal caregivers, especially those living with the person with MS. The stress and physical burden of caring for MS patients may have an adverse effect on the psychological and physical health of caregivers and increase their health care use.

We identified 13 studies—12 original studies and one systematic review—that addressed the indirect costs of informal caregivers: caregiver burden, caregiver labor force participation, and caregiver health and health care use. The research suggests two main findings: (1) the burden/stress on caregivers is substantial, but it is far less than it is on MS patients; and (2) the amount of burden/stress varies by level of disability. A conservative estimate of the economic value of stress/burden for caregivers is 10% of what is estimated for MS patients by EDSS level.

Closely related to the level of caregiver burden and stress is whether these factors result in negative health outcomes for caregivers. Only a few studies have addressed this issue at all. Almost all of the studies that report a negative impact do so for depression or some other mental health problem. Data on the impact of MS on caregivers' physical health are much less common and inconclusive.

CONCLUSIONS

The results of this literature review indicate that MS imposes substantial economic burdens on MS patients, on their families, and on society as a whole. Moreover, these burdens span a broad range of impacts, including prevalence of MS, direct costs, indirect costs, QOL, and other intangible costs.

THE WAY FORWARD

Multiple sclerosis is a common neurological disorder with life-long duration and significant severity. Apart from the personal suffering, the financial consequences for people with MS and their family and the economic impact on society are enormous.

In 2008, MSIF commissioned RTI International to undertake a comprehensive literature review identifying the current state of research in the epidemiology and economic impact of MS worldwide. This report provides independent quantitative evidence for estimating the global economic impact of MS. We hope it will be used by people affected by MS, national MS societies and governments to highlight the economic impact of MS nationally, regionally and globally and to develop initiatives to improve the quality of life of people affected by MS.

These initiatives could include (but are not limited to):

Employers

- Educating employers about nature and symptoms of MS and the roles of family members and carers and persuading employers to develop health policies to protect the rights of people with MS and other chronic diseases
- Encouraging employers to provide flexible disability and workplace benefits and job modifications or accommodations (e.g. flexible work schedules, accessible work area, adaptive aids, appropriate room temperature, etc) to enable people with MS (or their carers) to remain in work for longer

Government

- Improved government policy on resource allocation and better integrated healthcare service delivery that is cost effective, accessible and available to all pwMS with a view to keeping them in employment

Research

- Strategised / prioritised funding for research into the understanding of the causes of MS and development of better treatments, including treatments that may slow MS-progression to delay patients' exit from the work-force
- Cost benefit studies of therapies for MS and benefit of early treatment
- Studies on economic impact of MS in individual countries where the data doesn't exist (these studies can be used to raise awareness and in health policy decision making). The MSIF costing tool could help in some countries to provide estimates

Global Economic Impact of Multiple Sclerosis

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic, disabling disease that affects 2 million people worldwide and is typically diagnosed between ages 20 and 40 (WHO and MSIF, 2008). Common symptoms include upper and lower extremity disabilities, visual disturbances, balance and coordination problems, spasticity, altered sensation, abnormal speech, swallowing disorders, fatigue, bladder and bowel problems, sexual dysfunction, and cognitive and emotional disturbances. Comorbidities are relatively common, with approximately one third of patients reporting at least one physical comorbidity (Marrie et al., 2008). MS can substantially and adversely affect an individual's quality of life (QOL) and is associated with high costs for MS patients, their families, and society as a whole.

A key issue for policymakers and advocacy organizations is: What is the cost to society of MS? Cost-of-illness studies quantify the economic burden of specific diseases and can be used by policy makers to allocate research and service funding. Several cost-of-illness estimates for MS in many countries have been published over the past 10 years, with all finding a high cost on a per person basis.

Most MS cost analyses have estimated direct costs for the prevalent population with MS for a specified time period, such as one year. These analyses are known as prevalence-based cost studies. Cost analyses that focus on estimating the lifetime costs of MS are known as incidence-based cost analyses. A few MS cost studies have also provided lifetime cost estimates. In addition, a few studies address the cost of relapse.

Comparing the costs of MS across studies is challenging because of differences in the types of costs included in each study, methodological approaches, and differences in study locations and time periods for analysis. Some MS cost analyses use a bottom-up approach, where patients with MS are asked about the impact of the disease on their use of health care and other services and labor market effects, and those impacts are valued using unit cost estimates. In contrast, top-down approaches typically take aggregate spending on health care and allocate these costs to specific diseases, such as MS, based on information about disease prevalence and severity. Some studies provide total cost estimates for MS patients (Pope et al., 2002), whereas others attempt to estimate only the portion of costs that are attributable to MS by asking directly about resources used to treat MS (Kobelt et al., 2006a, 2006b) or by comparing costs for MS patients with costs for a matched control sample (Whetten-Goldstein, 1998).

Several cost-of-illness estimates for MS in many countries have been published in the past 10 years (Kobelt et al., 2006a, 2006b; Pope et al., 2002; Taylor et al., 2007; Whetten-Goldstein et al., 1998). Estimated per person costs from these studies vary widely. Some of these studies have included all medical, therapy, and equipment costs and earnings losses, regardless of whether they were specifically related to MS (e.g., Whetten-Goldstein et al., 1998), whereas others have included only costs that are clearly attributable to MS (e.g., Kobelt et al., 2006b). Most cost-of-illness analyses estimate annual costs

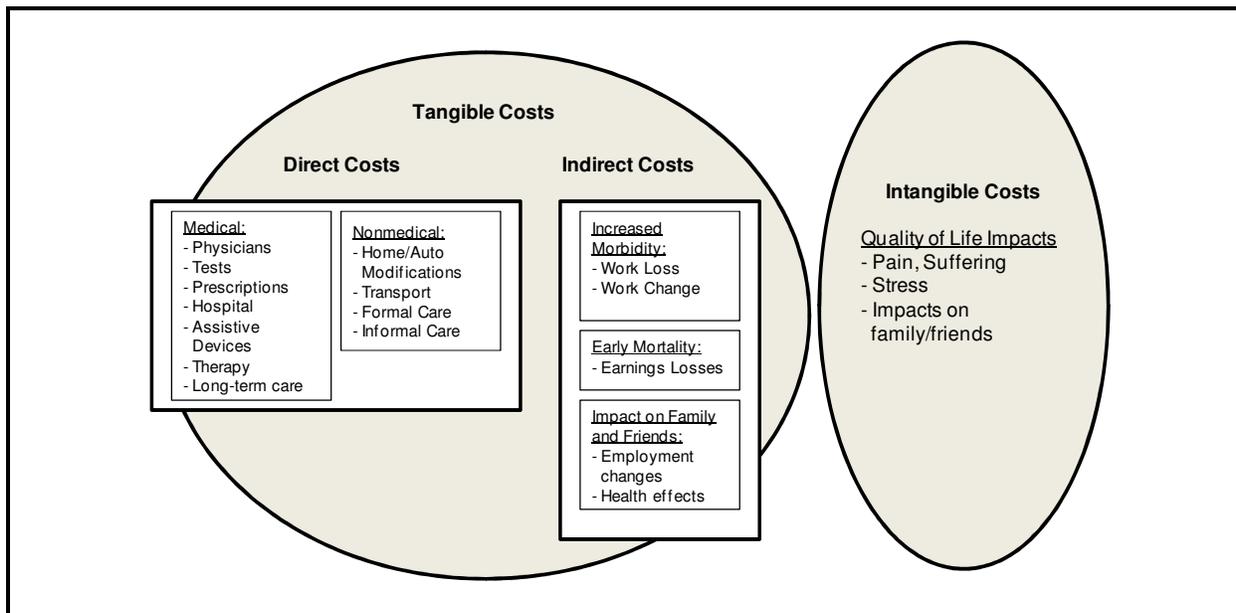
for the population at a single point in time, but a few estimate lifetime costs for the incident population (Rice, 1994).

To help raise awareness of the high global costs of MS, this literature review provides data that are useful for estimating the costs and quality of life impacts of MS at the national level. A companion report includes a template or cost calculator that can be used to estimate the economic impact of MS at the country level.

Figure 1 presents the conceptual model of the tangible and intangible costs of MS that was used to guide this literature review and the development of the template. This model categorizes the elements of costs that ideally should be included in a cost-of-illness study. The conceptual model divides the impact of MS into two broad categories—tangible and intangible costs. Tangible costs include direct medical and nonmedical costs. Direct medical costs include direct medical costs for things like prescription drugs, physician services, hospital stays, and nursing home stays. Nonmedical direct costs include home and automobile modifications, informal care provided by family and friends, and most home and community-based services. Indirect costs address the labor productivity loss and wages associated with withdrawal from the workforce by people with MS and premature death. Finally, intangible costs refer to the impact of MS on quality of life.

The following chapters summarize evidence on the topics included in this conceptual model and in the template. Chapter 2 presents the methodology used for the literature review. Chapter 3 reviews estimates of the prevalence of MS by country, for use in the template. Chapter 4 includes the literature review on direct costs of MS, including both medical and nonmedical costs. Chapter 5 presents the literature review on indirect costs of MS, including work loss for both people with MS and their informal caregivers and early mortality. Chapter 6 includes the literature review on the intangible costs of MS, covering generic measures of QOL, MS-specific QOL domains, utility measures, and impacts of MS on family and friends of patients. Chapter 7 presents conclusions regarding the economic burden of MS.

Figure 1. Conceptual Model of MS Cost Categories for Economic Burden Analysis



2. LITERATURE REVIEW METHODOLOGY

This literature review on the cost of MS included two steps. The first step involved conducting a detailed literature search, including electronic databases of peer-reviewed journal articles. The second step involved reviewing citations found in the literature search, selecting journal articles for more detailed review, and abstracting data on the economic burden of multiple sclerosis from the selected articles. A total of 1,608 possible articles were identified for review, of which 215 were abstracted. Relevant articles about 19 countries were identified.

2.1 Literature Search Procedures

To identify potential articles for the literature review, we searched electronic databases using a four-step process. The first step was to identify 11 databases believed to contain citations and abstracts relating to the burdens of MS:

British Nursing Index	Global Health
CINAHL	ISI Web of Science
Cochrane Database of Systematic Reviews	PsycINFO
EconLit	PubMed
EMBASE	Sociological Abstracts
	Social Work Abstract

RTI obtained access to each of these databases.

The second step was to identify inclusion and exclusion criteria for the electronic literature searches to limit the search results to articles expected to have the most value for this study:

Inclusion Criteria

- Studies on human subjects
- Studies on adults
- English language studies

Exclusion Criteria

- Letter to the editor
- Commentaries
- Editorials
- Studies published before 1998
- Studies evaluating specific prescription drugs, such as interferon
- Articles not published in peer-reviewed journals, with a few exceptions

The third step was to identify a series of key words to search these databases electronically. We focused on the Medical Subject Heading (MeSH) terms because they represent widely used categories for these types of database searches. Table 1 shows the categories and detailed MeSH terms used for this study.

Table 1. Categories and Key Words

Category	Key Words	
Disease	multiple sclerosis	
Costs and Quality of Life	budgets burden cost(s) cost analysis cost of illness costing economic(s) econometric models expenditure(s)	fee for service health care costs health expenditures pharmacoeconomics prescription fees quality of life quality-adjusted life years time factor(s) utility
Employment	absenteeism employment employability productivity retirement unemployment	work work capacity evaluation work change work loss workplace
Morbidity and Mortality	death and dying disability mortality morbidity severity of illness index	
Services and Care	assisted living caregivers carer cash welfare community services disability evaluation disability insurance family group homes health insurance health maintenance organizations husbands informal care	long-term care Medicaid Medicare outreach programs public assistance social assistance social care social services social security social welfare spouses welfare services wives
Adaptations	accommodations architectural accessibility automobile(s) automobile driving automobile modification(s) durable medical equipment	home modification(s) housing mobility aids motor vehicles transportation

The fourth step was to implement the electronic searches. To begin this process, a series of initial database searches was conducted to identify documents marked with both the disease MeSH term and one of the other MeSH terms (e.g., “multiple sclerosis AND cost of illness”). The results of these initial searches were then combined into a single database so that duplicate citations could be deleted. The titles and abstracts of the articles were then reviewed. Articles were excluded from further review if they did not give quantitative estimates (including review articles with no quantitative data), the article was primarily clinical, the article focused on biomedical processes, MS was listed only as multiple other chronic diseases and the analysis was not done separately, the article was a drug trial, or the article focused on measurement. Full copies of the remaining articles were obtained for review.

Copies of additional articles identified through examination of citations from reviewed articles and consultation with other MS researchers were also ordered if they addressed topics relating to the review. They were then reviewed in the same manner as articles identified through the electronic searches.

2.2 Literature Review Procedures

The literature review process involved abstracting each of the journal articles using a template designed to capture the key information on the direct cost, indirect cost, and intangible cost burdens of MS and the methods and limitations of the evidence presented in the article. The documents cited in this study encompassed research on the burdens of MS conducted in a wide range of countries, including the following:

Australia	Mexico
Austria	Netherlands
Belgium	New Zealand
Canada	Norway
Denmark	Spain
Finland	Sweden
France	Switzerland
Germany	United Kingdom
Ireland	United States
Italy	

3. PREVALENCE OF MS BY COUNTRY

The first step in determining the economic impact of multiple sclerosis (MS) in a particular country is to identify the total number of MS patients residing in that country. This can be calculated from estimates of the prevalence of MS in that country and the population of the country. Data on the prevalence of MS per 100,000 people were recently estimated for 122 countries by the World Health Organization (WHO) and the Multiple Sclerosis International Federation (MSIF) (WHO and MSIF, 2008). Globally, the median estimated prevalence of MS is 30 people per 100,000. Countries with the highest estimated prevalence included Hungary (176), Slovenia (150), Germany (149), United States (135), Canada (133), Czech Republic (130), Norway (125), Denmark (122), Poland (120), and Cyprus (110).

The prevalence data were collected through a survey of individual countries conducted by WHO and MSIF. The data were collected over a 2-year period from 2005 to 2007 and included countries from all continents and WHO regions. Country coordinators identified by either MSIF or WHO completed the data in a questionnaire on eight topics related to MS epidemiology, diagnosis, treatment, resources, quality of life (QOL), organizations, and other topics.

No country was found to be free of MS, although the study did find wide variations in prevalence. The unequal distribution of MS diagnostic tools (e.g., MRI scanners) is likely to result in under-diagnosis of MS in many low-income countries.

Estimated prevalence rates in most countries were based on national or local studies reported in the scientific literature. National or regional MS registries were found in only a few countries. As a result, the data regarding nationwide prevalence of MS represent estimates and were not calculated using strict epidemiological research methods.

A study by Pugliatti and colleagues (2006) on European MS epidemiology found broadly similar results as those reported in the MS Atlas, although the estimates differ for some countries. They conducted a literature review of studies published over the past three decades on the epidemiology of MS in Europe. They found an overall estimated prevalence rate of MS in Europe of 83 per 100,000, with higher rates in northern countries. They reviewed studies from 33 countries, with a wide range in prevalence rates from lows of 36 to 39 per 100,000 in Spain to highs of 116, 135, 165, 153, and 186 in Denmark, Ireland, Norway, Sweden, and the United Kingdom, respectively.

Pugliatti and colleagues concluded that comparing MS prevalence rates in Europe is challenging because of four factors: (1) variability of the surveyed populations in size, age structure, and ethnicity; (2) variations in the capability of studies to detect benign or early cases; (3) the variation in case finding based on the geographic and time setting, access to medical care, (especially neurologists), availability of newer diagnostic procedures, and public awareness of MS; and (4) the impact of different MS diagnostic criteria used and inter-observer variability when comparing prevalence rates between studies. They found that mean MS prevalence rates tended to be higher in countries where the degree of disease investigation is higher, where better survey methodologies are used, and where assessments have been repeatedly conducted over time, often based on nationwide surveys or registry systems.

General patterns of MS prevalence include variations by geography and ethnicity (WHO and MSIF, 2008). A number of studies have found lower rates in countries located closer to the equator and higher rates in northern and southern latitudes.

Lower prevalence rates have been found in nonwhite populations. For example, a study by Itoh and colleagues (2003) found a prevalence rate of 10 per 100,000 in the city of Asahikawa in northern Japan. The authors also cited a study in Hong Kong conducted at about the same time that found an MS prevalence rate of just 1 per 100,000. Both of those studies are broadly consistent with the MS Atlas, which listed Japan in the prevalence range of 5 to 20 and China in the prevalence range of 0 to 5 (WHO and MSIS, 2008).

In sum, these studies indicate that MS prevalence estimates vary depending on data from local studies and the methodologies used. Revised estimates or sensitivity testing may be appropriate for some countries where more recent epidemiological studies have become available or for larger countries where regional variation may be significant and regional prevalence estimates and economic burden estimates may be desired.

4. TOTAL COSTS

Total costs of MS varied substantially across countries for which studies have been conducted but are substantial in all countries. We compared costs across countries using the most recent published (if available; unpublished if not) study for each country that provided cost estimates for all three categories of MS costs that we reviewed (direct medical, direct nonmedical, and indirect costs). As shown in Table 2, for the 15 countries for which we have complete estimates, total average cost per person with MS in 2007 varied from a low of 16,400 U.S. international dollars in France to a high of 54,500 U.S. international dollars in Norway and Sweden, for an overall prevalence-weighted average of 41,000 U.S. international dollars (2007) using the MS Atlas. For this table, we used published estimates of per person MS costs for 15 different countries and converted the cost estimates in the literature to 2007 U.S. international dollars using Purchasing Power Parity Conversion Factors from the World Bank's World Development Indicators. We then inflated estimates to 2007 dollars using the price indices from the Organisation for Economic Co-operation and Development (OECD) for all OECD countries except those with high inflation. Estimates of the direct medical, direct nonmedical, and indirect costs of MS for the 15 countries are also shown.

Estimated costs varied because of the availability and costs of medical care, the use of paid and unpaid home and community-based services, and the extent to which people withdraw from the labor force and the resultant loss of income. Estimates also reflect differences in study methodologies and the specific categories of costs included across countries.

Total Costs of MS by Reference Country

In Table 2 below, although MS cost estimates from each study have been updated to a common currency and year, because of differences across studies in the time period for analysis and the methodologies used, cross-country comparisons of MS costs are not recommended. Differences in MS costs across countries are driven by differences in the categories of costs included in each study, differences in the typical care provided to MS patients during the time period of analysis, and differences in cost analysis approaches, in addition to underlying differences in the costs of MS treatment and management. For example, because the most recent published studies for Canada and France used patient data from 1995, treatment costs from those studies do not reflect patterns of treatment that have been adopted and in wide use after the late 1990s. Australian estimates use data as reported in Taylor (2007), but because that study did not include informal care costs and included only early retirement costs for those who had retired during the study year, Access Economics (2005) estimates of informal caregiving costs and indirect costs are also used to estimate annual MS costs for Australia.

Table 2 Total Costs of MS by Reference Country

Country	Total Direct Medical Cost (2007 Int'l Dollars)	Total Direct Non-Medical Cost (2007 Int'l Dollars)	Total Indirect Costs (2007 Int'l Dollars)	Total Cost (2007 Int'l Dollars)
Australia	\$18,809	\$16,167	\$6,890	\$41,866
Austria	\$20,738	\$10,010	\$17,569	\$48,317
Belgium	\$13,746	\$10,108	\$13,267	\$37,121
Canada	\$3,162	\$2,421	\$15,932	\$21,514
France	\$6,078	\$4,718	\$5,582	\$16,378
Germany	\$20,246	\$6,986	\$19,946	\$47,178
Italy	\$13,001	\$19,225	\$13,237	\$45,462
Netherlands	\$9,845	\$8,910	\$15,849	\$34,605
Norway	\$10,995	\$12,472	\$31,023	\$54,489
Poland	\$3,495	\$2,713	\$11,423	\$17,631
Spain	\$15,973	\$16,498	\$11,544	\$44,015
Sweden	\$15,431	\$21,607	\$17,427	\$54,465
Switzerland	\$10,211	\$13,365	\$14,473	\$38,048
United Kingdom	\$10,969	\$19,858	\$17,995	\$48,822
United States	\$23,975	\$7,844	\$18,888	\$50,707
Weighted average ^a	\$13,198	\$11,383	\$16,755	\$41,335

^a Weighted by prevalence of MS in each country.

Sources: Access Economics, 2005; Berg et al., 2006; Canadian Burden of Illness Study Group, 1998a; Kobelt et al., 2004a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006h, 2006i, 2006j; Murphy et al., 1998a; Orlewska et al., 2005; Svendsen et al., 2008 (unpublished); Taylor et al., 2007.

Tables 3 and 4 show additional categories of MS costs for the 15 countries with published cost estimates. The 6 cost categories shown in the table - early retirement, informal care, disease-modifying drugs (DMDs), professional home care, hospitalizations, and other prescriptions - combined represent more than 75 percent of the total cost of MS across the 15 countries. Costs vary considerably across countries within these categories, reflecting both differences in management and treatment of MS across countries and differences in study methodologies, data, and data collection time periods across studies. For example, informal care estimates range from \$0 in Canada, reflecting the exclusion of informal care costs from the analysis, to almost \$17,000 per person in Italy. Similarly, differences across countries in DMD costs reflect differences in utilization across countries, in study populations included in analyses, and in data collection time periods (where earlier studies have low DMD costs because they were conducted prior to widespread use of disease-modifying drugs). Table 3 provides estimates in 2007 U.S. international dollars, and Table 4 uses a currency conversion rate of 1 U.S. dollar to 0.7385 Euros to calculate annual MS costs in Euros.

Table 3. Annual Costs of Multiple Sclerosis for 15 Reference Countries, 2007 U.S. International Dollars

	Early Retirement	Informal Care	DMDs	Professional Home Care	Hospitalizations	Other Prescriptions	All other Costs	Total Costs
Australia	\$5,681	\$11,448	\$7,501	\$930	\$1,452	\$298	\$14,556	\$41,866
Austria	\$17,139	\$7,192	\$5,942	\$1,623	\$2,546	\$2,509	\$11,366	\$48,317
Belgium	\$11,285	\$7,125	\$6,647	\$1,650	\$2,154	\$582	\$7,678	\$37,121
Canada	\$3,364	--	--	\$1,211	\$581	\$691	\$15,666	\$21,514
France	\$5,123	\$3,454	\$2,742	\$663	\$682	\$428	\$3,286	\$16,378
Germany	\$17,058	\$5,198	\$10,883	\$527	\$2,411	\$1,156	\$9,945	\$47,178
Italy	\$12,714	\$16,650	\$5,527	\$1,737	\$1,221	\$1,301	\$6,313	\$45,462
Netherlands	\$15,106	\$4,149	\$4,949	\$3,187	\$654	\$570	\$5,988	\$34,605
Norway	\$26,896	\$4,297	\$3,278	\$4,574	\$1,130	\$499	\$13,814	\$54,489
Poland	\$10,483	\$1,986	\$1,577	\$381	\$392	\$246	\$2,566	\$17,631
Spain	\$10,392	\$13,186	\$8,320	\$1,434	\$1,468	\$428	\$8,787	\$44,015
Sweden	\$14,622	\$5,022	\$5,749	\$15,276	\$1,029	\$720	\$12,046	\$54,465
Switzerland	\$13,982	\$5,477	\$4,879	\$5,674	\$302	\$717	\$7,017	\$38,048
United Kingdom	\$17,590	\$15,299	\$2,810	\$2,722	\$673	\$928	\$8,800	\$48,822
United States	\$14,704	\$4,957	\$17,244	\$883	\$1,000	\$2,639	\$9,281	\$50,707

Costs have been converted from original currencies and years to 2007 U.S. international dollars using purchasing power parity conversion factors from the World Bank's World Development Indicators and inflating to 2007 U.S. international dollars using the total OECD price indices, excluding high inflation countries.

Costs for Canada, France, and Poland were calculated by taking a weighted average of severity specific costs: 0.53 Mild; 0.3 Moderate; 0.17 Severe

Note: Although MS cost estimates from each study have been updated to a common currency and year, because of differences across studies in the time period for analysis and the methodologies used, cross-country comparisons of MS costs are not recommended. Differences in MS costs across countries are driven by differences in the categories of costs included in each study, differences in the typical care provided to MS patients during the time period of analysis, and differences in cost analysis approaches, in addition to underlying differences in the costs of MS treatment and management. For example, because the most recent published studies for Canada and France used patient data from 1995, treatment costs from those studies do not reflect patterns of treatment that have been adopted and in wide use after the late 1990s.

Sources: Access Economics, 2005; Berg et al., 2006; Canadian Burden of Illness Study Group, 1998a; Kobelt et al., 2004a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006h, 2006i, 2006j; Murphy et al., 1998a; Orlewska et al., 2005; Svendsen et al., 2008 (unpublished); Taylor et al., 2007.

Table 4. Annual Costs of Multiple Sclerosis for 15 Reference Countries, 2007 Euros*

	Early Retirement	Informal Care	DMDs	Professional Home Care	Hospitalisations	Other Prescriptions	All Other Costs	Total Costs
Australia	€ 4,453	€ 8,972	€ 5,879	€ 729	€ 1,138	€ 233	€ 11,408	€ 32,812
Austria	€ 13,433	€ 5,637	€ 4,657	€ 1,272	€ 1,995	€ 1,966	€ 8,908	€ 37,869
Belgium	€ 8,844	€ 5,584	€ 5,210	€ 1,293	€ 1,688	€ 456	€ 6,018	€ 29,094
Canada	€ 2,637	--	--	€ 949	€ 456	€ 541	€ 12,279	€ 16,862
France	€ 4,015	€ 2,707	€ 2,149	€ 520	€ 534	€ 335	€ 2,576	€ 12,836
Germany	€ 13,369	€ 4,074	€ 8,530	€ 413	€ 1,890	€ 906	€ 7,795	€ 36,976
Italy	€ 9,965	€ 13,049	€ 4,331	€ 1,361	€ 957	€ 1,020	€ 4,948	€ 35,631
Netherlands	€ 11,840	€ 3,252	€ 3,879	€ 2,498	€ 513	€ 447	€ 4,693	€ 27,121
Norway	€ 21,080	€ 3,368	€ 2,569	€ 3,585	€ 886	€ 391	€ 10,827	€ 42,706
Poland	€ 8,216	€ 1,557	€ 1,236	€ 299	€ 307	€ 193	€ 2,011	€ 13,818
Spain	€ 8,145	€ 10,335	€ 6,521	€ 1,124	€ 1,151	€ 335	€ 6,887	€ 34,497
Sweden	€ 11,460	€ 3,936	€ 4,506	€ 11,973	€ 807	€ 565	€ 9,441	€ 42,687
Switzerland	€ 10,959	€ 4,292	€ 3,824	€ 4,447	€ 237	€ 562	€ 5,499	€ 29,820
United Kingdom	€ 13,786	€ 11,991	€ 2,203	€ 2,133	€ 528	€ 727	€ 6,897	€ 38,265
United States	€ 11,524	€ 3,885	€ 13,515	€ 692	€ 784	€ 2,068	€ 7,274	€ 39,742

Costs for Canada, France, and Poland were calculated by taking a weighted average of severity specific costs using weights of 0.53 for mild, 0.3 for moderate, and 0.17 for severe MS.

* Converted from 2007 U.S. international dollars using the currency conversion exchange rate of 1 U.S. dollar to 0.7838 Euros.

Note: Although MS cost estimates from each study have been updated to a common currency and year, because of differences across studies in the time period for analysis and the methodologies used, cross-country comparisons of MS costs are not recommended. Differences in MS costs across countries are driven by differences in the categories of costs included in each study, differences in the typical care provided to MS patients during the time period of analysis, and differences in cost analysis approaches, in addition to underlying differences in the costs of MS treatment and management. For example, because the most recent published studies for Canada and France used patient data from 1995, treatment costs from those studies do not reflect patterns of treatment that have been adopted and in wide use after the late 1990s.

Sources: Access Economics, 2005; Berg et al., 2006; Canadian Burden of Illness Study Group, 1998a; Kobelt et al., 2004a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006h, 2006i, 2006j; Murphy et al., 1998a; Orlewska et al., 2005; Svendsen et al., 2008 (unpublished); Taylor et al., 2007.

In addition to the studies that involved primary data collection, one study used estimates from the nine European MS cost studies conducted by Kobelt and colleagues to estimate costs for 19 other European nations (Sobocki et al., 2007). This study estimated per person direct costs in each country by adjusting for differences in health care spending, gross domestic product, and wages between the estimation country and the nine original European countries. Using this ratio approach, they estimated 2005 per person direct costs (medical and nonmedical) of MS ranging from less than €10,000 (2005) in Estonia to more than €30,000 in Sweden. Table 5 shows direct costs from the Sobocki and colleagues (2007) study for the total MS population in each country.

Table 5. Estimated Costs of MS for European Countries (2005 Euros in millions)

	Healthcare cost	Non-medical cost	Informal care	Indirect costs	Total cost
Austria*	178	19	76	48	321
Belgium*	164	24	67	57	311
Cyprus	5	1	2	2	10
Czech rep	122	24	49	40	235
Denmark	89	32	60	51	232
Estonia	5	1	1	1	8
Finland	112	30	55	47	244
France	811	166	231	204	1413
Germany*	1818	104	757	302	2980
Greece	57	15	27	22	121
Hungary	105	16	21	17	159
Iceland	5	2	3	3	12
Ireland	35	13	24	20	91
Italy*	855	118	397	761	2130
Latvia	11	2	2	2	16
Lithuania	11	2	2	2	17
Luxembourg	7	2	4	3	17
Malta	0	0	0	0	1
Netherlands*	165	52	113	46	377
Norway	73	27	40	35	176
Poland	184	33	92	77	385
Portugal	89	17	26	22	155
Slovakia	42	7	12	10	71
Slovenia	25	5	4	3	38
Spain*	386	52	124	207	769
Sweden*	293	224	147	68	732
Switzerland*	134	70	83	48	335
United Kingdom*	1123	328	814	1102	3367
Total	6903	1386	3233	3201	14 722

*Countries with original data derived from the European cost of illness study [3].

Source: Sobocki et al., 2007. Estimation of the cost of MS in Europe: Extrapolations from a multinational cost study.

5. DIRECT COSTS

Direct costs of a disease represent the value of all resources consumed to diagnose, treat, or accommodate people with the condition (Gold et al., 1996). A wide variety of multiple sclerosis (MS)-related direct costs are reported in the literature. Examples include the costs of neurologist visits, the costs of installing wheelchair ramps at home, and the value of caregiving provided by family or friends.

In this chapter, we summarize findings from the literature on the per person direct annual costs of MS (i.e., prevalence-based study findings). Our review considered two broad categories of direct costs—

direct medical and direct nonmedical costs—a categorization typically used in cost-of-illness and cost-effectiveness studies (Haddix, Teutsch, and Corso, 2003).

Estimated direct costs vary considerably across studies because of differences in cost categories included, in the costing methodologies used, in patient characteristics, and in health care and social support systems in place in different countries. However, the direct costs of MS are large and tend to increase two- to threefold as disease severity increases from Expanded Disability Status Scale (EDSS) level 2.0 to levels 4.0 or 6.5.

Many of the studies disaggregated direct costs of MS by EDSS category (usually grouped into mild = EDSS score of 0–3.5; moderate = EDSS score of 4.0–6.5; or severe = EDSS score of 7.0–9.5). Some studies provided costs only for EDSS levels and did not provide estimates for a typical patient with MS (e.g., Murphy et al., 1998a).

Another recent analysis used data from a United Kingdom-based MS cost study (Orme et al., 2007) to estimate the relationship between EDSS level (0 through 9) and direct annual medical and nonmedical costs funded by the U.K. government and direct annual medical and nonmedical costs paid out of pocket (Tyas et al., 2007). Tyas and colleagues (2007) found higher costs associated with each higher EDSS level, except for out-of-pocket nonmedical costs.

Several articles reviewed or synthesized the literature on MS direct cost estimates (Duff and Mordin, 2002; Henriksson and Jonsson, 2000; Kobelt, 2004b; Kobelt et al., 2006k; Orlewska, 2006; Patwardhan et al., 2005; Miltenburger and Kobelt, 2002). Some of these articles describe the approaches needed to perform cost-effectiveness analyses of DMDs or other new therapies for MS and discuss the advantages and disadvantages of alternative MS cost estimates in the literature.

Other reviews have attempted to compare costs for specific EDSS levels across published analyses. Comparing the direct costs of MS across EDSS levels, Kobelt and colleagues (2006k) found that the average direct costs for patients at EDSS level 6.5 are two to three times the average direct costs of patients at EDSS level 2.0.

In Orlewska (2006), relative costs were calculated as the ratio of costs for each EDSS level relative to costs for EDSS level 2.0. For about two thirds of the studies, the lowest EDSS level was 2.0. Relative costs differ across countries. For example, in Germany and Sweden, direct relative costs for EDSS level 4.0 are almost 2.5 times costs for EDSS level 2.0, whereas in Canada, Italy, Poland, the United Kingdom, and the United States, direct relative costs for EDSS level 4.0 are between 1.1 and 1.8. Similarly, direct relative costs for EDSS levels 7.0 and 8.0 are almost 5 and 7 for Germany and Sweden, respectively, but closer to 2 or 3 for France, Italy, the United Kingdom, and the United States. At EDSS level 8.0, the direct relative cost is only 1.48 for Poland but 4.75 for Canada.

Patwardhan and colleagues (2005) calculated relative costs by comparing EDSS-specific costs to costs for the lowest EDSS level reported in the study. Direct costs for patients at the highest EDSS levels are generally 2.5 to 7 times the direct costs of patients at the lowest EDSS levels.

5.1 Direct Medical Costs

Direct medical costs include all costs related to patient encounters with the health care system. Using lists of direct medical costs from Haddix, Teutsch, and Corso (2003) and Luce and Eixhauser (1990), we created the following list of direct medical costs of MS to help guide our review of the MS costs literature:

- institutional inpatient care (e.g., hospitals, nursing homes, rehabilitation hospitals),
- institutional outpatient services (e.g., hospital clinics, emergency rooms),
- physician services,
- ancillary services (e.g., psychologists, social workers, physical therapists),
- medications (e.g., disease-modifying drugs [DMDs], other prescription drugs, over-the-counter [OTC] drugs),
- medical supplies (e.g., pharmaceutical supplies), and
- diagnostic testing.

For the 15 countries for which we have data, direct medical costs varied from a low of 3,200 U.S. international dollars (2007) in Canada to a high of 22,900 U.S. international dollars in the United States (2007), for an overall prevalence-weighted average of 13,100 U.S. international dollars (2007). For these studies, direct medical costs accounted for 14 to 69 percent of total costs. Differences in use of disease-modifying drugs account for much of this variation.

5.1.1 Original Studies

We reviewed 30 recent studies (published after 1997) that describe original analyses of the direct medical or nonmedical costs of MS. These studies provide cost estimates for 14 countries: Australia, Austria, Belgium, Canada, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden, Switzerland, the United States, and the United Kingdom. Nine of the studies were conducted as part of an effort led by Gisela Kobelt and colleagues to estimate the costs of MS in nine European countries using a standardized approach. Most of the studies used a bottom-up approach to estimate direct costs, meaning they collected data on resource utilization from a sample of patients and estimated medical costs for those patients. Three studies used a top-down approach to allocate national estimates of health care spending to MS. One article provided estimates only for pain as a result of MS in Canada (Piwko et al., 2007), while an Australian study provided estimates of out-of-pocket costs only (McCabe and De Judicibus, 2003). Many of the earlier studies took place before the widespread use of DMDs or specifically excluded DMD costs from direct medical cost calculations.

Table 6 summarizes findings from the 30 studies on MS direct costs. In the table, we show the specific categories of medical costs included in each study, the direct medical cost estimate reported in the paper, and the year of costs.

Table 6. Direct Medical Costs of MS—Summary of Published Studies

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Taylor et al., 2007	Australia	Australian dollars	2002	20,374	Hospitalizations, consultations, drugs (immunomodulating therapies, immunosuppressive drugs and other drugs), laboratory and radiological tests	Data collection only for a single hospital's MS patients; data provided by neurologist; estimates also provided by EDSS level
Access Economics, 2005 (unpublished)	Australia	Australian dollars	2005	8,475	Hospitalizations, specialist and primary care and allied health, nursing home care, pharmaceuticals, and other health care costs	Data primarily collected by a top-down approach using government data
McCabe and Judicibus, 2003	Australia	Australian dollars	2001	813, Male; 1,294, Female	Hospital stay, inpatient (IP) and outpatient rehabilitation, general practitioners, specialists, allied health professionals, complementary health providers, prescription drugs, tests, respite care, continence aids, and dietary supplements	Collected out-of-pocket spending to treat MS versus costs for people without MS; relatively small sample: 31 men and 82 women
Kobelt et al., 2006c	Austria	Euros	2005	17,302	Hospital stay, IP rehabilitation, nursing home, outpatient (OP) day care, neurologist, internist, urologist, ophthalmologist, GP/nurse, psychiatrist, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, homeopath), optician, tests and imaging, disease-modifying drugs (DMDs), other prescription drugs, and over-the-counter (OTC) drugs	Collected costs for MS vs. costs for patients without MS.

(continued)

Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Kobelt et al., 2006d	Belgium	Euros	2005	12,020	Hospital stay, IP rehabilitation, nursing home, OP day care, neurologists, internists/GPs, urologist, ophthalmologist, psychiatrist, nurse, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, homeopath), optician, tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs specifically to treat MS vs. all medical costs for patients with MS
Carton et al., 1998	Belgium	ECU	1996	For Stage II, living at home: 1,010; for stage III, living at home: 2,119; for stage IV, living at home: 2,029; for all stages, Special Neurological Institutes: 48,920; all stages, NH: 26,919	Hospitalizations, special neurological (SPN) institutes, nursing homes, general practitioners, specialists, nurses, physiotherapist, occupational therapist, speech therapist, drugs and pharmaceutical supplies	Resource and cost data collected using 4-week diary in addition to interviews to collect data on home modifications, etc., in past 5 years; estimates provided by disability grade (I, II, III, or IV) and by residence (home, sheltered housing, special neurological institute, or nursing home); nursing home care and SNI care added to costs for patients residing in those facilities.

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Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Canadian Burden of Illness Study Group, 1998	Canada	Canadian dollars	1995	2,250 mild (EDSS ≤ 2.5), 1,969 moderate (EDSS 3.0 – 6.0), and 7,233 severe (EDSS ≥ 6.5)	Hospitalization, physician consults, consults, lab tests, procedures, drugs, and other medical expenses	No patients included who were treated with interferon B. 62 patients in mild stage, 68 moderate, and 68 severe; does not include long-term care costs for institutionalized; used 3 months of data and annualized costs
Grima et al., 2000	Canada	Canadian dollars	1997	Direct medical costs for patients in remission: 1,255 for EDSS 1, 1,717 for EDSS 2, 2,825 for EDSS 3, 2,377 for EDSS 4, 5,027 for EDSS 5, 8,691 for EDSS 6; additional cost of relapse (above remission costs): 1,141 for EDSS 1, 805 for EDSS 2, 1197 for EDSS 3, 329 for EDSS 4, 220 for EDSS 5, 1,112 for EDSS 6	Hospitalizations, outpatient resources, emergency room visits, physician assessments, optometrist, social worker, psychologist, massage therapist, naturopath, and home-based nursing or other care, laboratory tests, diagnostic imaging, dietician, occupational therapist, physiotherapist, home help, alternative therapies, home meal services, urinary catheters, prescription and OTC medications	Costs estimated by relapse status (remission or current relapse) and by EDSS (1–6); study conducted prior to common use of DMDs; small sample size for patients in relapse (42) especially by EDSS; note that some of the costs captured as direct medical costs could also be viewed as nonmedical costs (e.g., home help, home meal services), but are not shown separately in the paper

(continued)

Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Asche et al., 1997	Canada	Canadian dollars	1994	6,294	Hospitalizations, other institutions, physician consultations, other health care specialists, prescription drugs, and other health-related expenditures	Used top-down approach and estimated aggregate costs of MS in Canada as \$181,568,937; assuming 28,846 people with MS in Canada (1996 population of 28,846,761 and MS prevalence of 100 per 100,000); estimates of per-person costs by review authors
Murphy et al., 1998a	France, Germany, and UK	U.S. dollars	1996	Total societal costs. France: mild = 5,784; moderate = 11,823; severe = 17,034; control = 1,008 Germany: mild = 8,316; moderate = 6,168; severe = 17,103; control = 3,111 UK: mild = 15,375; moderate = 20,253; severe = 43,866; control = 9,303	Hospital inpatient, consultations, paramedical services, medication, lab/diagnostic tests, medical equipment and supplies; "nonmedical" costs captured value of workdays lost, time lost, transport, community assistance (home help, meals on wheels), informal care, and home modifications	Total costs (direct and indirect) provided by country, by perspective (health insurance or societal), and by EDSS grouping; figure 1 shows direct medical costs only, but the values are not provided in tables; totals here are for direct medical, nonmedical, and indirect costs; largely before use of DMDs.
Kobelt et al., 2001	Germany	DM	1999	15,911	Inpatient hospital inpatient, long-term care, outpatient hospital stays, general practitioner, neurologist, other specialist, nurses/physiotherapists, other; prescription and OTC drugs	Percentage of patients using interferons and glatiramer was adjusted downward to reflect use in Germany and does not reflect the sample.

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Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Kobelt et al., 2006e	Germany	Euros	2005	17,165	Hospital stay, inpatient rehabilitation, nursing home, OP day care, neurologist, internist, urologist, ophthalmologist, GP/nurse, psychiatrist, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, homeopath), optician, tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs specifically to treat MS vs. all medical costs for patients with MS
Kobelt et al., 2006f	Italy	Euros	2005	11,111	Hospital stay, inpatient rehabilitation, nursing home, outpatient day care, neurologist, internist, urologist, ophthalmologist, GP/Nurse, psychiatrist, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, homeopath), optician, tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs specifically to treat MS vs. all medical costs for patients with MS
Amato et al., 2002	Italy	ITL	1996	6,052,000	Hospitalizations, GP visits, nurse interventions, specialist visits, lab tests and other diagnostics, physical therapy, and drug therapies	Estimates reported for 3-month period; adjusted to annual costs by multiplying by 4; study time frame prior to use of DMDs; estimates provided by EDSS (5 levels)

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Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Kobelt et al., 2006 ⁱ	The Netherlands	Euros	2005	8,371	Hospital stay, inpatient rehabilitation, nursing home, outpatient day care, neurologists, internists/GPs, urologist, ophthalmologist, psychiatrist, nurse, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, homeopath), optician, tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs specifically to treat MS vs. all medical costs for patients with MS
Svendsen, Nyhr, Nyland, and Aarseth, 2008	Norway	Euros	2002	14,597	DMDs and other drugs, physician (including specialists), nurse, psychologists, physiotherapists, incontinence advisors, speech therapists, social workers, opticians, chiropodists, acupuncturists, homeopaths, chiropractors, healers, some therapists, other professionals, hospital stays, nursing home stays, and rehabilitation center stays	Aggregate cost estimates provided; those were divided by the estimated number with MS in Norway, 6,750; study collected cost estimates through a survey and asked for costs specifically to treat MS; estimates in Euros in the paper were calculated using a currency conversion rate of 7.51 Norwegian kroner to 1 Euro

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Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Orlewska et al., 2005	Poland	PLN	2002	Total direct costs (including nonmedical categories except informal care) is 9,766 for mild, 12,958 for moderate, and 14,424 for severe MS	Rehabilitation, hospitalization, physician and other health professional visits (ambulatory and long-term care), drugs, laboratory/diagnostic tests; also includes direct nonmedical costs: disability aids and house modifications, community assistance, payable home care, and transportation	Costs estimated over 5-month period; annual costs are reported costs * 2.4; utilization provided for each resource category, but total costs are shown only for the categories of direct cost, indirect cost, and total cost, where indirect cost captures productivity losses and the value of informal care
Kobelt et al., 2006g	Spain	Euros	2005	12,142	Hospital stay, IP rehabilitation, nursing home, OP Day care, neurologist, internist, urologist, ophthalmologist, GP/Nurse, psychiatrist, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, homeopath), optician, tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs specifically to treat MS vs. all medical costs for patients with MS

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Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Casado et al., 2006	Spain	Euros	2004	9,521	Hospitalization, GP visits, ambulance displacements, tests, rehabilitation, DMDs, and other prescription drugs	Costs reported as those as a result of MS and related diseases. Paper reports costs as a result of MS. Costs also provided by EDSS level
Berg et al., 2006	Sweden	Euros	2005	15,186	Hospital stay, inpatient rehabilitation, nursing home, outpatient day care, neurologists, internists/GPs, urologist, ophthalmologist, psychiatrist, nurse, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, homeopath), optician, tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs specifically to treat MS vs. all medical costs for patients with MS. Unit costs reported in Swedish kroner in Table 1
Henriksson et al., 2001	Sweden	Swedish kroner	1998	140,612	Hospitalization, inpatient rehabilitation, doctor visits, nurse visits, physiotherapist visits, DMDs, other prescription drugs, and OTC drugs	Bottom-up approach; collected data from patients of a hospital in Stockholm

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Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Henriksson and Jonsson, 1998	Sweden	Swedish kroner	1994 (and 1991 for comparison)	Aggregate costs (not per-person): 370 million (approximately 43,900 SEK per person)	Institutional care (hospital inpatient, long-term care), ambulatory care, and drugs	Used top-down approach; estimate of the number of MS patients in Sweden in 1994 is needed to estimate per-person annual costs. Prevalence is 96 per 100,000 and population estimated at 8,778,461 in 1994, resulting in estimated 8,427 people with MS. Conducted before use of DMDs
Kobelt et al., 2006h	Switzerland	Swiss francs	2005	17,404	Hospital stay, inpatient rehabilitation, nursing home, outpatient day care, neurologist, internist, urologist, ophthalmologist, GP/nurse, psychiatrist, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, homeopath), optician, gynecologist, ear nose and throat (ENT) specialist, tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs specifically to treat MS vs. all medical costs for patients with MS

(continued)

Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Stolp-Smith et al., 1998	U.S.	U.S. dollars	1993	1,072 mean inpatient charges (vs. 515 for controls); 2,427 mean outpatient charges (vs. 1,933 for controls)	Hospital inpatient and health care system outpatient charges (from billing records)	Used charges from billing records; costs by EDSS show no significant difference from costs for the non-MS controls. Median costs EDSS ≤ 4 and disease > 10yr 1,277 (inpatient + outpatient); median costs EDSS 4-7 and ≤ 4 and disease <10 yrs 1,250 (inpatient + outpatient); median costs EDSS ≥ 5,440; higher costs attributable to MS for the 23% with severe disability
Whetten-Goldstein et al., 1998	U.S.	U.S. dollars	1994	7,423	Hospital, nursing home, physician, other health professional, prescription drugs, and retraining (recorded here as occupational therapy)	Annual spending per person with MS shown; excess spending per person with MS (in excess of national means) was 5,079
Kobelt et al., 2006b and Kobelt et al., 2004a	U.S.	U.S. dollars	2004	22,313	Hospital stay, nursing home, OP admission, ER, neurologists, internists/GPs, cardiologist, neuropsychologist, urologist, ophthalmologist, psychiatrist, nurse, physical therapy, counselor/psychologist/social worker, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, massage therapist,), optician, other/unknown ambulatory care, tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs specifically to treat MS vs. all medical costs for patients with MS. Reports drug use by disease severity and total direct and drug costs by disease severity (mild, moderate, severe)

(continued)

Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Pope et al., 2002	U.S.	U.S. dollars	varies by insurance status (1995 for privately insured, 1997 for Medicare, and 1991-1996 for Medicaid)	7,677 (private insurance, 1995\$; vs. 2394 total population 18-64); 13,048 (Medicare excludes drugs, 1997\$; vs. 6,006 total Medicare); 11,331 (Medicaid disabled, 1991-1996\$; vs. 4713 non-MS beneficiary.)	Hospital inpatient and outpatient, physician services, prescription drugs (available for private insurance and Medicaid only), home health, durable medical equipment, and nursing facility (Medicare covers only short-term post-hospitalization skilled nursing facilities; Medicaid covers long-term stays)	Captures insured expenditures, which includes both insurer payments and enrollee cost sharing (e.g., deductible, copay)
Kobelt et al., 2006j	U.K.	Pounds	2005	6,810	Hospital stay, inpatient rehabilitation, nursing home, outpatient day care, GPs/specialists/nurses, physical therapy, counselor/psychologist, occupational therapy, speech therapy, alternative medicine (acupuncture, chiropractor, chiropodist, reflexologist), tests and imaging, DMDs, other prescription drugs, and OTC drugs	Collected costs for MS vs. costs for patients without MS

(continued)

Table 6. Direct Medical Costs of MS—Summary of Published Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
McCrone et al., 2008	UK	Pounds	2006–2007	4,328	Hospital inpatient (neurology, ICU, other), neurology outpatient, other outpatient, day hospital, nursing home, GP, physiotherapist, social worker, nurse (practice, district), speech therapist, home help, acupuncturist, homeopath, herbalist, aromatherapy, reflexologist, tests/investigations, medication	Data collected in 2005 for 2003–4 values, but inflated to 2006–7 values for paper; captured costs for MS and those not specifically for MS; medication costs only for DMDs and drugs to treat spasticity. Direct medical costs of 2,164 for 6 months; home help is included in direct medical cost estimates.

Note: Cross-country comparisons of MS costs are not recommended due to differences across studies in the time period for analysis and the methodologies used. Differences in MS costs across countries are driven by differences in the categories of costs included in each study, differences in the typical care provided to MS patients during the time period of analysis, and differences in cost analysis approaches, in addition to underlying differences in the costs of MS treatment and management. For example, because the most recent published studies for Canada and France used patient data from 1995, treatment costs from those studies do not reflect patterns of treatment that have been adopted and in wide use after the late 1990s.

All of the studies show that MS is associated with large direct medical costs. Yet, even after converting costs to a common currency and focusing on those studies that included similar categories of costs, the direct medical costs of MS vary a great deal across countries. For example, in the nine European countries examined by Kobelt and colleagues (2006k) using a standardized approach, direct costs varied from €8,835 in the Netherlands to €18,367 in Germany. Differences in the direct costs are driven by the levels of resource utilization and unit prices for a resource. Kobelt and colleagues (2006a) point out that DMD use is much lower in the United Kingdom (about 20% of the sample reported using DMDs) than in most of the other eight countries, where almost half of the sampled patients report DMD use. In addition, unit costs and utilization for direct medical services may differ across countries because of differences in health care systems. In countries where payments for hospital inpatient stays are based on diagnosis-related groups, hospitalizations and lengths of stay are lower than in countries where payments are made based on per diem rates (Kobelt et al., 2006a). The largest share of direct medical costs was for hospitalization.

Some studies focused on estimating direct medical utilization for a specific type of service. For example, Pucci and colleagues (2004) and Apel and colleagues (2006) estimated the utilization of alternative and complementary medicine for MS patients in Italy and Germany, respectively.

5.2 Direct Nonmedical Costs

Direct nonmedical costs include all nonmedical resources that are consumed to care for MS patients. Our literature review focused on the following categories of nonmedical direct costs of MS:

- paid nonmedical home care (e.g., personal care or help with activities of daily living),
- informal care provided by family and friends,
- MS adult day care,
- home or automobile modifications,
- mobility devices (e.g., wheelchairs, scooters),
- transportation services,
- job retraining, and
- other (e.g., childcare, housekeeping).

For the 15 countries for which we have complete cost data, direct nonmedical costs varied from a low of 2,400 U.S. international dollars (2007) in Canada to a high of 22,100 U.S. international dollars (2007) in Sweden, for an overall prevalence-weighted average of 11,200 U.S. international dollars (2007). For these studies, direct nonmedical costs accounted for 10 to 42 percent of total costs. The largest share of nonmedical costs of MS is for informal care. For example, informal care costs in the United States are 63 to 73 percent of total nonmedical costs. Differences in informal care costs across countries are sensitive to differences in the amount of paid home and community-based services provided by government and other sources. Informal care costs are also higher in countries with lower female labor force participation rates, such as in Spain and Italy.

5.2.1 Original Studies

We reviewed 26 recent studies that describe original analyses of the direct nonmedical costs of MS. These studies provide cost estimates for 14 countries: Australia, Austria, Belgium, Canada, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden, Switzerland, the United States, and the United Kingdom. Most of the studies that captured direct medical costs also estimated direct nonmedical costs, except Pope and colleagues (2002) and Stolp-Smith and colleagues (1998), which both used health insurance claims; and the two top-down costing studies (Asche et al., 1997; Henriksson and Jonsson, 1998). One study focused solely on estimating informal care costs (Carton et al., 2000).

Table 7 summarizes findings from the 26 studies on MS direct nonmedical costs. In the table, we show the specific categories of nonmedical costs included in each study, the direct nonmedical cost estimate reported in the paper, and the year of costs.

Table 7. Direct Nonmedical Costs of MS—Summary of Studies

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Taylor et al., 2007	Australia	Australian dollars	2002	5,215	Transportation, mobility aids, auto modifications, personal care assistance, home help, district nursing, and child care	Data collection only for a single hospital's MS patients; data provided by neurologist; estimates also provided by EDSS level
Access Economics (unpublished)	Australia	Australian dollars	2005	18,219	Informal care, aids and modifications, community-care services	Informal care is the overwhelming majority of direct non-medical costs. Calculated using replacement costs and data from the Australian MS Longitudinal Study
McCabe and Judicibus, 2003	Australia	Australian dollars	2001	2,551 males; 1,966 females	Travel costs, transportation, auto modifications, wheelchairs, beds, lifts, walking aids, home modifications, personal care assistance, nursing care at home, housework assistance, gardening, child care, home maintenance	Collected out of pocket spending to treat MS versus costs for people with MS; relatively small sample: 31 men and 82 women
Kobelt et al., 2006c	Austria	Euros	2005	8,351	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses, walking aids), home care (nurse visits and home help), transportation, and informal care	Informal care received by 58% of sample

(continued)

Table 7. Direct Nonmedical Costs of MS—Summary of Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Carton et al., 1998)	Belgium	ECU	1996	Stage I, living at home: 216; stage II, living at home: 868; stage III, living at home: 332	Social assistance (home care, ADL help and social workers) and annualized costs of home adaptations, automobile adaptations, mobility aids, prosthetics and devices	Resource and cost data collected using 4-week diary in addition to interviews to collect data on home modifications, etc., in past 5 years; estimates provided by disability grade (I, II, III, or IV) and by residence (home, sheltered housing, special neurological institute [SNI], or nursing home); no costs for nonmedical goods for SNI and nursing home patients social assistance includes social worker costs, a direct medical cost; collected data only on costs resulting from MS
Carton et al., 2000	Belgium	Euros	1996	Stage IV, living at home: 23,681	Informal care (unpaid caregiving)—direct patient assistance: mobility help, nursing care, personal care, surveillance	Minutes of direct patient assistance in 28 days (about 1 month) were from 113 patients for Stage I, 532 patients for stage II, 2882 patients for stage III, and 13,975 patients for stage IV; valued using replacement cost method; used minimum wage in the health care system of €7.8 for an unskilled laborer in 1996
Kobelt et al., 2006d	Belgium	Euros	2005	8,842	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses), home care (nurse visits and home help), transportation, and informal care	

(continued)

Table 7. Direct Nonmedical Costs of MS—Summary of Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Grima et al., 2000	Canada	Canadian dollars	1997	Patients in remission: 1701 for EDSS 1, 1366 for EDSS 2, 4554 for EDSS 3, 1501 for EDSS 4, 5914 for EDSS 5, and 3704 for EDSS 6; additional cost of relapse: 177 for EDSS 1, 383 for EDSS 2, 1462 for EDSS 3, 0 for EDSS 4, 318 for EDSS 5, 1809 for EDSS 6	Unpaid caregiver time (i.e., informal care)	Costs estimated by relapse status (remission or current relapse) and by EDSS (1–6); costs for relapse are incremental above remission patient costs; small sample size for patients in relapse (42) especially by EDSS; caregiver time valued using average weekly wage of 597 Canadian dollars
Canadian Burden of Illness Study Group, 1998	Canada	Canadian dollars	1995	912 mild, 1663 moderate, and 7787 severe	Nonmedical expenses, personal expenses, transportation (details not provided about what types of spending were coded as nonmedical or personal)	
Murphy et al., 1998a	France	U.S. dollars	1996	Total societal costs. France: mild = 5784; moderate = 11,823; severe = 17,034; control = 1008;	Hospital inpatient, consultations, paramedical services, medication, lab/diagnostic tests, medical equipment and supplies; “nonmedical” costs captured value of workdays lost, time lost, transport, community assistance (home help, meals on wheels), informal care and home modifications	Total costs (direct and indirect) provided by country, by perspective (health insurance or societal), and by EDSS grouping; Figure 1 shows direct medical costs only, but the values are not provided in tables; totals here are for direct medical, nonmedical, and indirect costs

(continued)

Table 7. Direct Nonmedical Costs of MS—Summary of Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Murphy et al., 1998a	Germany	U.S. Dollars	1996 (?)	Germany: mild = 8316; moderate = 6168; severe = 17,103; control = 3111;		
Murphy et al., 1998a	UK	U.S. Dollars	1996 (?)	UK: mild = 15,375; moderate = 20,253; severe = 43,866; control = 9303		
Kobelt et al., 2006e	Germany	Euros	2005	5,922	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses, walking aids), home care (nurse visits and home help), transportation, and informal care	Informal care received by 48% of sample
Kobelt et al., 2001)	Germany	DM	1999	21,780	Home care, home help, and other services; adaptations or investments to kitchen, bathroom, other part of house, car; stair lift, walking aids, wheelchair, spectacles, other; informal care	60% received care from family or friends—average of 27 hours per week

(continued)

Table 7. Direct Nonmedical Costs of MS—Summary of Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Amato et al., 2002	Italy	Lire	1996?	15,244	Disability aids (e.g., wheelchairs, home adaptations), travel expenses, and informal care	Estimates reported for 3-month period; adjusted to annual costs by multiplying by 4; note that informal care uses replacement cost approach
Kobelt et al., 2006f	Italy	Euros	2005	16,424	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses, walking aids), home care (nurse visits and home help), transportation, and informal care	Informal care received by 56% of sample
Svendsen, Nyhr, Nyland, and Aarseth, 2008	Norway	Euros	2002	10,794	Home and auto modifications, job adaptations, assistive devices (e.g., wheelchairs, special furniture, walking sticks, special writing devices), home care (nurse visits, home care, personal assistant, domestic help, etc.), and informal care valued according to time used by caregiver or work loss for caregiver	Aggregate cost estimates provided; those were divided by the estimated number with MS in Norway, 6,750; study collected cost estimates through a survey and asked for costs specifically to treat MS; estimates in Euros in the paper were calculated using a currency conversion rate of 7.51 Norwegian kroner to 1 Euro

(continued)

Table 7. Direct Nonmedical Costs of MS—Summary of Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Orlewska et al., 2005	Poland	PLN	2002	Total direct costs (including nonmedical categories except informal care) is 9766 for mild, 12,958 for moderate, and 14,424 for severe MS; total indirect costs (including productivity losses and informal care) is 16,526 for mild, 24,490 for moderate, and 29,890 for severe	Direct nonmedical costs: disability aids and house modifications, community assistance and payable home care, and transportation; also includes direct medical costs; indirect costs include productivity losses and informal care	Bottom-up approach with prospective data collection; costs of informal care treated as indirect cost; costs are for 5-month period; we show reported costs times 2.4
Kobelt et al., 2006g	Spain	Euros	2005	12,540	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses, walking aids), home care (nurse visits and home help), transportation, and informal care	Informal care received by 53% of sample
Casado et al., 2006	Spain	Euros	2004	6071	Taxi displacements, home adaptations, car adaptations, workplace adaptations, and informal care	Costs reported as those as a result of MS. Costs also provided by EDSS level
Berg et al., 2006	Sweden	Euros	2005	21,264	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses, cooling vest, recreational aid), home care (nurse visits, home help, and personal assistants), transportation, and informal care	

(continued)

Table 7. Direct Nonmedical Costs of MS—Summary of Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Henriksson et al., 2001	Sweden	Swedish kroner	1998	156,287	Services (personal assistant, home help, home care, child care, transportation), home and auto adaptations, mobility aids, and informal care	Bottom-up approach; collected data from patients of a hospital in Stockholm
Kobelt et al., 2006h	Switzerland	Swiss francs	2005	22,780	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses, walking aids), home care (nurse visits and home help), transportation, and informal care	Informal care received by 48% of sample
Kobelt et al., 2006i	The Netherlands	Euros	2005	7,576	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses), home care (nurse visits and home help), transportation, and informal care	
Kobelt et al., 2006b (122) and Kobelt et al., 2004a	U.S.	Dollars	2004	7,321	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses), home care (nurse visits and home help), day care, child care, meals on wheels, and informal care	

(continued)

Table 7. Direct Nonmedical Costs of MS—Summary of Studies (continued)

Source (#)	Country	Currency	Year	Total Annual Per Patient Cost	Cost Captures	Notes
Whetten-Goldstein et al., 1998	U.S.	U.S. dollars	1994	8,799	Personal health services: formal care, domestic help, and informal (unpaid) care; equipment, including home alterations (e.g., ramps, lifts, grab bars, widening doors); vehicle alterations (e.g., hand controls, one vehicle purchase); and other equipment (e.g., special bed, wheelchair, exercise equipment)	Total expenditures for people with MS of \$7,699 are shown, plus the estimated \$1,100 per person per year cost of equipment; excess expenditures on nonmedical services (i.e., excluding equipment) calculated as \$6,759
McCrone et al., 2008	UK	Pounds	2006-7	12,482	Informal care provided by friends and family and aids and adaptations	Informal care received by 76% of sample; mean of 19.8 hours per week; valued at 14 pounds per hour; estimate does not include home help of 183 per patient per 6-month period
Kobelt et al., 2006j	UK	Pounds	2005	12,298	Investments in home and auto modifications, assistive devices (e.g., wheelchairs, glasses), home care (nurse visits and home help), transportation, and informal care	

Note: Cross-country comparisons of MS costs are not recommended due to differences across studies in the time period for analysis and the methodologies used. Differences in MS costs across countries are driven by differences in the categories of costs included in each study, differences in the typical care provided to MS patients during the time period of analysis, and differences in cost analysis approaches, in addition to underlying differences in the costs of MS treatment and management. For example, because the most recent published studies for Canada and France used patient data from 1995, treatment costs from those studies do not reflect patterns of treatment that have been adopted and in wide use after the late 1990s.

5.2.2 Summary of Findings

The largest share of nonmedical costs of MS is for informal care. For example, informal care costs in the United States are 63 to 73 percent of total nonmedical costs (Kobelt et al., 2004a; Kobelt et al., 2006b; Whetten-Goldstein et al., 1998). Differences in informal care costs across countries are likely driven by differences in the amount of paid home and community-based services provided by government and other sources. For example, in Sweden, generous formal support is provided, and informal care costs are a much smaller share of total costs than in countries with less extensive government support for in-home personal assistance (Kobelt et al., 2006a). Informal care costs are also higher in countries with lower female labor force participation rates, such as in Spain and Italy (Kobelt et al., 2006f; Kobelt et al., 2006g). Informal care costs may be considerably higher for women MS patients who use informal care than for men (Grimaud, 2005).

Most studies used a replacement cost method to value informal care, meaning they applied the hourly wage rate for those who provide home care or personal assistance to the time spent by family members providing care for the person with MS. The nine European studies used a disposable income approach, where the value assigned to home care was net income after social contributions and income tax.

The cost of investments in home and auto modifications and mobility aids averaged about 1,000 Euros (2005) per person per year across the nine Kobelt studies. Additionally, other than in Sweden, per person costs for home help and personal assistance was close to 2,000 Euros (2005) per year.

Costs for nonmedical costs other than informal care do not appear to increase as much with increasing levels of disability as do medical costs. For example, Tyas and colleagues (2007) found little difference in the estimated nonmedical out-of-pocket costs attributable to EDSS level 7 (€1,498) as compared to costs for EDSS level 2 (€1,035).

6. INDIRECT COSTS

6.1 Work Loss

People with MS often have difficulty continuing to work in the same ways as people without MS, because of the disabilities, fatigue, cognitive impairments, transportation difficulties, speech impairments, and other aspects of the disease. A substantial body of research documents the adverse impact of MS on labor force participation. These costs include short- and long-term absence from work, reduced hours of work, changing the type of work to a less physically challenging and stressful nature (usually at lower pay), and early retirement. Although these costs vary by disability level, these factors result in reduced productivity and substantial income loss for MS patients. For the 15 countries for which we have complete cost data, indirect costs, mostly work loss, varied from a low of 3,600 U.S. international dollars (2007) in Australia to a high of 31,000 U.S. international dollars (2007) in Norway, for an overall prevalence-weighted average of 16,800 U.S. international dollars (2007). For these studies, indirect costs accounted for 13 to 76 percent of total MS costs.

In addition to work loss by people with MS, there is additional work loss by informal caregivers, mainly family members. Much less is known about the extent of this work loss and these costs have not been incorporated into existing estimates of the cost of MS.

6.1.1 Studies of Labor Participation by MS Patients

We identified a total of 24 original studies, one synthesis article, and one systematic review that contained quantitative data on labor force participation by MS patients. A total of 10 original studies and one synthesis article were conducted by Kobelt and colleagues; 12 original studies and one systematic review were conducted by other investigators. Because the Kobelt and colleagues studies used the same methodology and generally report on the variables, we have grouped these studies separately from the other studies. The relatively uniform methodology is a great strength of this series, as is the actual estimation of costs attributable to the reduction in labor force participation. On the other hand, the survey response rates for most of the countries are low, raising issues about the representativeness of the sample. Table 8 presents general background information on the Kobelt and colleagues studies, and Table 9 provides general background on the other studies that address labor force participation. All together, these studies were conducted in 13 countries: Australia, Austria, Belgium, Canada, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, the United Kingdom, and the United States.

Table 8. Kobelt and Colleagues Studies That Address Labor Force Participation of People with Multiple Sclerosis

Geographic Area	Citation	Sample Size	Sample Description
Europe (Austria, Belgium, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom)	Kobelt, Berg, Lindgren, Fredrikson, and Jonsson (2006a)	13,186 patients and varied by country from 799 (Belgium) to 2048 (UK) Response rate varied from 19% to 52%	Sample was developed from neurology clinics and national multiple sclerosis societies
Austria	Kobelt, Berg, Lindgren, Baumhackl, and Berger (2006c)	1,019 respondents, with a 35% response rate	Patients recruited from national multiple sclerosis society

(continued)

Table 8. Kobelt and Colleagues Studies That Address Labor Force Participation of People with Multiple Sclerosis

Geographic Area	Citation	Sample Size	Sample Description
Belgium	Kobelt, Berg, Lindgren, Decoo, Guillaume, Neymark, Sindic and Vandegaer (2006d)	799 respondents with a 38% response rate	Patients recruited from specialized neurology clinics
Germany	Kobelt, Berg, Lindgren, Berger, Elias, Flachenecker, Freidel, Konig, N., Limmroth, and Straube (2006e)	2,793 respondents with 35% response rate	Patients recruited from clinics specializing in MS care
Italy	Kobelt, Berg, Lindgren, Battaglia, Lucioni, and Uccelli (2006f)	921 respondents, with 31% response rate	Patients recruited from the national multiple sclerosis society
The Netherlands	Kobelt, Berg, Lindgren, Anten, Ekman, Jongen, Polman, and Uitdenhaag (2006i)	1,549 respondents with a response rate of 52%	Patients recruited from three centers specializing in MS care
Spain	Kobelt, Berg, Lindgren, Izquierdo, and Sanchez-Solino (2006g)	1,848 respondents, with a 32% response rate	Patients recruited from the national multiple sclerosis society
Sweden	Berg, Lindgren, Fredrikson, and Kobelt (2006)	1,339 respondents, with a 75% response rate	Patients recruited from the national multiple sclerosis society
Switzerland	Kobelt, Berg, Lindgren, and Gerfin (2006h)	1,101 respondents, with 45% response rate	Patients were recruited from the national multiple sclerosis society
United Kingdom	Kobelt, Berg, Lindgren, Kerrigan, Russell, and Nixon (2006j)	2,947 respondents with a 19% response rate	Patients recruited from the national multiple sclerosis society
United States	Kobelt, Berg, Atherly, and Hadjimichael (2006b)	1,909 respondents, with 50% response rate	Patients recruited from the North American Committee on Multiple Sclerosis Patient Registry

Table 9. Additional Studies of Labor Force Participation

Country	Citation	Sample Size	Sample Description
Systematic literature review	Pompeii, Moon, and McCrory (2005)	NA	Articles in English of predictors of ability to work among MS patients
Tasmania, Australia	Taylor, McDonald, Fantino, Sedal, MacDonald, Pittas, and Groom (2007)	100 persons with MS	Patients recruited from one hospital
Victoria, Australia	McCabe and De Judicibus (2006)	113 persons with MS	Patients were members of the regional MS society
Australia	Access Economics (2005) (unpublished)	Not available	Australian MS Longitudinal Survey and other published parameters
Alberta, Canada	Busche, Fiske, Murray, and Metz (2003)	96 persons with MS	Patients who attended the Calgary MS Clinic, which is the only source of MS care in region
Canada	Grima, Torrance, Francis, Rice, Rosner, and Lafortune (2000)	153 persons with MS	Two groups of patients—patients in remission and patients experiencing a relapse—being served at two MS clinics
Germany	Flachenecker, Stuke, Elias, Freidel, Haas, Pitschnau-Michel, Schimrgk, Zettl, and Rieckmann (2008)	3,223 persons with MS	Persons were listed in a nationwide multiple sclerosis registry, established under the auspices of the German MS Society
Italy	Amato, Battaglia, Caputo, Fattore, Gerzeli, Pitaro, Reggio, Trojano, for the Mu. S. I. C. Study Group (2002)	552 persons with MS	Patients recruited from 40 MS centers
Norway	Svendsen, Myhr, Nyland, and Aarseth (2008)	423 persons with MS	Patients recruited in collaboration with the local MS society in Hordaland County
Poland	Orlewska, Mierzejewski, Zaborski, Kruszewska, Wicha, Fryze, Drosdowski, Skibicka, Mirowska-Guzel, Czlonkowski, and Czlonkowska (2006)	148 persons with MS	Patients recruited at three MS centers in Warsaw, Bialystok, and Gdansk
Catalonia, Spain	Casado, Martinez-Yelamos, Martinez-Yelamos, Carmona, Alonso, Romero, Moral, Gubieras, and Arbizu (2006)	200 persons with MS	Persons monitored by the MS unit of a hospital in Barcelona

(continued)

Table 9. Additional Studies of Labor Force Participation (continued)

Geographic Area	Citation	Sample Size	Sample Description
Stockholm, Sweden	Henriksson, Fredrikson, Masterman, and Jonsson (2001)	413 persons with MS	Patients with MS who used the Division of Neurology at a hospital
Vasterbotten County, Sweden	Sundstrom, Nystrom, Svenningsson, and Forsgren (2003)	399 persons with MS	Not specified in the article, although it says that it is a "prevalence study"
London, England, United Kingdom	O'Connor, Cano, Torrentia, Thompson, and Forsgren (2005)	100 working age MS patients	Patients attending an outpatient clinic in London
USA	Iezzoni, Ngo, and Kinkel (2007)	983 working age MS patients	2004 mailing list of the National Multiple Sclerosis Society, with an oversample of people residing in low-income zip codes

6.1.2 Summary of Findings from Studies

All of the studies reviewed found that MS has a major negative impact on the labor force participation of people with the disease. Tables 10, 11, and 12 summarize the results from the Kobelt and colleagues studies; Tables 13, 14, and 15 summarize the findings from the additional studies. Table 16 summarizes the cost of productivity losses as a percentage of the estimated cost of MS across the identified studies. The main findings of the studies are as follows:

The Kobelt and colleagues studies found that labor force participation rates are inversely related to disability levels as measured by Expanded Disability Status Scale (EDSS) scores. Labor force participation across European countries ranged from 68 to 83 percent for persons with EDSS scores 0–1 but fell to 1 to 9 percent for persons with EDSS scores of 8–9. These findings were consistent with other studies (Amato et al., 2002; Busche et al., 2003; Casado et al., 2006; Flachenecker et al., 2008; Grima et al., 2000; O'Connor et al., 2005; Orlewska et al., 2006; Pompeii, Moon, and McCorry, 2005; Sundstrom et al., 2003).

Table 10. Labor Force Participation by EDSS Score, by Country (%)

EDSS Score	Country									
	Austria	Belgium	Netherlands	Spain	UK	Sweden	Switzerland	Germany	Italy	USA
0,1	75	77	77	68	77	77	83	73	79	NA
2	56	58	46	46	54	67	57	60	62	NA
3	40	38	41	33	44	66	55	58	60	NA
4	40	66	54	53	66	76	51	43	61	NA
5	15	44	23	20	29	49	28	21	42	NA
6	19	25	22	15	17	44	34	21	31	NA
6.5	10	16	11	12	14	27	23	15	20	NA
7	7	10	8	9	6	33	21	10	14	NA
8,9	1	4	3	1	1	9	7	4	7	NA

Source: Country studies led by Kobelt and colleagues (Berg et al., 2006; Kobelt et al., 2006b-j).

Overall, the Kobelt and colleagues studies reported that labor force participation was very low for a primarily working age population. Across the European countries, only 30.0 to 40.9 percent of MS patients were employed at all; the proportion of people working full-time ranged from 5.5 to 20.4 percent. The proportion of people who retired as a result of MS ranged from about one third to two fifths of people surveyed; significant proportions of the MS population has either changed working hours or their type of work to accommodate their illness. In addition, the MS population uses a substantial amount of short- and long-term sick leave. The findings of Kobelt and colleagues were consistent with other studies (Taylor et al., 2007; Grima et al., 2000; Flachenecker et al., 2008; Amato et al., 2002; Orlewska et al., 2006; Casado et al., 2006; Henrikson et al., 2001; Sundstrom et al., 2003; O'Connor et al., 2005; Iezzoni, Ngo, and Kinkel, 2007).

The costs of productivity losses are high on a per person basis. The Kobelt and colleagues studies found that total productivity losses in terms of cost per patient per year (2005) ranged from € 8,775 in Spain to € 38,218 in Sweden, with most countries ranging from € 11,000 to € 16,000 Euros. The bulk of these costs are because of early retirement.

In Australia, Taylor and colleagues (2007) found that the average cost of full-time absence for illness was \$2,562 Australian (2002) (6-month costs multiplied by 2) and the average cost of part-time absence for illness was \$1,068 Australian (2002) (6-month costs multiplied by 2); the costs of leaving employment and changing from full- to part-time employment were \$384 and \$640 Australian (2002) (6-month costs multiplied by 2), respectively.²

In Italy, Amato and colleagues (2002) estimated that the total average cost to reduction and loss of working activity per "user" was 43,412,000 Italian lira and the average cost over all persons with MS was 12,112,000 Italian lira (3-month costs multiplied by 4).³

In Spain, Casado and colleagues (2006) estimated that total productivity losses due strictly to MS were €7,719 (2004) and total productivity losses as a result of MS and related reasons were €8,412 (2004). This estimate is extremely close to the costs of €8,775 (2005) calculated by Kobelt and colleagues (2006g).

In Sweden for 1998, Henriksson and colleagues (2001) estimated the cost of short-term sickness absence, long-term sickness, and early retirement to be €20,757 (2005), which is lower than the €38,218 estimated by Berg and colleagues (2006).

Productivity losses account for between one third and two fifths of the total estimated cost of MS in the studies reviewed. Only in Spain and Sweden was there more than one recent study to compare. In Spain, the Kobelt and colleagues (2006g) estimate of productivity loss as a percentage of total estimated cost of MS was at least 10 percentage points below the estimate of Casado and colleagues (2006). On the other hand, in Sweden, the estimates by Henriksson and colleagues (2001) and Berg, Lindgren, Fredrikson, and Kobelt (2001) were virtually identical.

² Taylor et al. (2006) are not clear in their article whether the estimated costs are per user or spread over all patients. The authors are also not clear on what year the costs are estimated.

³ Amato et al. (2002) do not specify the year for the cost estimates.

Table 11. Labor Force Participation, Sick Leave, and Retirement, by Country (%)

Characteristic	Country									
	Austria	Belgium	Netherlands	Spain	UK	Sweden	Switzerland	Germany	Italy	USA
Currently employed	30.4	39.7	37.4	30.0	28.2	40.8	34.7	40.9	42.1	NA
Working full-time	20.4		10.6	17.9	5.5	12.4	0	17.1	14.1	NA
Working reduced hours		33.9				21.7				
Long-term illness leave	0.6	5.8	1.9	3.8	0.9	6.7	1.2	2.3	0.6	NA
Short-term sick leave (3 months)	26.5		14.0	5.5	11.5	24.9	4.5	11.0	22.4	NA
Changed working hours	6.7		15.7	3.9	10.9	52.0 ^a	16.3	9.7	12.3	NA
Changed type of work	5.6		10.4	6.8	10.8	38.8 ^a	7.6	6.6	11.8	NA
Retired early because of MS	44.5	32.9	42.2	34.1	44.3	35.7	33.9	33.9	33.9	NA

^aOf those currently employed.

Source: Country studies led by Kobelt and colleagues (Berg et al., 2006; Kobelt et al., 2006b-j).

Table 12. Productivity Losses by Country

	% of Patients									
	Austria	Belgium	Netherlands	Spain	UK	Sweden	Switzerland	Germany	Italy	USA
Short-term absence	25.0	8.8	9.5	5.5	8.4	10.2	4.6	11.0	22.4	NA
Patients on actual leave	25.0	8.8	9.5	5.5	8.4	10.2	4.6	11.0	22.4	NA
Long-term sick leave	0.6	5.8	1.9	3.8	0.9	6.7	1.2	5.6	0.6	NA
Patients on actual leave	0.6	5.8	1.9	3.8	0.9	6.7	1.2	5.6	0.6	NA
Early retirement	44.5	32.9	42.2	34.1	44.3	35.7	33.9	33.9	33.9	NA
Patients actually retired	44.5	32.9	42.2	34.1	44.3	35.7	33.9	33.9	33.9	NA
Total productivity costs										
	# of Days									
	Austria	Belgium	Netherlands	Spain	UK	Sweden	Switzerland	Germany	Italy	USA
Short-term absence	1.4	1.5	1.7	1.5	1.2	1.6	0.5	2.1	2.3	NA
Patients on actual leave	17.3	17.0	17.3	28.3	13.9	25.1	11.0	19.2	10.3	NA
Long-term sick leave										
Patients on actual leave	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0
Early retirement										
Patients actually retired	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0	90.0
Total productivity costs										
	Cost/Patient/Year					(2005 Euros)				
	Austria	Belgium	Netherlands	Spain	UK	Sweden	Switzerland	Germany	Italy	USA*
Short-term absence	421	224	604	96	33	1,085	166	1,259	1,000	475
Patients on actual leave	5,236	2,552	6,321	1,751	394	10,679	3,553	11,452	1,000	
Long-term sick leave	86	1,587	427	182	185	24,261	259	878	4,470	
Patients on actual leave	14,606	27,562	22,809	21,122	19,930	36,087	21,969	38,932	119	
Early retirement	14,150	9,793	12,445	7,867	10,956	13,643	15,502	14,774	1,222	12,207
Patients actually retired	31,830	29,752	29,565	23,186	24,931	29,752	46,029	43,712	10,191	
Total productivity costs	14,657	11,604	13,476	8,775	11,174	38,218	15,928	16,911	11,310	

Note: Short-term absence in the United States is \$533 (2004 dollars), reduced working time is \$3,362 (2004 dollars), and early retirement in the United States is \$13,685 (2004 dollars). All other costs are in 2005 Euros.

Source: Country studies led by Kobelt and colleagues (Berg et al., 2006; Kobelt et al., 2006b-j).

Table 13. Findings From Additional Studies of Labor Force Participation

Citation and Geographic Location	Findings															
Pompeii, Moon, and McCrory (2005), Systematic literature review	Review finds six articles showing that increased disability is associated with reduced labor force participation, but all of the studies used data that are more than 10 years old															
Taylor, McDonald, Fantino, Sedal, MacDonald, Pittas, and Groom (2007), Australia	28% employed, 16% full-time, 12% part-time Per patient cost of short-term sickness absence over 6-month period, \$1,281 (Aus \$, 2002) for full-time workers; 17.0% of patients; \$534 (Aus \$, 2002) for part-time workers; 7.1% of patients worked Change in work status over last year: Left employment, \$192 (Aus \$, 2002), 2.5% of patients; changed from full- to part-time, \$320 (Aus \$, 2002), 4.2% of patients															
McCabe and De Judicibus (2006), Victoria, Australia	44% of males and 32% of females lost income															
Access Economics (2005) (unpublished) Australia	Annual average cost of \$9,856 Australian Labor force participation much lower for people with MS Of those who are employed, more work part-time and far fewer full-time than general population															
Busche, Fiske, Murray, and Metz (2003), Alberta, Canada	Unemployment was strongly related to EDSS score, disease course, and disease duration EDSS Scores and Employment Status <table border="1" data-bbox="631 982 1385 1234"> <thead> <tr> <th data-bbox="688 993 829 1018">EDSS Score</th> <th data-bbox="927 993 1084 1018">Employed (%)</th> <th data-bbox="1162 993 1349 1018">Unemployed (%)</th> </tr> </thead> <tbody> <tr> <td data-bbox="643 1045 716 1071">0–2.5</td> <td data-bbox="984 1045 1040 1071">60.0</td> <td data-bbox="1235 1045 1292 1071">06.5</td> </tr> <tr> <td data-bbox="643 1098 724 1123">3.0–5.5</td> <td data-bbox="984 1098 1040 1123">28.0</td> <td data-bbox="1235 1098 1292 1123">32.6</td> </tr> <tr> <td data-bbox="643 1150 716 1176">6.0–8.0</td> <td data-bbox="984 1150 1040 1176">12.0</td> <td data-bbox="1235 1150 1292 1176">41.3</td> </tr> <tr> <td data-bbox="643 1203 724 1228">8.5–9.5</td> <td data-bbox="1000 1203 1024 1228">0</td> <td data-bbox="1235 1203 1292 1228">19.6</td> </tr> </tbody> </table> <p data-bbox="602 1241 1409 1356">66.0% of employed patients had relapsing-remitting MS; 78.3% of unemployed patients had progressive MS At follow-up in 1999/2000, the risk of becoming unemployed was 17.5 times greater for those with EDSS scores of >5.5 compared with those with <3.0</p>	EDSS Score	Employed (%)	Unemployed (%)	0–2.5	60.0	06.5	3.0–5.5	28.0	32.6	6.0–8.0	12.0	41.3	8.5–9.5	0	19.6
EDSS Score	Employed (%)	Unemployed (%)														
0–2.5	60.0	06.5														
3.0–5.5	28.0	32.6														
6.0–8.0	12.0	41.3														
8.5–9.5	0	19.6														
Grima, Torrance, Francis, Rice, Rosner, and Lafortune (2000), Canada	Costs in 1997 Canadian dollars Costs during remission varied by EDSS score, including for patient work losses: EDSS 1—\$6,341; EDSS 2—\$5,899; EDSS 3—\$15,995; EDSS 4—\$15,622; EDSS 5—\$26,614; EDSS 6—\$24,513 Work status varies by EDSS level for remission survey patients, with more disabled patients working less A relationship between cost during relapse and EDSS score was not observed, although this may be a result of the small number of relapse patients in the sample for some EDSS scores															

(continued)

Table 13. Findings from Additional Studies of Labor Force Participation (continued)

Citation and Geographic Location	Findings																																						
Flachenecker, Stuke, Elias, Freidel, Haas, Pitschnau-Michel, Schimrgk, Zettl, and Rieckmann (2008), Germany	<p>Employment declined substantially by age, starting at 25–34. 27.9% were employed full-time; 8.9% were employed part-time; 6.0% were unemployed; 39.4% were on partial disability benefits/full disability benefits/early retirement; 14.7% were housewife/husband, receiving MS-related vocational training, or in school</p> <p>Retirement varies by EDSS score; about 18% were retired at EDSS 1; 70% at EDSS Score 5; and 100% at EDSS Score 9 and 10</p>																																						
Amato, Battaglia, Caputo, Fattore, Gerzeli, Pitaro, Reggio, Trojano, for the Mu. S. I. C. Study Group (2002), Italy	<p>41.9% were employed, 7.5% unemployed, 27.6% retired</p> <p>Productivity losses varied by EDSS for 3 months</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">EDSS Score</th> <th style="text-align: center;">% of Patients with Working Days Lost</th> <th style="text-align: center;">Average Working Days Lost Per User</th> <th style="text-align: center;">Average Working Days Lost Per Patient</th> <th style="text-align: center;">% of Patients with Reduction and Loss of Working Activity</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">0–1.5</td> <td style="text-align: center;">33.8</td> <td style="text-align: center;">7.9</td> <td style="text-align: center;">2.7</td> <td style="text-align: center;">11.3</td> </tr> <tr> <td style="text-align: center;">2.0–3.5</td> <td style="text-align: center;">44.3</td> <td style="text-align: center;">12.2</td> <td style="text-align: center;">5.4</td> <td style="text-align: center;">20.1</td> </tr> <tr> <td style="text-align: center;">4.0–5.5</td> <td style="text-align: center;">34.6</td> <td style="text-align: center;">14.6</td> <td style="text-align: center;">5.0</td> <td style="text-align: center;">30.8</td> </tr> <tr> <td style="text-align: center;">6.0–6.5</td> <td style="text-align: center;">19.1</td> <td style="text-align: center;">18.1</td> <td style="text-align: center;">3.6</td> <td style="text-align: center;">38.2</td> </tr> <tr> <td style="text-align: center;">>7.0</td> <td style="text-align: center;">14.1</td> <td style="text-align: center;">5.3</td> <td style="text-align: center;">1.3</td> <td style="text-align: center;">47.1</td> </tr> <tr> <td style="text-align: center;">Total</td> <td style="text-align: center;">32.2</td> <td style="text-align: center;">12.5</td> <td style="text-align: center;">4.0</td> <td style="text-align: center;">27.9</td> </tr> </tbody> </table>				EDSS Score	% of Patients with Working Days Lost	Average Working Days Lost Per User	Average Working Days Lost Per Patient	% of Patients with Reduction and Loss of Working Activity	0–1.5	33.8	7.9	2.7	11.3	2.0–3.5	44.3	12.2	5.4	20.1	4.0–5.5	34.6	14.6	5.0	30.8	6.0–6.5	19.1	18.1	3.6	38.2	>7.0	14.1	5.3	1.3	47.1	Total	32.2	12.5	4.0	27.9
EDSS Score	% of Patients with Working Days Lost	Average Working Days Lost Per User	Average Working Days Lost Per Patient	% of Patients with Reduction and Loss of Working Activity																																			
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>7.0	14.1	5.3	1.3	47.1																																			
Total	32.2	12.5	4.0	27.9																																			
	<p>Indirect costs vary by EDSS, in Italian lira</p> <p>Patient working days lost over 3 months, according to EDSS (million Italian Lira) (year not specified)</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">EDSS Score</th> <th style="text-align: center;">Average Cost Per User</th> <th style="text-align: center;">Average Cost Per Patient</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">0–1.5</td> <td style="text-align: center;">1.5</td> <td style="text-align: center;">0.5</td> </tr> <tr> <td style="text-align: center;">2.0–3.5</td> <td style="text-align: center;">2.1</td> <td style="text-align: center;">1.0</td> </tr> <tr> <td style="text-align: center;">4.0–5.5</td> <td style="text-align: center;">2.2</td> <td style="text-align: center;">0.8</td> </tr> <tr> <td style="text-align: center;">6.0–6.5</td> <td style="text-align: center;">3.1</td> <td style="text-align: center;">0.6</td> </tr> <tr> <td style="text-align: center;">>7.0</td> <td style="text-align: center;">1.8</td> <td style="text-align: center;">0.3</td> </tr> <tr> <td style="text-align: center;">Total</td> <td style="text-align: center;">2.1</td> <td style="text-align: center;">0.7</td> </tr> </tbody> </table>				EDSS Score	Average Cost Per User	Average Cost Per Patient	0–1.5	1.5	0.5	2.0–3.5	2.1	1.0	4.0–5.5	2.2	0.8	6.0–6.5	3.1	0.6	>7.0	1.8	0.3	Total	2.1	0.7														
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6.0–6.5	3.1	0.6																																					
>7.0	1.8	0.3																																					
Total	2.1	0.7																																					

(continued)

Table 13. Findings from Additional Studies of Labor Force Participation (continued)

Citation and Geographic Location	Findings		
Amato, Battaglia, Caputo, Fattore, Gerzeli, Pitaro, Reggio, Trojano, for the Mu. S. I. C. Study Group (2002), Italy (continued)	Patients' reduction and loss of working activity (million Italian Lira) (year not specified)		
	EDSS Score	Average Cost Per User	Average Cost Per Patient
	0–1.5	9.9	1.1
	2.0–3.5	10.6	2.1
	4.0–5.5	11.1	3.4
	6.0–6.5	10.7	4.1
	>7.0	11.3	5.3
	Total	10.9	3.0
Svendsen, Myhr, Nyland, and Aarseth (2008), Norway	<ul style="list-style-type: none"> • Over 65% of patients reported an employment status of not working • Average work loss for sick leave was 17.1 days per patient per year • Average work loss for rehabilitation was 2.8 days per patient per year • Across the patient population of approximately 6750 in Norway, estimated years of work loss because of early retirement was 3,816 • Estimated per patient cost of work loss was 35,425 Euros per year 		
Orlewska, Mierzejewski, Zaborski, Kruszewska, Wicha, Fryze, Drosdowski, Skibicka, Mirowska-Guzel, Czlonkowski, and Czlonkowska (2006), Poland	<ul style="list-style-type: none"> • Patients' productivity loss varies by EDSS 		
		EDSS <3.5	EDSS 4.0–6.0
	EDSS >6.5		
%	66	84	89
Median (days/user/month)	14.0	17.7	17.7
<p>In all MS stages (see above), patients' workdays lost constituted the major indirect cost driver (77%, 62%, and 63% of the indirect costs)</p> <p>Work loss cost €2,586 (2002, converted by purchasing power parity) for persons with EDSS < 3.5 for 5-month period; 3,089 Euros for EDSS 4.0–6.0; and €3,827 for EDSS >6.5</p>			

Table 13. Findings from Additional Studies of Labor Force Participation (continued)

Citation and Geographic Location	Findings
Casado, Martinez-Yelamos, Martinez-Yelamos, Carmona, Alonso, Romero, Moral, Gubieras, and Arbizu (2006), Catalonia, Spain	<p>Indirect costs strongly related to EDSS scores</p> <p>Total average indirect costs due strictly to MS and because of MS and related reasons were €7,719 and €8,412, respectively</p> <p>Productivity losses for short-term sickness absences because of MS varied from €1,415 for people with EDSS of 1.5-3.0 to €2,113 for people with EDSS of > 7.5</p> <p>Productivity losses because of long-term sickness absences ranged from €4,046 for people with EDSS of 1.5-3.0 to €15,779 for people with EDSS of > 7.5</p>
Henriksson, Fredrikson, Masterman, and Jonsson (2001), Stockholm, Sweden	<p>40% of patients had a job last month, of which 40% were full-time</p> <p>12% have changed working hours; 4% have changed assignment; 11% have changed both assignment and working hours; 43% have been forced to quite their job because of MS</p> <p>In 1998, the cost per MS patient for short-term absence was €949; for long-term sickness absence and early retirement, €16,569; and €17,518 for the two</p> <p>In 1998, the indirect costs per MS patient were €9,680 for persons with EDSS <3.0; €15,445 for persons with EDSS (3.5–6.0); and €25,009 for persons with EDSS >6.5</p>
Sundstrom, Nystrom, Svenningsson, and Forsgren (2003), Vasterbotten County, Sweden	<p>Among people 18–64, 34.5% were not sick listed, 20.5% were partially sick listed, and 45% were fully sick listed</p> <p>The percent fully sick listed was strongly related to EDSS scores. Between 80-90% of people with EDSS scores greater than 6.0 were fully sick listed, compared to about 17% of people with EDSS scores of 0 to 2.5 and about 42% of people with EDSS scores of 3.0 to 5.5</p> <p>36% of MS patients received a disability pension</p>
O'Connor, Cano, Torrentia, Thompson, and Playford (2005), London, England, United Kingdom	<p>Unemployment was very strongly related to duration of MS</p> <p>At time of survey, 36% of respondents were employed</p> <p>People who were unemployed had higher EDSS scores</p> <p>Of the 36 people working, 24 reported that MS affected their ability to work</p> <p>Half of unemployed expressed a desire to return to work if possible</p>
Iezzoni, Ngo and Kinkel (2007), USA	<p>In 2004, 36% of the study population had federal disability insurance or means-tested income assistance</p> <p>2.7% of all Americans had Social Security Disability Insurance, compared to 33% of study population</p> <p>2.2% of working aged Americans had means-tested disability income assistance, compared to 8.6% of study population</p> <p>60% of study population unemployed</p>

Table 14. Productivity Losses by MS Patients as a Percentage of the Total Cost of Illness

Country	Citation	Percentage
Australia	Taylor, McDonald, Fantino, Sedal, MacDonnell, Pittas, and Groom (2007)	13.1 ^a
Australia	Access Economics (2005) (unpublished)	26.4
Austria	Kobelt, Berg, Lindgren, Baumhackl, and Berger (2006c)	36.3
Belgium	Kobelt, Berg, Lindgren, Decoo, Guillaume, Neymark, Sindic and Vandegaer (2006d)	35.8
Canada	Grima, Torrance, Francis, Rice, Rosner, and Lafortune (2000)	For remission costs: 59.8 for EDSS 1, 45.7 for EDSS 2; 57.0 for EDSS 3; 59.6 for EDSS 4; 51.4 for EDSS 5; and 47.4 for EDSS 6 For relapse costs: 23.3 for EDSS 1; 37.9 for EDSS 2; 33.3 for EDSS 3; 80.9 for EDSS 4; 75.6 for EDSS 5; and 49.3 for EDSS 6. EDSS >6 were excluded from the study
Germany	Kobelt, Berg, Lindgren, Berger, Elias, Flachenecker, Freidel, Konig, N., Limmroth, and Straube (2006e)	42.2
Italy	Amato, Battaglia, Caputo, Fattore, Gerzeli, Pitaro, Reggio, Trojano, for the Mu. S. I.C. Study Group (2002)	49.2
Italy	Kobelt, Berg, Lindgren, Battaglia, Lucioni, and Uccelli (2006f)	29.1
The Netherlands	Kobelt, Berg, Lindgren, Anten, Ekman, Jongen, Polman, and Uitdenhaag (2006i)	45.8
Norway	Svendsen, Myhr, Nyland, and Aarseth (2008)	43.0

Continued

Table 14. Productivity Losses by MS Patients as a Percentage of the Total Cost of Illness (continued)

Country	Citation	Percentage
Poland	Orlewska, Mierzejewski, Zaborski, Kruszewska, Wicha, Fryze, Drosdowski, Skibicka, Mirowska-Guzel, Czlonkowski, and Czlonkowska (2006)	48.4 for EDSS < 3.5, 40.5 for EDSS 4.0-6.0; and 42.5 for EDSS >6.5
Spain	Casado, Martinez-Yelamos, Martinez-Yelamos, Carmona, Alonso, romero, Moral, Gubieras, and Arbizu (2006)	35 overall, with 39 for EDSS 0, 35 for EDSS 1.5-3.0; 34 for EDSS 3.5-5.5; 42 for EDSS 6.0-7.0; and 30 for EDSS >7.5.
Spain	Kobelt, Berg, Lindgren, Izquierdo, and Sanchez-Solino (2006g)	26.2
Sweden	Berg, Lindgren, Fredrikson, and Kobelt (2006)	32.0
Sweden	Henriksson, Fredrikson, Masterman, and Jonsson (2001)	32.9 overall, with 50.2 for EDSS <3.0; 42.3 for EDSS 3.5-6.0; and, 27.2 for EDSS >6.5
Switzerland	Kobelt, Berg, Lindgren, and Gerfin (2006h)	38.0
United Kingdom	Kobelt, Berg, Lindgren, Kerrigan, Russell, and Nixon (2006j)	36.9
United States	Kobelt, Berg, Atherly, and Hadjimichael (2006b)	44.0

^aIn contrast to most studies, Taylor and colleagues (2007) only included early retirement costs for persons who “left employment” during the last year.

6.1.3 Work Loss by Informal Caregivers

People with MS often require help performing daily tasks because of health care problems and functional and cognitive impairments. This care is mostly provided by informal caregivers, principally spouses and other relatives. To care for persons with MS, informal caregivers may have to adjust their work schedules, reduce work hours, or even quit their jobs and leave the labor force, which creates another indirect cost. The economic cost, however, has not been estimated.

All of the seven studies that examined the effect of caring for a person with MS on labor force participation found that this role had a negative impact or that there was work-related strain because of work adjustments. This research is fairly limited and is summarized in Table 15. The range of results is as follows:

From 39 (Amato et al., 2002) to 65 percent (Kahn, Pallant, and Brand, 2007) of caregivers report some work adjustments or losing at least some work because of caregiver responsibilities.

The amount of work days lost varies from 7.3 days a year (Quig et al., 2007) to 12 days a year (Amato et al., 2002).

The proportion of caregivers who reduced or gave up their work varied from 6.5 (Amato et al., 2002) to 27.5 percent (Rivera-Navarro, Morales-Gonzalez, and Benito-Leon, 2003).

The amount of work loss because of caregiving is reported to vary by EDSS score in one study (Amato et al., 2002).

Table 15. Summary of Studies of Impact on Labor Force Participation of Caregivers

Citation and Geographic Location	Results
McKeown, Porter-Armstrong, and Baxter (2003), systematic international literature review of articles from 1990 to 2002	<ul style="list-style-type: none"> ▪ Although there are conflicting findings, the majority of studies find adverse financial impact
Kahn, Pallant, and Brand (2007), Melbourne, Australia	<ul style="list-style-type: none"> ▪ 65% of caregivers reported “there have been work adjustments”; 18% reported that the work adjustments have been “severe” or “extreme” ▪ 42% of caregivers worked; 26% of caregivers worked full-time ▪ 34% of caregivers were on pension (54 was the mean age of all caregivers) ▪ Caregivers worked 26 hours per week on average ▪ 18% of caregivers reported financial strain had been “severe” or “extreme”

(continued)

Table 15. Summary of Studies of Impact on Labor Force Participation of Caregivers (continued)

Citation and Geographic Location	Results																																										
Amato et al. (2002), Italy	<ul style="list-style-type: none"> ▪ 39.3% of caregivers lost working days; among caregivers who lost work, the average was 7.8 days over 3 months; 3.1 days averaged over all patients for a mean cost of ITL 569,000 per patient over 3 months ▪ Three-Month Work Loss for Caregivers Varied by EDSS score <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th>EDSS Score</th> <th>Caregivers with Workings Days Lost (%)</th> <th>Average Caregiver Working Days Lost per User</th> <th>Average Caregiver Working Days Lost per Patient</th> </tr> </thead> <tbody> <tr> <td>0–1.5</td> <td>22.5</td> <td>5.2</td> <td>1.2</td> </tr> <tr> <td>2.0–3.5</td> <td>45.9</td> <td>6.3</td> <td>2.9</td> </tr> <tr> <td>4.0–5.5</td> <td>44.2</td> <td>8.7</td> <td>3.9</td> </tr> <tr> <td>6.0–6.5</td> <td>42.7</td> <td>9.5</td> <td>4.1</td> </tr> <tr> <td>≥7</td> <td>65.6</td> <td>10.3</td> <td>3.2</td> </tr> <tr> <td>Total</td> <td>39.3</td> <td>7.8</td> <td>3.1</td> </tr> </tbody> </table> <ul style="list-style-type: none"> ▪ 6.5% of caregivers reduced or gave up their work at a mean cost of ITL 604,000 per patient ▪ Percent of Caregivers Reducing or Giving Up Their Work <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th>EDSS Score</th> <th>Percent of Caregivers</th> </tr> </thead> <tbody> <tr> <td>0–1.5</td> <td>0</td> </tr> <tr> <td>2.0–3.5</td> <td>3.6</td> </tr> <tr> <td>4.0–5.5</td> <td>10.6</td> </tr> <tr> <td>6.0–6.5</td> <td>5.6</td> </tr> <tr> <td>≥7</td> <td>21.3</td> </tr> <tr> <td>Total</td> <td>6.5</td> </tr> </tbody> </table>	EDSS Score	Caregivers with Workings Days Lost (%)	Average Caregiver Working Days Lost per User	Average Caregiver Working Days Lost per Patient	0–1.5	22.5	5.2	1.2	2.0–3.5	45.9	6.3	2.9	4.0–5.5	44.2	8.7	3.9	6.0–6.5	42.7	9.5	4.1	≥7	65.6	10.3	3.2	Total	39.3	7.8	3.1	EDSS Score	Percent of Caregivers	0–1.5	0	2.0–3.5	3.6	4.0–5.5	10.6	6.0–6.5	5.6	≥7	21.3	Total	6.5
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Total	6.5																																										
Patti et al. (2007), Italy	<ul style="list-style-type: none"> ▪ With average age of 50, 88.3% were employed; 11.7% were unemployed 																																										
Rivera-Navarro, Morales-Gonzalez, and Benito-Leon (2003), Madrid, Spain	<ul style="list-style-type: none"> ▪ Only 25% of MS patients in the study had a “primary caregiver” defined as spending at least 1 hour per day in the care of the MS patient ▪ Among primary caregivers, 27.5% reported “work-related changes” 																																										

(continued)

Table 15. Summary of Studies of Impact on Labor Force Participation of Caregivers (continued)

Citation and Geographic Location	Results
Chipcase and Lincoln (2001) Nottingham, England, United Kingdom	<ul style="list-style-type: none"> ▪ 50% of carers reported feeling strain because of “work adjustments”
Quig et al. (2007), USA	<ul style="list-style-type: none"> ▪ 53% of caregivers reported missing work over the past year ▪ Caregivers reported missing an average of 7.3 days of work ▪ 7% of caregivers reported changing their employment altogether because of caregiving ▪ Work loss varied by type of MS, with caregivers of primary progressive MS patients missing more than four times as many days as caregivers of relapsing-remitting MS patients

6.2 Early Mortality

Premature death from MS or its complications causes an economic burden because of the underlying economic value of the lost years of healthy life. Once the number of lost years associated with MS is identified, they can then be assigned an economic value using valuation methods for each year lost. However, doing so is complicated and fraught with value judgments regarding the value of a life that are often controversial and misunderstood.

MS is usually viewed as a disease that results primarily in morbidity, disability, and loss of quality of life, but without dramatic impacts on life expectancy. However, recent studies have shown a consistent, significant impact on life expectancy because of MS. This impact has been found across multiple countries.

Ekestern and Lebhart (2004) studied death records in Austria and found that the median age at death from 1990 to 2001 was 59 years for MS patients and 74 for the overall population. This suggested a decreased life expectancy of about 15 years for people affected by MS compared with the total Austrian population.

Torkildsen and colleagues (2008) studied patterns of survival and cause of death among the 878 people diagnosed with MS in Hordaland County in western Norway over a 50-year period from 1953 to 2003. They compared actual death rates for MS patients with expected death rates based on population mortality tables adjusted for age, sex, and calendar year that were obtained from Statistics Norway. Median survival time from onset of the MS was 41 years versus 49 years in the corresponding population. The total number of deaths, 198, was much higher than the 74 deaths they projected for those people using a statistical model for the general population. This analysis resulted in a standardized mortality ratio (SMR) calculation of 2.7, indicating a statistically significant increase in mortality for MS patients (95% CI: 2.31–3.06). Torkildsen and colleagues found that, according to the death certificates, 57 percent of the MS patients had died as a result of MS. They noted that death directly because of MS exacerbation is

probably rare, but death is probably more often a result of secondary complications of MS, such as infections.

Ragonese and colleagues (2008) conducted a literature review on studies investigating MS mortality rates, causes of death, excess mortality, and decreased life expectancy because of MS. They concluded that population-based studies show a significant increase in mortality of persons with MS compared with the general population. They also found these results to be homogeneous across studies. For example, they reviewed a recent Danish study that reported SMRs—the proportion of deaths caused by a disease compared with those expected in the general population—of 3.14 for women and 2.66 for men. Reduced life expectancy with respect to the general population ranged between 10 and 12 years.

Despite the limitations of comparing results between studies performed with different methodologies, Ragonese and colleagues identified several inferences that could be drawn from their literature review that are relevant for this study on the global economic burden of MS:

Mean survival time of MS patients is long, ranging from 20 to nearly 45 years from the onset of disease symptoms.

The average number of years of life lost as a result of MS ranges between 5 and 10 per person.

MS is not generally lethal by itself, but death is usually the result of high levels of disability, increasing age, or concurrent diseases. Treatments adopted to improve MS symptoms and to prevent and cure complications in more disabled persons may result in improved survival for MS patients.

In sum, estimates of reduced life expectancy as a result of MS in these studies ranged from 5 to 15 years. As a result, a reasonable starting point for calculating the economic burden of years of life lost because MS is 10 years per person.

7. INTANGIBLE COSTS

Quality of Life (QOL) has become a widely used health care outcome measure. For chronic diseases, it is important because diseases such as MS can dramatically affect the QOL of patients for many years without causing death. As a result, a significant but unquantifiable component of the economic burden of MS is its impact on QOL. QOL can be measured for general domains common across multiple diseases and for disease-specific domains that are more closely related to the morbidity or disability impacts of MS.

7.1 Quality of Life—Generic Domains

Studies of the generic QOL impact of MS consistently show substantial negative effects from the disease. Overall, 13 studies were identified that analyze the impacts of MS on generic QOL across multiple domains. The effects on physical functioning were larger than those on social functioning or mental functioning. In addition, the physical health QOL impacts increase as the disease progresses over time and physical impairments become more severe. Significant effects on social and mental functioning were also found. Overall, these studies indicate a 30 percent decline in physical functioning for mild MS, increasing to 40 percent for moderate MS and 50 percent for severe MS. A 20 percent decline in social

functioning can be identified for mild and moderate MS, increasing to 30 percent for severe MS. Mental functioning declined by about 10 percent across the range of severity levels.

7.1.1 European Studies

United Kingdom. Riazi and colleagues (2003) recruited a sample of 638 MS patients from a range of sources, including a random sample from a postal survey of Great Britain and Northern Ireland, 150 consecutive patients attending an MS clinic at the National Hospital for Neurology and Neurosurgery in London, and a sample of MS patients admitted to that hospital. They also used a general population comparison sample of 2,056 from across the United Kingdom.

The SF-36 survey instrument was used to measure generic QOL in the MS and general population samples. Results indicated that MS patients had worse health than the UK general population for all eight domains measured by the SF-36 (see Table 16). By domain, the differences were physical functioning (58 points), role physical (56 points), social functioning (35 points), role emotional (31 points), general health (25 points), vitality (25 points), bodily pain (21 points), and mental health (10 points).

Table 16. SF-36 Scores for MS Patients Compared to UK Norms

Domain	MS Patients	United Kingdom Norms
Physical functioning	25	83
Role physical	24	80
Bodily pain	57	78
General health perceptions	46	71
Vitality	38	63
Social functioning	52	87
Role emotional	56	87
Mental Health	67	77

Controlling for age, sex, marital status, social class, employment and ethnicity.

Source: Riazi et al. (2003).

Norway. Nortvedt and colleagues (1999) conducted a study of generic QOL for MS patients in Norway. They studied all of the patients with onset of MS between 1976 and 1986 and diagnosis before 1995 in Hordaland County in western Norway. A total of 194 patients agreed to participate in the study, which represented 94 percent of those in this cohort who were still alive in 1995. Mean duration of the disease at the time of the study was 14 years, and mean Expanded Disability Status Scale (EDSS) was 4.1. There was a general population comparison group of 2,323 Norwegians.

Results indicated that the MS patients had significantly lower mean SF-36 scores for all eight health dimensions compared with the age- and sex-adjusted scores in the general population comparison group. The differences between the MS patient and general population norms were especially large for the physical functioning, general health, role physical, vitality, and social functioning scales; mean scores in

the MS population were more than one standard deviation below those in the general population for those measures. For the physical functioning scale, the mean score for MS patients was more than two standard deviations below that of the general population.

Netherlands. Janssens and colleagues (2003) conducted a study of generic QOL for 101 MS patients in the Netherlands. Patients in their sample were consecutive patients with MS at neurology clinics in four hospitals in the Erasmus region and in Amsterdam. The mean age of the patients was 38, 70 percent were female, mean time since diagnosis was 8 months (shorter than the other studies reviewed here), and median EDSS was 2.5.

Data collection included the SF-36 for generic QOL, the Hospital Anxiety and Depression Scale, and the Impact of Event scale that measures psychological distress. The results indicated that generic QOL was significantly worse in patients compared with a general population control group, particularly among those with higher levels of disability as measured by the EDSS. The differences were consistent across all SF-36 scales compared with controls from the general population, except for bodily pain. All of the differences were statistically significant at $p < 0.001$.

The authors noted that previous studies showing reduced QOL in MS patients have typically investigated MS patients within more advanced stages of the disease. These data show that a major impact of the disease on QOL was also found in recently diagnosed patients.

Austria. Lobentanz and colleagues (2004) conducted a study of generic QOL with members of the Vienna chapter of the Austrian MS Society. This study included 504 MS patients and 1,049 healthy subjects as a comparison group. The MS patients had a mean age of 51, were 72 percent female, mean disease duration was 16 years, and mean EDSS was 6 (higher than the other studies reviewed in this section).

QOL data were collected using the Quality of Life Index (QLI) survey instrument. The authors used the QLI because it includes additional questions about interpersonal functioning; social, emotional, and community services support; and personal and spiritual fulfillment. The results indicated that MS patients had significantly worse QOL over all nine domains of the QLI and for its overall QOL scale as well. All of the differences were statistically significant at the $p < 0.001$ level.

This study had two main limitations. First, the MS patients were drawn from just one city, so they may not be representative of the overall MS patient population in Austria. Second, study participants had higher mean EDSS disability scores than most other studies of generic QOL.

Cross-National Study (France, Germany, and United Kingdom). Murphy and colleagues (1998b) conducted one of the few cross-national studies of generic QOL in MS, collecting data at one point in time in France, Germany, and the United Kingdom. They recruited 90 patients and 30 healthy controls from each country. The 90 patients were split equally into three groups of 30 each with mild MS (EDSS 1.0–3.5), moderate MS (EDSS 4.0–6.0), and severe MS (EDSS 6.5–8.0). They were recruited by neurologists at two medical centers in each country. Control group members were recruited by general practitioners in neighboring practices in each country and were matched to the MS patients by age and sex.

QOL was assessed in this study using the Functional Status Questionnaire (FSQ). The authors chose this instrument because it includes more data on work-related QOL than most generic QOL instruments, such as the SF-36.

The results showed that scores for the physical functioning and general well-being scales for patients with MS were between 40 and 50 percent lower than those of the comparison group. In addition, scores for the psychological functioning scales and social role functioning scales were about 20 percent lower than in the control group.

One limitation of this study is that the MS patients were selected to include equal numbers of patients at the three levels of disease severity, which may not be representative of the overall patient population in each country. Another limitation is the small number of geographic regions represented in each country, which may also affect the comparability of this patient sample to the overall MS population in each country.

7.1.2 North American Studies

Canada. The Canadian Burden of Illness Study Group (1998) conducted a nationwide study of generic QOL for 198 MS patients recruited from 14 MS clinics. Patient recruitment was stratified into three severity groups, mild MS (EDSS \leq 2.5), moderate MS (EDSS 3.0–6.0), or severe MS (EDSS \geq 6.5). As a result, the final patient sample was split almost evenly between these three severity groups, with 61 patients in the mild MS group and 68 patients each in the moderate and severe MS groups.

Generic QOL was measured using the SF-36. Results indicated that scores from all eight SF-36 scales were substantially reduced even in the disease for patients in the mild MS group. For the mild MS group, the scale scores were on average 30 percent lower for all SF-36 patients compared with the normal population controls. With EDSS progression, MS patients in the moderate and severe groups had further declines in the physical functioning, role physical, social functioning, and physical component summary domains. The absence of further declines in the mental SF-36 scales for the moderate and severe MS groups may reflect patient adaptation to the disease or effective support care.

One limitation of this study is that the MS patients were selected to include equal numbers of patients at the three levels of disease severity, which may not be representative of the overall patient population in Canada.

Hopman and colleagues (2007) studied patients who attended the MS Clinic at Kingston General Hospital in Kingston, Ontario, during 2000 and 2001. All 387 eligible patients were invited to participate in this study and 300 agreed, for a response rate of 78 percent. Participants had a mean age of 47, mean duration of MS of 14 years, mean EDSS of 3.8, and median EDSS of 3.5; 75 percent were female.

The MS Quality of Life Inventory (MSQLI) survey instrument was used in this study, because it includes a combination of generic and disease-specific QOL measures. The MSQLI includes the SF-36 as a generic core and eight other scales that measure MS-specific issues: fatigue, pain, bladder control, bowel control, sexual satisfaction, visual impairment, perceived deficits (cognitive impacts), and social support.

The results showed that MS patients had worse QOL compared to age- and sex-adjusted normative population data for all eight SF-36 scales and for the two component summary scales. All of these differences were statistically significant at $p < 0.001$.

One limitation of this study is that the patients were all sampled from one MS clinic at a large teaching hospital, so they may not be representative of the overall MS patient population in Canada. However, the authors noted that other MS studies have shown the patients at the Kingston MS clinic to be nationally representative.

Aronson (1997) conducted a study of generic QOL through a mail survey of MS patients and their caregivers in Ontario. The patients were identified from a random sample of the Canadian MS Society membership in Ontario, stratified by urban/rural status and recent attendance at MS clinics. This sampling approach was intended to ensure that the study would include respondents who had not recently attended a clinic, unlike other MS QOL studies that have focused on recruiting respondents from clinic attendees.

The study included 417 MS patients and 345 caregivers. QOL questions were taken from the General Social Survey (GSS) of Statistics Canada to allow for comparison of the MS patient results to results for the general population. As a result, a large comparison group of 1,692 disabled and 1,692 able-bodied persons of approximately the same sex, age, and education level was identified from the Canadian general population. MS patients in this study had a mean age of 48, and 70 percent were female.

Results were presented by comparing MS patients with people with disabilities in the GSS and comparing caregivers of MS patients with the able-bodied population in the GSS. However, the authors concluded that MS patients were less satisfied to a statistically significant degree with health, job or major activity, and life as a whole than were either disabled or able-bodied persons in the GSS. Less satisfaction with several QOL components was evident for those with MS compared with the disabled in the Canadian general population, and for caregivers compared with the able-bodied general population. Poorer QOL as a whole among those with MS was associated with unemployment, MS symptoms of moderate or worse, fatigue, mobility limitations on stairs, a disease course other than stable, and was most strongly related to interference by MS in social activities.

United States. One of the earliest studies on generic QOL was conducted by Vickrey and colleagues (1995). It included a sample of 179 consecutive MS patients treated at a UCLA medical center and 2,474 people from a U.S. general population comparison group. The MS patients were matched to the comparison group by age and gender. The SF-36 was used to measure generic QOL.

The results showed significantly lower functioning in this sample of MS patients relative to the general population on most of the eight SF-36 scales. MS patients scored 48 points lower than the general U.S. population on both the physical functioning and role limitation physical scales. Social functioning scale scores were 25 points lower. The energy/fatigue scale (also known as vitality), health perceptions (also known as general health), and role limitation emotional scores were about 20 points lower for MS patients. The other scales were also lower but by smaller amounts.

One limitation is that this sample represents MS patients referred to a tertiary medical center, so they probably have greater impairment in QOL than the overall MS patient population. Another limitation is that the MS patients were all from the Los Angeles area and thus may not be representative of the overall MS patient population in the United States.

A study by Pittock and colleagues (2004) found negative impacts for MS on most SF-36 scales but positive results on one. This study included 185 MS patients in Olmsted County, Minnesota, who were interviewed in a clinic setting or at home if they were unwilling to be seen in the clinic. They had an average MS disease duration of 19 years and a median EDSS of 3.0.

Data were analyzed using standardized MS patient scores for comparison with those from an age- and sex-adjusted U.S. general population. The results showed clinically significantly worse health for MS patients for the physical functioning, role physical, general health, vitality, and the physical health component scales. Better health was found for the mental health component summary scale. All of these differences were statistically significant.

A limitation of this study is its focus on MS patients from just one county in Minnesota. Thus, patients may not be representative of the overall population of MS patients in the United States.

7.1.3 Australian Studies

McCabe and McKern (2002) studied generic QOL for 381 patients drawn from a random sample of the MS register for the province of Victoria in Australia. This register includes about 80 percent of the MS patients in that province, so it can be viewed as an approximation of the MS population for that province. They were compared with a general population sample of 291 people with similar characteristics who were drawn from the electoral register that includes all people of voting age in the province of Victoria.

This study used the WHOQOL-100 instrument to measure QOL. It includes both objective and subjective measures for four dimensions of QOL: physical health, psychological health, social relationships, and environmental adjustment. Objective QOL is the person's actual, measurable situation in relation to a particular domain (e.g., actual income). Subjective QOL refers to the individual's level of satisfaction with the domain (e.g., satisfaction with income).

The results showed that MS patients scored significantly worse than the general population on seven of the eight generic QOL measures included in the WHOQOL-100 instrument. Among the objective and subjective physical health, psychological, social relationship, and environmental measures, only psychological-objective was not statistically significantly lower for the MS population than for the MS population.

Spain and colleagues (2007) also studied QOL for MS patients in Victoria province. They recruited patients through the MS Society and public and private neurology clinics. A total of 687 patients were recruited, with a mean age of 47, median duration of MS of 9 years, and median EDSS of 3.5; 79 percent were female.

The SF-36 was used to measure generic QOL. Scores for all eight scales of the SF-36 were statistically significantly below the U.S. population mean. One limitation of this study is that the results were compared with U.S. population norms for the SF-36 scales. It is possible that Australian population norms could provide different results.

Using secondary data, Access Economics (2005) calculated total Disability Adjusted Life Years (DALYs) for people with MS using secondary data on prevalence, mortality, and an assumption of \$6.5 million Australian per DALY. They concluded that about one third of the disease burden was a result of premature mortality and about two thirds was a result of disability associated with MS.

7.1.4 Middle Eastern Study

Kuwait. Alshubaili and colleagues (2007) conducted the first controlled study of generic QOL for MS patients in the Middle East. They studied 169 consecutive MS clinic attendees at the national neurological hospital in Kuwait. The patients had a mean age of 32, mean duration of illness was 5 years, and mean EDSS was 2.7; 65 percent were female, and 85 percent had relapsing-remitting MS (RRMS).

A comparison group of 171 people from the general population were also studied to provide controls. They were matched to the MS patients by age, gender, education, occupation, and marital status.

Data collection included the WHOQOL survey instrument and the Beck depression inventory. The instruments were translated into Arabic.

The results showed that MS patients had lower QOL across multiple domains, including physical health, psychological health, independence, social relations, spiritual health (men only), and general health. Most differences were statistically significant at $p < 0.0001$.

7.2 Quality of Life—MS-Specific Domains

7.2.1 Introduction

MS has a broad range of impacts on QOL, and many of them are not captured in the generic measures of utility and QOL. Generic measures are by definition intended to cover the major impacts that are found across a wide range of diseases and conditions and so are not expected to capture all of the specific impacts of each disease. As a result, a comprehensive assessment of the burden of MS needs to include supplemental analysis of the effects of MS that are not captured by the generic measures.

Two types of supplemental QOL impact analysis are possible. The first includes impacts of MS that are not included explicitly in the generic measures. Cognitive disability, bladder dysfunction, bowel dysfunction, sleep problems, and sexual dysfunction are common symptoms experienced by MS patients that are not explicitly included in the generic measures. Some portion of the impact of these problems may be captured by broad concepts included in the generic measures, such as the “general health” scale in the SF-36 and the “usual activities” item in the EQ-5D. However, without explicit measurement of these MS-specific impacts, some or most of the scope and depth of these impacts will be lost.

The second type of supplemental analysis includes impacts of MS that are included in sometimes very limited detail in the generic measures. Fatigue is an impact that is not included in any direct way in the EQ-5D, but the SF-36 includes a Vitality scale, although it is based on responses from only four items. In contrast, fatigue-specific scales such as the Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale include 21 and 9 items, respectively.

Depression is an example of a QOL impact that is common in MS but measured only indirectly in the generic measures. The EQ-5D includes one item that covers “anxiety/depression.” Thus, it merges two psychological concepts that are usually considered distinct impacts and includes only one question to assess both. The SF-36 includes a Mental Health scale that is calculated from five items but also merges depression with other mental health issues. In contrast, scales that measure only depression will commonly include many more items just for that one concept. For example, the Beck Depression Inventory has a 7-item version, the CES-D has 10 items, and the PHQ-9 has 9 items. Including larger numbers of items focused on just one concept increases reliability and validity for measuring the impact of depression.

7.2.2 QOL Impacts Not Included in Generic QOL and Utility Measures

Cognitive Disability

Cognitive disability is not included in any of the generic measures. In principle, it is difficult to measure cognitive disability using self-reported survey instruments such as the SF-36 and EQ-5D, because self-perceived cognitive problems may not be accurate assessments when cognitive deficits are present. The cognitive nature of this disability undermines the validity of using self-reported or patient-reported measures (NMSS, 1997). For example, Benedict and colleagues (2004) developed an MS-specific cognitive disability measure, the MS Neurological Questionnaire (MSNQ). However, testing of two versions of the MSNQ, one for objective observers and one for patient self-report, revealed that the patient self-report version sometimes failed to distinguish between cognitive disability and depression, while the objective version had stronger validity.

At the same time, cognitive disability is a major impact of the disease for about half or more of MS patients. Bagert and colleagues (2002) estimated the prevalence of cognitive dysfunction in MS patients at 45 to 65 percent, based on their review of studies on this issue. For example, they cite a natural history study by Amato and colleagues (2002) that found 56 percent of MS patients had cognitive dysfunction in a 10-year follow-up assessment of patients with early-onset MS.

Bagert and colleagues (2002) found that natural history studies of cognitive dysfunction in MS indicated that, once the deficits develop, they are unlikely to improve, and while they may remain stable over time, they may also progress. MS patients with cognitive dysfunction were found to have fewer social interactions, more sexual dysfunction, increased difficulty with household tasks, increased difficulty in operating a car safely, and higher rates of unemployment than MS patients without cognitive dysfunction.

Bagert and colleagues (2002) also indicated that cognitive dysfunction in MS is widely under-recognized. This may be a result of the insensitivity to cognitive dysfunction of the standard neurological history and

physical examination and the standard MS outcome measures such as the EDSS. Even some objective, clinician-reported measures, such as the Mini-Mental Status Examination, have been found to be insensitive to cognitive dysfunction in MS.

Another issue in cognitive dysfunction is that it includes a range of different types of specific cognitive deficits, some of which are found more frequently in MS than others. Bagert and colleagues' (2002) review of the literature found that problems with encoding memory, free recall memory, learning, attention, verbal fluency, and information processing were more frequently observed in MS patients than deficits in executive function, conceptual reasoning, recognition memory, auditory span, or visual span.

Benedict and colleagues (2005) studied cognitive dysfunction in 120 patients with MS recruited consecutively from one MS clinic. Mean age was 44, mean years of education were 15, and mean disease duration was 12 years; 71 percent were female. The MS patients were compared with 44 healthy controls, matched on age, education, race, and gender.

Cognitive function was measured using eight standard neuropsychological tests. Results showed lower (worse) scores for all eight cognitive functioning measures for the MS patients versus the healthy controls.

Limitations of the Benedict and colleagues (2005) study were the moderate sample size and recruitment of MS patients from a single MS clinic in one geographic location. Thus, the magnitude of the differences found in this study may not be generalizable to the population of MS patients. Nonetheless, the very high levels of statistical significance and use of matched healthy controls indicate strong evidence for cognitive impacts of MS.

Prakash and colleagues (2008) conducted a formal meta-analysis of 57 studies of cognitive impairment of patients with relapsing-remitting MS. These studies had 3,891 participants, including 2,042 with RRMS and 1,849 healthy controls, and yielded a total of 755 effect sizes. They found that the impact of relapsing-remitting MS on overall cognitive function was statistically significant and moderate in magnitude compared with healthy controls. Prakash and colleagues (2008) also analyzed the average effect sizes associated with 10 different cognitive domains. Statistically significant impacts of RRMS were found for all 10 domains, with effect sizes that were moderate overall by Cohen's definition (0.4–0.6) but were large for two domains (0.7+).

De Sousa and colleagues (2002) conducted a review of MS literature on cognitive impairments in MS. They found that the consensus among investigators is that 45 to 65 percent of MS patients experience some form of cognitive dysfunction. Their review indicated that cognitive impairment can develop at any time during the course of the disease and in the presence or absence of neurological disability. They indicated that a meta-analysis of 36 published papers on memory impairment in MS found significant abnormalities in all domains of memory function compared with controls.

Simioni and colleagues (2007) studied 106 patients in Switzerland in the early stages of MS. They focused on patients with EDSS \leq 2.5 and disease duration of \leq 5 years. Neuropsychological testing was

conducted on three domains—long-term memory, executive functions, and attention—with impairment defined as performance that was two standard deviations below the mean.

Simioni and colleagues (2007) found that, overall, 29 percent of the early MS patients were cognitively impaired, including 24 percent for memory, 10 percent for attention, and 6 percent for executive functions. The authors concluded that impaired cognition is evident in many MS patients even at early stages of the disease. Impaired cognition may be an initial symptom of MS in patients without neurological disability. This highlights the importance of clinicians looking for cognitive difficulties even at early stages of the disease, because they can have significant impacts on a patient's social, professional, and occupational abilities.

Bladder Dysfunction

Urinary or bladder dysfunction is a symptom commonly reported by MS patients, and it can affect many aspects of daily life. Fear of incontinence or embarrassment may affect QOL by limiting social activities. Residual urine may cause discomfort and increase the risk of urinary tract infections.

Nortvedt and colleagues (2007) studied the prevalence of bladder dysfunction among all 56 MS patients residing in Hordaland County in Norway from 1998 to 2000. Bladder problems were assessed using the International Prostate Symptom Score (I-PSS). Respondents included 54 MS patients, who had mean age of 33 years and mean EDSS of 3.4; 72 percent were female, and 82 percent had a relapsing course of MS.

Results indicated that 79 percent of the males and 49 percent of the females had moderate or severe symptoms of bladder dysfunction according to the summary scale of the I-PSS. Although there was no population-based control group in this study, none of the MS patients had these symptoms at onset of MS so the association of these symptoms with MS seems highly probable. Urological examinations were accepted by 43 patients. All of the males tested exceeded 20mL of residual urine, while 73 percent of the females also exceeded 20mL.

Nortvedt and colleagues (2007) concluded that bladder problems were common among these MS patients, even though they had MS for a relatively short time. The frequency of bladder problems was consistent with the relatively high levels of residual urine found.

Marrie and colleagues (2007) studied bladder symptoms among MS patients participating in the NARCOMS patient registry in the United States and Canada. Their sample included 9,688 MS patients who completed the NARCOMS survey form. These respondents had a mean age of 53, a mean disease duration of 22 years, and a median EDSS score of 3; 75 percent were female.

Data were collected using the bladder/bowel subscale of the Performance Scales disability self-report measures. Urinary symptoms experienced by these respondents included incontinence of small amounts of urine (28%), nocturia (21%), urinary frequency (17%), urgency (17%), difficulty with bladder emptying (13%), urge incontinence (8%), moderate abdominal discomfort (7%), and severe abdominal discomfort (3%).

In addition to symptoms, urinary tract infections (UTIs) were also common: 65 percent of participants reported at least one UTI in the past 6 months, and 8 percent had three or more. The mean number of UTIs was 0.75. Overall, 166 participants were hospitalized for a UTI.

Marrie and colleagues (2007) did not report population-based comparison data for health controls, so some portion of the frequency of urinary symptoms may be because of age or other factors. The overall frequency of UTIs is much higher than the general population; however, self-reported 12-month incidence of UTIs in adult women is much lower than for these MS patients at 11 percent.

Wollin and colleagues (2005) studied continence issues for MS patients in Australia. Participants included 89 MS patients who responded to an advertisement for a survey study. Of those, 62 responded to the full mail survey for a response rate of 70 percent. The mean age of the respondents was 49, and 82 percent were female.

Results indicated that 90 percent reported some bladder difficulties, including bladder urgency (68%), night emptying (64%), frequency (61%), leaking (59%), hesitancy (51%), urge incontinence (47%), incomplete emptying (45%), interrupted stream (39%), and stress incontinence (31%). In addition, 25% reported recurrent UTIs.

This study also included patient focus groups on the problems reported to result from incontinence, which included not working in their usual jobs, reduced productivity, increased fatigue, and frustration. Patients also reported being reluctant to discuss and seek advice and treatment for incontinence issues.

Wollin et al. (2005) concluded that urinary incontinence is common among MS patients and that incontinence adversely affects their day-to-day lives. Limitations of this study include the small sample size and self-selected patient sample. Consequently, the results may not be generalizable to the population of MS patients.

Sleep Problems

Bamer and colleagues (2008) conducted a mail survey study of the prevalence of sleep problems in MS patients through the Greater Washington (state) Chapter of the U.S. National MS Society. The study included 1,063 responses from an initial sample of 7,806 MS patients on the chapter's mailing list. Study participants had a mean age of 51 and mean MS disease duration of 14 years; 81% were female.

Data on sleep outcomes were collected using the Medical Outcomes Study Sleep (MOSS) measure and the Women's Health Initiative Insomnia Rating Scale (WHIIRS). MS patients were found to have significantly greater sleep problems compared with a U.S. general population sample of 1,011 individuals who were previously surveyed using the MOSS. The greater sleep problems for MS patients were statistically significant ($p < 0.001$) across the following domains:

- sleep disturbance (initiation and maintenance),
- respiratory (shortness of breath),
- sleep adequacy,

- daytime somnolence, and
- sleep problems index.

Bamer and colleagues (2008) found that overall 65 percent of MS patients had sleep problems according to the MOSS single indicator of sleep problems. This included 30 percent with severe sleep problems, 22 percent with moderate problems, and 13 percent with mild problems.

Bamer and colleagues (2008) concluded that MS patients have significantly more sleep problems than the general population. This study is vulnerable to recruitment bias because of the low initial response rate of 19 percent. However, the authors indicated that the demographics of their study population are similar to those of the Sonya Slifka MS study population, a cohort believed to be representative of the overall MS population in the United States. This representativeness, combined with the large sample size and high levels of statistical significance, indicate that it is unlikely that recruitment bias would account for all of the differences in sleep problems found in this study between MS patients and the general population, although the true differences may be somewhat higher or lower.

Lobentanz and colleagues (2004) studied sleep quality in a sample of 504 MS patients in Austria and 1,049 healthy subjects as a control group. Data were collected through a postal survey mailed to 1,000 members of the Vienna chapter of the Austrian MS Society, so the overall response rate was 50 percent. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), which includes 19 self-reported questions. The MS patients had a mean age of 51, mean EDSS of 6, and mean disease duration of 16 years; 72 percent were female. The control group had a mean age of 44, and 53 percent were female.

Lobentanz and colleagues (2004) found that sleep quality and sleep efficiency were markedly reduced in comparison to health controls. Overall, reduced sleep quality was almost twice as frequent for MS patients than for the healthy controls (62% versus 32%). Statistically significant differences ($p < 0.001$) between the MS patients and the healthy controls were found across the following domains of the PSQI:

- subjective sleep quality,
- sleep latency,
- habitual sleep efficiency,
- sleep disturbances,
- use of sleep medication,
- daytime dysfunction, and
- global PSQI.

This study is vulnerable to recruitment bias because of the survey response rate of 50 percent. However, the large sample size and high levels of statistical significance indicate that recruitment bias is unlikely to account for all of the differences in sleep problems found in this study between MS patients and the general population, although the true differences may be somewhat higher or lower.

Clark and colleagues (1992) studied sleep problems in a sample of 143 patients with MS. They found the prevalence of sleep problems to be 25 percent among the MS sample and only 8 percent in a control group. They also found that sleep problems were correlated with higher levels of depression and lesion sites that subserve supplemental motor areas.

Sexual Dysfunction

Nortvedt and colleagues (2007) studied the prevalence of bladder dysfunction among all 56 MS patients residing in Hordaland County in Norway from 1998 to 2000. Sexual functioning was measured using the five-question sexual scale from the MSQOL-54, modified to permit an additional response category for each question (i.e., “not relevant to me”) in addition to the original response categories ranging from 1 (no problem) to 4 (very problematic). Respondents included 54 MS patients, who had mean age of 33 years and mean EDSS of 3.4; 72 percent were female, and 82 percent had a relapsing course of MS.

Results indicated that 50 percent of the males and 14 percent of the females reported being somewhat or very dissatisfied with their sexual functioning during the 4 weeks before the investigation. Difficulty getting or keeping an erection was the most frequent problem among the males, whereas difficulty having an orgasm was the most frequent problem among the females. Nortvedt and colleagues (2007) concluded that sexual problems were common among these MS patients. A limitation of this study is the lack of a population-based control group.

7.2.3 QOL Impacts Measured Briefly or Indirectly in Generic QOL and Utility Measures

Fatigue

Fatigue is a common complaint of MS patients, although until recently, it was not assessed in detail by physicians treating MS. Patients have raised concerns that fatigue is not taken seriously by doctors or their family members because it is a “hidden” symptom, with no obvious external manifestations comparable to problems with mobility or upper extremity disabilities. Clinicians have also raised concerns about the potential for multiple causes of fatigue, some of which may be transient and associated with acute relapses, and some of which may be chronic and cause persistent impacts on QOL.

Fatigue can be measured through detailed symptom-specific scales, such as the Modified Fatigue Impact Scale (MFIS) that has 21 items in its complete version and 5 items in a short version, and the Fatigue Severity Scale (FSS) that includes 9 items. A similar scale for Vitality, which is calculated from four items, is included as one of the eight scales in the SF-36. The EQ-5D does not include any item that directly addresses fatigue.

Benedict and colleagues (2005) studied fatigue in 120 patients with MS recruited consecutively from one MS clinic. Mean age was 44, mean years of education was 15, and mean disease duration was 12 years; 71 percent were female. The MS patients were compared with 44 healthy controls who were matched on age, education, race, and gender.

Fatigue was measured with the Fatigue Severity Scale (FSS). Results showed higher fatigue for MS patients than for the healthy controls, with a mean FSS of 4.7 for the MS patients versus 2.7 for the healthy controls ($p < 0.001$).

Tellez and colleagues (2006) studied the prevalence of fatigue and changes in fatigue over time in a cohort of 206 MS patients. The patient sample was drawn from a group of consecutive MS patients seen in an outpatient clinic in Barcelona, Spain. The primary measure of fatigue was the FSS, with data also collected on the Modified Fatigue Impact Scale (MFIS), Beck Depression Inventory (BDI), Expanded Disability Status Scale (EDSS), and incidence of relapses.

Among respondents, the mean age was 36 years, 68 percent were female, median time since diagnosis was 7 years, and 73 percent had relapsing-remitting MS. At first assessment, 114 or 55 percent of the sample had fatigue, 15 percent had borderline fatigue, and 30 percent were non-fatigued.

After a mean follow-up period of 18 months, 99 of the 114 (87%) patients fatigued at baseline remained fatigued. Only 6 of the 114 (5%) had shifted to the non-fatigued group. Of the 62 patients in the non-fatigued group at baseline, 36 (58%) remained non-fatigued at follow-up, while 16 (25%) had shifted to the fatigued group.

Statistical analysis showed that the mean FSS score increased somewhat over time, but the changes were only weakly statistically significant ($p = 0.08$). Correlation analysis indicated that changes in depression over time measured by the BDI were only modestly correlated with changes in FSS over time ($r = 0.31$), but this correlation was statistically significant ($p < 0.0001$). Changes in physical disability measured by the EDSS were not correlated with changes in FSS ($r = 0.01$).

The authors concluded that fatigue is a persistent symptom of MS. Most patients with fatigue remain with fatigue over a follow-up period averaging 18 months. Moreover, the levels of fatigue remain stable or increase modestly over time.

Hemmett and colleagues (2004) studied fatigue and other MS symptoms, SF-36 QOL scores, and EQ-5D utility scores using two consecutive postal surveys in a sample of 8,614 MS patients and caregivers who were in the database of the UK MS Trust. Of the MS patients responding to the first survey, 1,993 of 2,265 MS patients (88%) reported moderate or severe fatigue.

The second survey included 1,992 MS respondents to the first survey who agreed to participate in the second survey. Of these, 1,554 responded to the second survey for a response rate of 78 percent. This survey included the SF-36 and EQ-5D. The large impact of fatigue was indicated by the vitality scale in the SF-36, which had a mean score of 31, lower than all other scale scores except physical functioning and role-physical.

The authors concluded that the prevalence of fatigue in MS is important and may not have received sufficient attention from care providers or policy makers, who may use measures of disease severity that do not address fatigue, such as the EDSS and EQ-5D. Limitations of this study include the low response rates, which mean the respondents may be a self-selected group that is not representative of the overall

MS population. Nonetheless, the large numbers of respondents and very high prevalence of reported fatigue mean that low levels of fatigue are unlikely to be found in a population-based sample.

Depression

Solari, Ferrari, and Radice (2006) conducted a longitudinal study of depression in a sample of 400 MS patients randomly selected from the Lombardy Region Health Register who resided in Milan (Italy). Data were collected in 1999 and 2004. Depression was measured using the Chicago Multiscale Depression Inventory (CMDI), which includes 42 self-reported items, for the 2004 data collection wave only. A total of 181 eligible MS patients responded to the 2004 CMDI survey, for a 45 percent response rate from the original 1999 cohort sample.

Results showed that impaired CMDI mood was found for 27 percent of MS patients and 19 percent of their significant others. The latter figure was twice the rate found for healthy controls in a separate CMDI validation study. The authors concluded that depressive symptoms were common in this cohort of MS patients. Limitations of this study are the low response rate and that MS patients were from only one city in Italy. Thus, the magnitude of the results may not be generalizable to the population of MS patients, where the rates of depression may be somewhat higher or lower.

Benedict and colleagues (2005) studied depression in 120 patients with MS recruited consecutively from one MS clinic. Their mean age was 44, mean years of education was 15, and mean disease duration was 12 years; 71 percent were female. The MS patients were compared with 44 healthy controls who were matched on age, education, race, and gender.

Depression was measured with the Beck Depression Inventory (BDI), the BDI-Fast Screen (BDI-FS), and the Center for Epidemiological Studies Depression Scale (CESD-10). Results showed higher (worse) depression scores for all three depression measures for the MS patients versus the healthy controls.

7.3 Utility Measures

7.3.1 Introduction

Utility measures are similar to QOL measures, although they are based in economic theory rather than psychological theories that underlie QOL concepts. In particular, one of the foundations of the economic theory of consumer behavior is that consumers are “utility maximizers,” and by analyzing the factors affecting their utility functions their economic behavior can be predicted.

Utility measures have been applied frequently in cost-effectiveness analysis of pharmaceutical therapies, including MS disease-modifying drugs. Utilities are defined as preferences for health states on a scale from 1.0, representing full health or ideal health, down to 0.0, representing death. Negative utility scores are also sometimes allowed for “states worse than death,” such as continuous suffering or severe pain. The utility scores are thus expressed as proportions between 0 and 1 and can be used to weight remaining years of life for patients to calculate quality-adjusted life years (QALYs). For example, a disease-modifying drug that is partially effective for MS may result in a measurable gain in QALYs by increasing the average utility score for the remaining years of life for an MS patient from, hypothetically,

0.55 to 0.75, if some disability is delayed and some relapses are prevented, even if the expected life span for the patient remains the same.

An advantage of utility scores is that they provide a single metric for health and thus enable calculations of QALYs for economic studies. Other QOL scales are multidimensional, providing separate scores for domains such as physical health, social health, mental health, and fatigue. This multidimensional nature makes it difficult to calculate metrics such as QALYs for comparison with costs in economic studies.

On the other hand, the advantage of multidimensional scales is that they provide a more detailed and comprehensive understanding of the range of domains affecting a person's QOL. Thus, there is a tradeoff in choosing between utilities (which provide a single metric for QALY analysis but less detailed and less comprehensive information on QOL issues) and QOL scales (which provide more detailed and comprehensive analysis of QOL issues but are difficult to translate into a single metric for QALY analysis).

Utility scores have generally been calculated using a well-validated, generic survey instrument, the EQ-5D, or EuroQol. The EQ-5D can contain two different measurement approaches. The first is a descriptive method that includes five survey questions on five domains of health-related QOL: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The response categories for each item include three levels for each domain, indicating "no problems," "some problems," or "major problems." The answers to these questions are related to a health state classification system and used to calculate utility scores. The second measurement approach is a visual analog scale that asks respondents to directly indicate their current level of overall health on a scale from 0 to 100.

Several other utility measurement instruments are available, including the SF-6D (derived from the SF-36) and the Health Utilities Index Mark III (Fisk et al., 2005). However, the EQ-5D has been the most widely used in cost-effectiveness and cost-utility studies. A recent head-to-head comparison of these three utility measures with MS patients found them all to be acceptable in terms of validity and reliability, and their results were correlated (Fisk et al., 2005). Fisk and colleagues (2005) found fairly good correlations from all three utility measures with clinical measures of disability used in MS.

The loss in utility as a result of MS was consistent across the European and American studies at between 0.20 and 0.31 out of a range of 0.0 to 1.0. Thus, an overall estimate of the burden of MS in terms of utility is an average loss of 0.25. Using the U.K. population norm for the overall population of 0.86 as a baseline, this 0.25 decline in utility can be interpreted as a loss of 29 percent of utility by people with MS compared with an overall population norm.

7.3.2 Utility Studies in MS

Until recently, most studies of utility scores in MS focused on cost-effectiveness analysis for pharmaceutical research. Large-scale population studies of utility scores in MS suitable for analysis of the economic burden of MS have become available mainly within the past 5 years. European studies are more numerous, although a study in the United States was also recently conducted.

European Studies. McCrone and colleagues (2008) conducted a mail survey of a random sample of 4,000 MS patients who were members of the MS Society of Great Britain and Northern Ireland. Surveys were completed by 1,942 members, or 49 percent of the sample. The EQ-5D was included along with Guy's Neurological Disability Scales and other measures of service use and costs. Among respondents, the mean age was 55 years, 72 percent were female, and the mean duration of the disease was 179 months (15 years).

McCrone and colleagues (2008) noted that the population norm for the EQ-5D has been reported to be 0.86 for the United Kingdom by Kind and colleagues (1999). Therefore, utility scores for the MS patients in this sample were significantly lower. In addition, the mean score of 0.41 for MS patients was lower than the mean utility scores found by Brazier and colleagues (2004) for a number of other diseases or characteristics: irritable bowel syndrome was 0.66, lower back pain was 0.64, older age was 0.61, leg ulcers was 0.55, chronic obstructive pulmonary disease was 0.54, and osteoarthritis was 0.44. From McCrone and colleagues (2008), the mean utility score was 0.41, the median score was 0.52, and the range was -0.59 to 1.0.

A limitation of this study is the survey response rate of 49 percent, which could result in some nonrespondent bias. However, the authors reported that the characteristics of their sample were similar to those of the sample used by Kobelt and colleagues (2006) in a similar study of U.K. costs and utilities for MS patients.

Kobelt and her colleagues (2006a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006h, 2006i, 2006j) recently conducted a series of studies with similar methodologies on MS costs and utility scores in nine European countries. They used mail surveys of MS patients drawn from a range of sources in different countries, including members of national MS patient organizations and MS Societies and MS patients from clinics or MS centers. The EQ-5D was used to measure utility in all of the studies and they all used a similar data collection methodology. These studies provide a broad range of data on the impact of MS on utility scores.

Table 17 summarizes the results from these nine European studies. The mean utility scores are quite consistent, ranging from 0.51 to 0.62, despite the range in survey response rates and differences in patient characteristics between countries. The mean losses in utility, compared with an age- and gender-matched general population, are also quite consistent at between 0.20 and 0.31.

A limitation of these studies is the low response rates, which were below 50 percent in seven of the nine countries studied. Nonetheless, the mean utility score results were consistent across countries.

Table 17. Summary of Kobelt et al. Studies of MS EQ-5D Utility Scores in Nine European Countries

	United Kingdom	Germany	Netherlands	Belgium	Sweden	Switzerland	Austria	Spain	Italy
Sampling frame	12,968	7,325	3,000	2,150	2,100	2,500	2,995	5,800	3,000
Respondents	2,048	2,793	1,549	799	1,339	1,101	1,019	1,848	921
Response rate	16%	38%	52%	37%	64%	44%	34%	32%	31%
Mean age	51 years	45	47	48	53	53	50	45	46
Percent female	75%	72%	69%	68%	73%	64%	70%	64%	66%
Percent employed	28%	41%	37%	40%	41%	35%	30%	30%	42%
Mean time since diagnosis (years)	12	7	10	13	14	16	15	12	12
Percent mild MS	21%	47%	48%	46%	29%	38%	41%	36%	31%
Percent moderate MS	60%	36%	40%	33%	46%	36%	36%	45%	47%
Percent severe MS	19%	12%	11%	20%	25%	23%	22%	18%	20%
Mean EDSS		3.8	3.9	4.2	5.1	4.5	4.4	4.5	4.6
Mean utility score	0.51	0.62	0.61	0.51	0.55	0.59	0.55	0.55	0.53
Utility loss vs. matched general population		0.2	0.24	0.3	0.23	0.3	0.27	0.28	0.31

Source: Kobelt et al., 2006a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006h, 2006i, 2006j.

United States Study. Kobelt and colleagues (2006b) also conducted a mail survey in the United States using 4,000 members of the NARCOMS MS patient registry who were taking MS disease-modifying drugs. Respondents included 1,909 patients, representing a 48 percent response rate from the original sampling frame. The mean age of the patients was 49 years, 75 percent were female, 41 percent were employed, and mean time since diagnosis was 13 years. EDSS scores showed that 35 percent of the sample had mild MS (EDSS \leq 3.5), 43 percent had moderate MS (EDSS 4.0–6.0), and 22 percent had severe MS (EDSS \geq 6.5). As a result, the respondents in this U.S. study had broadly similar characteristics to the patients in the European studies.

EQ-5D scores were available for 1,878 patients. The mean utility score was 0.70. This score and those at each severity level were lower than those for age- and sex-matched sample from the general population (using U.K. values).

Kobelt and colleagues (2006b) transformed the average utility loss into an average loss of 0.255 QALYs per patient per year. A willingness to pay figure of \$60,000 per QALY gained was taken from an estimate made by several U.S. health economists (Cutler and Richardson, 1998). This allowed the intangible costs of lost utility as a result of MS to be calculated as \$15,315 per patient per year.

A limitation of this study is that it includes mainly MS patients who were taking MS disease-modifying drugs. As a result, they may not be representative of the entire population of MS patients. Another limitation is the survey response rate of 48 percent, which could result in some nonrespondent bias. However, the authors reported that there was no difference in the age or gender distribution between respondents and nonrespondents.

7.4 Impacts on Family and Friends

People with MS often require help performing daily tasks because of health care problems and functional and cognitive impairments. This care is mostly provided by informal caregivers, principally spouses and other relatives. In addition to the direct cost related to the hours of care that informal caregivers provide, the disabling aspects of the disease, its impact on mortality, the financial burdens, and MS's uncertain course often create additional psychological burdens, stress, and anxiety for the informal caregivers, especially those living with the person with MS. The stress and physical burden of caring for MS patients, especially for those with severe impairments, may have an adverse effect on the psychological and physical health of caregivers and increase their health care use. Interestingly, the stress of caring for someone with cognitive impairment due to MS can cause as much or more stress than caring for an MS patient with severe physical disabilities.

Calculating the indirect costs of stress/burden and increased psychological health problems is difficult and arguably subjective, but the research suggests that they are a significant portion of the burden of MS to society. The studies summarized below suggest two main findings: (1) the burden/stress on caregivers is substantial, but it is far less than it is on MS patients; and (2) the amount of burden/stress varies by level of disability. A conservative estimate of the economic value of stress/burden for caregivers is 10 percent of what it is estimated for MS patients by EDSS level.

7.4.1 *Characteristics of Studies Addressing the Indirect Costs to Informal Caregivers*

We identified 13 studies—12 original studies and one systematic review—that addressed the indirect costs of informal caregivers: caregiver burden, caregiver labor force participation, and caregiver health and health care use. These studies were conducted in Australia, Canada, Italy, the Netherlands, Norway, the United Kingdom, and the United States. Key characteristics of these studies are summarized in Table 18. Many of these studies have small sample sizes, and the representativeness of the sample is open to challenge for almost all of the studies. Most of the studies did not provide data by the level of impairment of the person with MS, and some did not provide scores for their total sample. Few of the studies estimated financial costs of the indirect burdens incurred by caregivers.

Table 18. Key Characteristics of Studies on the Indirect Costs to Informal Caregivers of MS Patients

Geographic Location	Citation	Sample Size	Sample Description
Systematic international literature review	McKeown, Porter-Armstrong, and Baxter (2003)	No patients	Articles published 1990 to 2002
Melbourne, Australia	Kahn, Pallant, and Brand (2007)	62 caregivers; 101 patients recruited from 200 patients invited to participate	Patients recruited from an MS database maintained by a tertiary hospital; participants in the database were recruited through the MS Society Victoria and public and private neurology clinics
Queensland, Australia	Pakenham (2001)	89 MS caregivers and their care recipients derived from 140 persons with MS	Recruited from hospitals, local MS Society, and via advertisements
Ontario, Canada	Aronson (1997)	345 caregivers of MS patients; comparison group of 1,692 able-bodied persons of approximately the same sex, age, and education from the general Canadian population	Random sample of the MS Society membership, stratified by urban/rural location; and consecutive visits over a 6–8 week period to the five MS clinics in Ontario
Italy	Amato et al. (2002)	552 patients with MS and their caregivers	Outpatients with MS were enrolled at 44 treatment centers across Italy
Italy	Patti et al. (2007)	445 caregivers; comparison group is Italian normative sample for SF-36 results that included 2,031 people from the general population	Six MS centers
Milan, Italy	Solari, Ferrari, and Radice (2006)	205 patients with MS, 151 of their significant others	Study is a 5-year follow-up of 251 people who participated in 1999 postal survey who were reassessed in 2004; the sample was drawn from the Lombardy Region Health Register.
Rotterdam and Amsterdam, the Netherlands	Janssens et al. (2003)	101 recently diagnosed patients with MS and 78 of their partners	Departments of neurology of hospitals in the area

(continued)

Table 18. Key Characteristics of Studies on the Indirect Costs to Informal Caregivers of MS Patients (continued)

Geographic Location	Citation	Sample Size	Sample Description
Rogaland and Hordaland counties, Norway	Figved et al. (2007)	76 of 93 caregivers of MS patients in sample	Patients at neurology departments of the two main hospitals in the counties
Madrid, Spain	Rivera-Navarro, Morales-Gonzalez, and Benito-Leon (2003)	91 patients and their "primary" caregivers (i.e., who spent at least 1 hour per day caring for a person with MS); of 371 MS patients, only 91 had a caregiver that met this definition	Sample drawn from larger sampling frame of MS patients recruited at 13 Madrid Hospital Neurology Outpatients Clinics
Nottingham, England, United Kingdom	Chipcase and Lincoln (2001)	51 caregivers	Patients at MS management clinic at hospital with a large neurology unit
USA	Quig et al. (2007)	1,461 caregivers were recruited by asking approximately 12,000 patients to refer their caregivers to a survey	Caregivers of persons with MS participating in the North American Research Committee on Multiple Sclerosis (NARCOMS) database
Detroit area, United States	Sherman et al. (2007)	74 "significant others of MS patients"	MS patients recruited from an MS clinic at a tertiary care teaching hospital

7.4.2 Caregiver Burden and Quality of Life

Caregiver burden refers to the psychological and emotional stress that occurs as a result of the help and support that caregivers provide to people with MS or other persons with disabling chronic illnesses. Caregiver burden is important but difficult to define and meaningfully measure. According to one definition, caregiver burden is the extent to which caregivers feel that their emotional or physical health, social life, and financial status have suffered as a result of caring for their relatives (Zarit, Reever, and Bach-Peterson, 1980). Several measures of caregiver burden were used in these studies, although the Zarit Caregiver Burden Scale and the Caregiver Stress Index were both used in more than one study. The SF-36 was used in several studies to measure health-related quality of life. In only a few studies were results compared to the general population or to a population that was not caring for people with disabilities. The results from these studies are summarized in Table 19.

All of the studies found at least some caregiver burden or at least some adverse impact on QOL of caring for a person with MS. In general, the level of burden varied by the level of disability of the person with MS: at low levels of EDSS scores, the burden was low; at high levels of EDSS scores, the burden was high.

As expected, the strain of MS was less on the caregivers than on the persons with MS. The following studies compared the study results with another population:

Kahn, Pallant, and Brand (2007) reported that, measured by the Assessment of Quality of Life (AQoL), caregivers scored 0.83 compared to 0.44 for MS patients. In addition, measured by the General Self Efficacy Scale, caregivers scored 16.77 compared to 8.88 for MS patients.

Using the SF-36, Patti and colleagues (2007) found that caregivers scored lower on health-related QOL than the Italian normative sample, except for physical functioning and bodily pain. However, the magnitude of these differences was often small. The biggest differences were for the mental health, vitality, and general health scores.

Using the SF-36, Solari, Ferrari, and Radice (2006) reported that the profile of significant others was similar to that of Italian norms, except for a worse score in the role limitation-emotional domain and, to a lesser extent, in the role limitation-physical and pain domains.

Using the SF-36, Janssens and colleagues (2003) found that partners of recently diagnosed patients with MS had statistically significantly more severe stress, although scores on most domains were not different.

Calculating distress scores, Figved and colleagues (2007) reported that MS spouses had much higher levels of distress than the friends of MS patients.

Using the Global Symptom Index of the Brief Symptom Inventory, Sherman and colleagues (2007) found that caregivers had higher average levels of psychological stress than in a normative sample. Using the Satisfaction with Life Scale, average satisfaction was comparable to college students and health workers.

Table 19. Summary of Studies on Caregiver Burden and Quality of Life

Citation and Geographic Location	Results																				
McKeown, Porter-Armstrong, and Baxter (2003) Systematic Review	<ul style="list-style-type: none"> ▪ Two studies demonstrated negative impact of being a caregiver on quality of life 																				
Kahn, Pallant, and Brand (2007), Melbourne, Australia	<ul style="list-style-type: none"> ▪ Measured by the Caregiver Strain Index (CSI), 42% of caregivers were strained ▪ Measured by the caregiver Self-Reported Burden (SRB), the mean was 35 (with a possible range of 0–100) ▪ Significant differences in caregiver strain measured by SRB by EDSS groups, with severe EDSS scores recording higher scores than mild and moderate groups, but not with CSI ▪ Measured by the Assessment of Quality of Life (AQoL), caregivers scored 0.83 compared to 0.44 for MS patients ▪ Measured by the General Self Efficacy Scale, caregivers scored 16.77 compared to 8.88 for MS patients 																				
Pakenham (2001), Queensland, Australia	<p data-bbox="526 730 1032 762">Frequency of Problems Reported by Caregivers</p> <table border="1" data-bbox="526 768 1409 1220"> <thead> <tr> <th data-bbox="743 779 841 810">Problem</th> <th data-bbox="1166 779 1295 810">Percent (%)</th> </tr> </thead> <tbody> <tr> <td data-bbox="526 821 862 852">Illness limitations and demand</td> <td data-bbox="1214 821 1247 852">17</td> </tr> <tr> <td data-bbox="526 863 740 894">Emotional distress</td> <td data-bbox="1214 863 1247 894">16</td> </tr> <tr> <td data-bbox="526 905 878 936">Demands on caregiver's routine</td> <td data-bbox="1214 905 1247 936">11</td> </tr> <tr> <td data-bbox="526 947 902 978">Care recipient behavioral changes</td> <td data-bbox="1214 947 1247 978">10</td> </tr> <tr> <td data-bbox="526 989 748 1020">Financial difficulties</td> <td data-bbox="1214 989 1247 1020">10</td> </tr> <tr> <td data-bbox="526 1031 837 1062">Physical strain of caregivers</td> <td data-bbox="1214 1031 1247 1062">8</td> </tr> <tr> <td data-bbox="526 1073 927 1104">Dependence-independence conflicts</td> <td data-bbox="1214 1073 1247 1104">7</td> </tr> <tr> <td data-bbox="526 1115 716 1146">Loss of intimacy</td> <td data-bbox="1214 1115 1247 1146">6</td> </tr> <tr> <td data-bbox="526 1157 813 1188">Sustained family relations</td> <td data-bbox="1214 1157 1247 1188">5</td> </tr> </tbody> </table>	Problem	Percent (%)	Illness limitations and demand	17	Emotional distress	16	Demands on caregiver's routine	11	Care recipient behavioral changes	10	Financial difficulties	10	Physical strain of caregivers	8	Dependence-independence conflicts	7	Loss of intimacy	6	Sustained family relations	5
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Sustained family relations	5																				
Aronson (1997), Ontario, Canada	<ul style="list-style-type: none"> ▪ Using the QOL questions from the General Social Survey/Canada, caregivers were less likely to be very satisfied with their finances, family relations, friendships, and life as a whole ▪ Poorer QOL was associated with being a spouse, longer duration of caregiving, moderate or worse symptoms in the MS patient, and instability in the disease 																				

(continued)

Table 19. Summary of Studies on Caregiver Burden and Quality of Life (continued)

Citation and Geographic Location	Results																																				
Patti et al. (2007), Italy	<ul style="list-style-type: none"> ▪ Using the SF-36, caregivers were lower on health-related QOL than the Italian normative sample, except for physical functioning and bodily pain. However, the magnitude of the effect was often small; biggest differences were for the mental health, vitality, and general health scores <p style="margin-left: 20px;">Distribution of SF36 Scores of Caregivers and an Italian Normative Sample</p> <table border="1" style="margin-left: 20px; width: 100%;"> <thead> <tr> <th style="text-align: center;">SF-36 Dimension</th> <th style="text-align: center;">Caregivers</th> <th style="text-align: center;">Normative</th> <th style="text-align: center;">P-value</th> </tr> </thead> <tbody> <tr> <td>Physical functioning</td> <td style="text-align: center;">86</td> <td style="text-align: center;">84</td> <td style="text-align: center;">0.239</td> </tr> <tr> <td>Role physical</td> <td style="text-align: center;">74</td> <td style="text-align: center;">78</td> <td style="text-align: center;">0.025</td> </tr> <tr> <td>Role emotional</td> <td style="text-align: center;">71</td> <td style="text-align: center;">76</td> <td style="text-align: center;">0.010</td> </tr> <tr> <td>Social functioning</td> <td style="text-align: center;">75</td> <td style="text-align: center;">77</td> <td style="text-align: center;">0.027</td> </tr> <tr> <td>Bodily pain</td> <td style="text-align: center;">80</td> <td style="text-align: center;">74</td> <td style="text-align: center;"><0.001</td> </tr> <tr> <td>Mental health</td> <td style="text-align: center;">61</td> <td style="text-align: center;">67</td> <td style="text-align: center;"><0.001</td> </tr> <tr> <td>Vitality</td> <td style="text-align: center;">58</td> <td style="text-align: center;">62</td> <td style="text-align: center;"><0.001</td> </tr> <tr> <td>General health</td> <td style="text-align: center;">61</td> <td style="text-align: center;">65</td> <td style="text-align: center;"><0.001</td> </tr> </tbody> </table>	SF-36 Dimension	Caregivers	Normative	P-value	Physical functioning	86	84	0.239	Role physical	74	78	0.025	Role emotional	71	76	0.010	Social functioning	75	77	0.027	Bodily pain	80	74	<0.001	Mental health	61	67	<0.001	Vitality	58	62	<0.001	General health	61	65	<0.001
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Solari, Ferrari, and Radice (2006), Milan, Italy	<ul style="list-style-type: none"> ▪ Using the SF-36, the profile of significant others was similar to that of Italian norms, except for worse scores in the role limitation-emotional domain and, to a lesser extent, in the role limitation-physical and pain domains ▪ Role-limitation-emotional domain, mean 66.1; norms, mean 76.2 																																				
Janssens et al. (2003), Rotterdam and Amsterdam, the Netherlands	<ul style="list-style-type: none"> ▪ Using the SF-36, 40% of partners of recently diagnosed MS patients had clinically high levels of anxiety, significantly higher than a general Dutch population sample (mean score of partners 6.4 vs. 5.1 for controls) ▪ Using the SF-36, 24% of partners of recently diagnosed MS patients had severe distress, significantly higher than a general Dutch population sample ▪ Scores on the SF-36 depression were not significantly different, although partners were more depressed than the general Dutch population ▪ Partners did not differ significantly in mean SF-36 scores from general population controls, except that they reported less pain ▪ Partners of patients with EDSS scores of less than 3.0 had consistently better scores than partners of patients with EDSS scores of 3.0 or higher 																																				

(continued)

Table 19. Summary of Studies on Caregiver Burden and Quality of Life (continued)

Citation and Geographic Location	Results																		
Figved et al. (2007), Rogaland and Hordaland counties, Norway	<ul style="list-style-type: none"> ▪ The study did not compare caregiver results to individuals not involved with a person with disability; however, they did compare results with friends of MS patients, who might be expected not to be greatly affected by the problems of the person with MS ▪ Caregiver totals in the paper appear to be in error because the numbers given are those of MS spouses, although they were a substantial vast majority of respondents 																		
Distress Scores for MS Spouses and MS Friends																			
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th data-bbox="695 722 797 749">Measure</th> <th data-bbox="980 722 1127 749">MS Spouses</th> <th data-bbox="1216 722 1349 749">MS Friends</th> </tr> </thead> <tbody> <tr> <td data-bbox="561 764 813 791">Personal distress scale</td> <td data-bbox="1029 764 1078 791" style="text-align: center;">5.6</td> <td data-bbox="1256 764 1305 791" style="text-align: center;">0.9</td> </tr> <tr> <td data-bbox="561 806 732 833">Life upset scale</td> <td data-bbox="1029 806 1078 833" style="text-align: center;">4.1</td> <td data-bbox="1256 806 1305 833" style="text-align: center;">0.3</td> </tr> <tr> <td data-bbox="561 848 802 875">Negative feeling scale</td> <td data-bbox="1029 848 1078 875" style="text-align: center;">3.0</td> <td data-bbox="1256 848 1305 875" style="text-align: center;">0.3</td> </tr> <tr> <td data-bbox="561 890 911 917">Relative Stress Scale total score</td> <td data-bbox="1013 890 1094 917" style="text-align: center;">12.6</td> <td data-bbox="1256 890 1305 917" style="text-align: center;">1.4</td> </tr> <tr> <td data-bbox="561 932 894 995">General Health Questionnaire, 12-item version</td> <td data-bbox="1013 932 1094 959" style="text-align: center;">14.1</td> <td data-bbox="1240 932 1321 959" style="text-align: center;">12.1</td> </tr> </tbody> </table>		Measure	MS Spouses	MS Friends	Personal distress scale	5.6	0.9	Life upset scale	4.1	0.3	Negative feeling scale	3.0	0.3	Relative Stress Scale total score	12.6	1.4	General Health Questionnaire, 12-item version	14.1	12.1
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	<ul style="list-style-type: none"> ▪ Using the Neuropsychiatric Inventory (NPI) Caregiver Distress Scale, the average score for caregivers was 4.7 ▪ Using the NPI, 51% of caregivers reported at least one neuropsychiatric symptom 																		
Rivera-Navarro, Morales-Gonzalez, and Benito-Leon (2003), Madrid, Spain	<ul style="list-style-type: none"> ▪ Using a modified version of the Zarit Caregiver Burden Interview, 53.8% of primary caregivers reported no burden, 22% reported mild burden, and 24% reported severe burden ▪ Only 25% of MS patients in the study had a “primary caregiver” defined as spending at least 1 hour per day in the care of the MS patient 																		

(continued)

Table 19. Summary of Studies on Caregiver Burden and Quality of Life (continued)

Citation and Geographic Location	Results																										
Chipcase and Lincoln (2001), Nottingham, England, United Kingdom	<ul style="list-style-type: none"> ▪ Average Caregiver Strain Index was 6.38, with 54% of carers not strained and 46% of carers strained <p>Percentage of Carers Reporting Strain, by Domain</p> <table border="1" data-bbox="526 432 1377 940"> <tbody> <tr><td>Sleep disturbance</td><td>48</td></tr> <tr><td>Inconvenience</td><td>46</td></tr> <tr><td>Physical strain</td><td>30</td></tr> <tr><td>Confinement</td><td>51</td></tr> <tr><td>Family changes</td><td>40</td></tr> <tr><td>Personal plan changes</td><td>58</td></tr> <tr><td>Other demands on time</td><td>52</td></tr> <tr><td>Emotional adjustments</td><td>48</td></tr> <tr><td>Upsetting behavior</td><td>52</td></tr> <tr><td>Partner/child has changed</td><td>56</td></tr> <tr><td>Work adjustments</td><td>50</td></tr> <tr><td>Financial strain</td><td>54</td></tr> <tr><td>Feeling overwhelmed</td><td>52</td></tr> </tbody> </table>	Sleep disturbance	48	Inconvenience	46	Physical strain	30	Confinement	51	Family changes	40	Personal plan changes	58	Other demands on time	52	Emotional adjustments	48	Upsetting behavior	52	Partner/child has changed	56	Work adjustments	50	Financial strain	54	Feeling overwhelmed	52
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Quig et al. (2007), USA	<ul style="list-style-type: none"> ▪ Using the Zarit Caregiver Burden Interview, the overall burden was very mild (22.9) ▪ Average Zarit scores varied by type of MS: no burden (19.1) for relapsing-remitting (mild-moderate burden starts at 20), mild-moderate (26.7) burden for primary progressive, and mild-moderate (20.4) burden for secondary progressive 																										
Sherman et al. (2007), Detroit, USA	<ul style="list-style-type: none"> ▪ Using the Global Symptom Index of the Brief Symptom Inventory, significant others' psychological distress scores were converted to T scores based on a nonclinical population stratified by gender; the mean level of psychological stress (56.5) was higher than that observed in the normative sample (50.0) ▪ Nearly half (46%) of the significant others reported stress levels with T scores of 60 and above and 23% of the sample reported stress levels with T scores of 63 and higher, which is the cutoff for clinical significance ▪ Using the Satisfaction with Life Scale, average satisfaction with life score was 24.3, which is comparable to college students (23.7) and health workers (23.6); 12.2% of the significant others had life satisfaction scores more than one standard deviation below the normative mean ▪ Using the interpretative guidelines for the Satisfaction with Life Scale, 6.8% of caregivers were very or extremely dissatisfied with their life 																										

Closely related to the level of caregiver burden and stress is whether these factors result in negative health outcomes and increased health care utilization for caregivers. Only a few studies have addressed the issue of health of caregivers. The studies reporting data on this issue are summarized in Table 20. Almost all of the studies that report a negative impact do so for depression or some other mental health problem. Data on the impact on physical health are much less common.

Table 20. Summary of Study of Impact on Caregiver Health and Use of Health Services

Citation and Geographic Location	Results
McKeown, Porter-Armstrong, and Baxter (2003), Systematic international literature review of articles from 1990 to 2002	<ul style="list-style-type: none"> ▪ Five studies found that MS caregivers reported deficits in their physical health ▪ Two studies that attempted to establish a causal link between caregiving and health have conflicting results ▪ One study found inverse relationship between care recipient dependency and health-promoting behavior
Kahn, Pallant, and Brand (2007), Melbourne, Australia	<ul style="list-style-type: none"> ▪ 12% of caregivers were receiving treatment for depression ▪ Caregivers took an average of one medication
Solari, Ferrari, and Radice (2006), Milan, Italy	<ul style="list-style-type: none"> ▪ Using the Chicago Multiscale Depression Inventory, the study found that 19% of caregivers had a depressed mood—twice as high as healthy controls
Figved et al. (2007), Rogaland and Hordaland counties, Norway	<ul style="list-style-type: none"> ▪ Using the Neuropsychiatric Inventory (NPI) Caregiver Distress Scale, the average score for caregivers was 4.7 ▪ Using the NPI, 51% of carers reported at least one neuropsychiatric symptom
Janssens et al. (2003), Rotterdam and Amsterdam, the Netherlands	<ul style="list-style-type: none"> ▪ Examining newly diagnosed patients and their partners, study found that they did not differ from controls in mean scores for depression ▪ In the early phase after diagnosis of MS, patients and their partners experienced substantial emotional burden of disease: approximately 50% of patients and partners had clinically relevant levels of either anxiety or distress
Rivera-Navarro, Morales-Gonzalez, and Benito-Leon (2003), Madrid, Spain	<ul style="list-style-type: none"> ▪ Only 25% of MS patients in the study had a “primary caregiver” defined as spending at least 1 hour per day in the care of the MS patient ▪ 13.2% of primary caregivers reported taking an antidepressive drug ▪ Eight studies found providing care can have a detrimental effect on psychological well-being
Quig et al. (2007), USA	<ul style="list-style-type: none"> ▪ 28% of caregivers reported high blood pressure ▪ 26% reported high cholesterol ▪ 13% reported chronic headache ▪ 13% reported persistent trouble sleeping ▪ 17% reported depression or anxiety

8. CONCLUSIONS

This literature review finds that multiple sclerosis (MS) imposes substantial economic burdens on MS patients, their families, and society as a whole. Moreover, these burdens span a broad range of impacts, including direct costs, indirect costs, quality of life (QOL), and other intangible costs.

Globally, the median estimated prevalence of MS is 30 people per 100,000. However, the median prevalence is higher in Europe and North America. Countries with the highest estimated prevalence include Hungary (176), Slovenia (150), Germany (149), United States (135), Canada (133), Czech Republic (130), Norway (125), Denmark (122), Poland (120), and Cyprus (110).

Estimated direct costs of MS vary considerably across studies because of differences in cost categories included, the costing methodologies used, and health care and social support systems in place in

different countries. Differences in patient characteristics and the representativeness of study samples may also impact costs because some study samples represent a mild MS population, whereas others are more representative of patients with severe MS. However, the direct costs of MS are large and tend to increase two- or threefold as disease severity increases from Expanded Disability Status Scale (EDSS) level 2.0 to levels 4.0 or 6.5. These relative cost estimates may be useful for estimating the direct cost of MS for countries in which limited data are currently available.

Indirect costs are also substantial. Labor force participation rates are low for the predominantly working-age population of MS patients. The proportion working full-time in several European studies ranged from 6 to 20 percent. At least one third of the total costs of MS are associated with this type of indirect cost. In addition, MS is associated with reduced life expectancy of between 5 and 15 years on average.

Intangible costs are diverse but also represent large economic burdens of MS. Significant impacts of MS on generic QOL were documented across multiple domains. Several patterns across different QOL domains were identified. First, the impacts on physical functioning were larger than those on social functioning or mental functioning. In addition, the physical health QOL impacts increased as the disease progressed over time and physical impairments became more severe. However, significant impacts on social functioning and mental functioning were also found. Quantifying the impacts of MS on generic QOL is complicated by the varying patient populations in the different studies and the different QOL measures used. Overall, a starting point for quantifying the QOL impacts of MS can be to summarize these results as generally indicating a 30 percent decline in physical functioning for mild MS, increasing to 40 percent for moderate MS and 50 percent for severe MS. A 20 percent decline in social functioning can be identified for mild and moderate MS, increasing to 30 percent for severe MS. Mental functioning declined by about 10 percent across the range of severity levels. Individual countries can use these initial estimates as a starting point and then modify them to calculate the own economic burden of MS based on their own experience and data.

MS-specific QOL domains are also important, because some of those are not captured by the generic QOL measures. For example, cognitive disability is a major impact of the disease for about 45 to 65 percent of MS patients. Other MS-specific impacts not measured directly by the generic QOL measures include bladder dysfunction, sleep problems, and sexual dysfunction. Moreover, fatigue and depression cause a great deal of problems for MS patients and are only measured in a limited way by the generic QOL measures.

The loss in utility scores as a result of MS was consistent across European and American studies at between 0.20 and 0.31 on the standard utility scale of 0.0 to 1.0. Thus, an overall estimate of the burden of MS in terms of utility is an average loss of 0.25. Using the U.K. population norm of 0.86 as a baseline, this can be expressed as a loss of 29 percent of utility compared with a healthy population.

Informal caregivers of MS patients also bear significant indirect and intangible costs as a result of caregiver burden/stress or reduced QOL; possibly increased health problems, largely related to depression or anxiety; and reduced labor force participation. Calculating the indirect costs of stress/burden and increased psychological health problems is difficult and arguably subjective, but

excluding them ignores a substantial portion of the burden of MS to society. A conservative estimate would be that the economic value of stress/burden for caregivers is 10 percent of what is estimated for MS patients by EDSS level.

In sum, significant economic impacts of MS were found across all of the domains. Documenting and quantifying these economic burdens should raise awareness of the broad range of impacts of MS among policy makers, health care providers, and the public. Individual countries can pursue that type of analysis using the companion template.

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